Companion handbook

to the WHO guidelines for the programmatic management of drug-resistant tuberculosis

THE END TB STRATEGY

World Health Organization

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This book is a companion handbook to existing WHO policy guidance on the management of multidrug-resistant tuberculosis, including the *WHO guidelines for the programmatic management of drug-resistant tuberculosis, WHO interim policy guidance on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis,* and the *WHO interim policy guidance on the use of delamanid in the treatment of multidrug-resistant tuberculosis* which were developed in compliance with the process for evidence gathering, assessment and formulation of recommendations, as outlined in the WHO Handbook for Guideline Development (version March 2010; available at http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf).

WHO Library Cataloguing-in-Publication Data

Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis.

1.Antitubercular agents – administration and dosage. 2.Tuberculosis, Multidrug-Resistant – drug therapy. 3.Treatment outcome. 4.Guideline. I.World Health Organization.

ISBN 978 92 4 154880 9 (NLM classification: WF 360)

Printed by the WHO Document Production Services, Geneva, Switzerland.

WHO/HTM/TB/2014.11

Editing and design by Inis Communication – www.iniscommunication.com

Contents

PART 5 – ANNEXES

Abbreviations and acronyms

aDSM	active drug-safety monitoring and management
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
API	active pharmaceutical ingredients
ART	antiretroviral therapy
AST	aspartate aminotransferase
BCG	Bacillus Calmette–Guérin
BMI	body mass index
BMU	Basic Management Unit
CBO	community-based organization
CDC	United States Centers for Disease Control and Prevention
CHW	community health worker
CMV	cytomegalovirus
CNS	central nervous system
CEM	cohort event monitoring
CPC	cetylpyridinum chloride
CPT	cotrimoxazole preventive therapy
CRI	colourimetric redox indicator
CSO	civil society organization
CU	compassionate use
CYP3A4	cytochrome P450 3A4
DOT	directly-observed therapy
DOTS	core approach underpinning the Stop TB strategy for TB control
DRS	drug resistance surveillance
DST	drug susceptibility testing
EA	expanded access
EQA	external quality assessment
ERP	Expert Review Panel
FBO	faith-based organization
FDC	fixed-dose combination
FQ	fluoroquinolone
FT4	free thyroxine
GDF	Global Drug Facility
GFR	glomerular filtration rate
HIV	human immunodeficiency virus
IHR	International Health Regulations
IM	intramuscular
ISTI	integrase strand transfer inhibitor
LFT	liver function test
LED	light emitting diode
LPA	line probe assays
MDR	multidrug resistance

MDR-TB	multidrug-resistant tuberculosis
MIC	minimum inhibitory concentration
MODS	microscopic observation of drug susceptibility
MOTT	mycobacteria other than tuberculosis
MSH	Management Sciences for Health
M/XDR-TB	multi- or extensively drug-resistant TB
NCB	NGO coordinating body
NGO	nongovernmental organization
NPV	National pharmacovigilance centre
NRA	nitrate reductase assay
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NTM	non-tuberculous mycobacteria
NTP	national TB control programme
PAS	*p*-aminosalicylic acid
PCR	polymerase chain reaction
PI	protease inhibitor
PIH	Partners In Health
PMDT	programmatic management of drug-resistant tuberculosis
PPD	purified protein derivative
PPM	public–private mix
PQP	Prequalification of Medicines Programme
rGLC	Regional Green Light Committee
SGPT	serum glutamic-pyruvic transaminase
QA	quality assurance
QC	quality control
QMS	quality management system
QTcF	QT interval corrected for heart rate (Fridericia method)
SAE	serious adverse event
SCC	short-course chemotherapy
SMX	sulfamethoxazole
SOP	standard operating procedure
SRA	Stringent Drug Regulatory Authority
SRL	Supranational Reference Laboratory
SSRI	selective serotonin re-uptake inhibitor
TB	tuberculosis
TB/HIV	HIV-related TB
TMP	trimethroprim
TSH	thyroid stimulating hormone
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNION	International Union Against Tuberculosis and Lung Disease
USAID	United States Agency for International Development
UVGI	ultraviolet germicidal irradiation
WHO	World Health Organization
XDR-TB	extensively drug-resistant TB

Anti-tuberculosis drug abbreviations

GROUP	DESCRIPTION	DRUG	ABBREVIATION
1	First-line oral anti-TB drugs	Isoniazid	H
		Rifampicin	R
		Ethambutol	E
		Pyrazinamide	Z
		Rifabutin	Rfb
		Rifapentine	Rpt
2	Injectable anti-TB drugs (injectable agents or parenteral agents)	Streptomycin	S
		Kanamycin	Km
		Amikacin	Am
		Capreomycin	Cm
3	Fluoroquinolones (FQs)	Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
		Ofloxacin	Ofx
4	Oral bacteriostatic second-line anti-TB drugs	Ethionamide	Eto
		Prothionamide	Pto
		Cycloserine	Cs
		Terizidone	Trd
		p-aminosalicylic acid	PAS
		p-aminosalicylate sodium	PAS-Na
5	Anti-TB drugs with limited data on efficacy and/or long-term safety in the treatment of drug-resistant TB (This group includes new anti-TB agents).	Bedaquiline	Bdq
		Delamanid	Dlm
		Linezolid	Lzd
		Clofazimine	Cfz
		Amoxicillin/Clavulanate	Amx/Clv
		Imipenem/Cilastatin	Ipm/Cln
		Meropenem	Mpm
		High-dose isoniazid	High dose H
		Thioacetazone	T
		Clarithromycin	Clr

Antiretroviral drug abbreviations

DRUG CLASS	NAME	ABBREVIATION
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz	EFV
	Nevirapine	NVP
Nucleoside reverse transcriptase inhibitors (NRTIs)	Abacavir	ABC
	Didanosine	ddI
	Zalcitabine	ddC
	Emtricitabine	FTC
	Lamivudine	3TC
	Stavudine	D4T
	Tenofovir	TDF[a]
	Zidovudine	AZT
Protease Inhibitors (PIs)	Atazanavir + ritonavir	(ATV/r)
	Darunavir + ritonavir	(DRV/r)
	Lopinavir/ritonavir	(DRV/r)
Integrase strand transfer inhibitors (INSTIs)	Raltegravir	RAL

[a] TDF is a nucleotide reverse transcriptase inhibitor but is typically grouped with this class.

Acknowledgements

The production of this *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* was coordinated by Ernesto Jaramillo under the guidance of Karin Weyer and Mario Raviglione of WHO's Global TB Programme. The contribution of the following experts and technical groups is gratefully acknowledged.

Chief editors

Michael Rich (Harvard Medical School-Partners In Health, USA)
Ernesto Jaramillo (WHO)

Co-authors and peer-reviewers

Jaime Bayona (Darmouth College, USA), Elizabeth Barrera-Cancedda (Partners In Health), Vineet Bhatia (WHO), Jose A. Caminero (The Union/Hospital Gran Canaria Dr Negrin, Las Palmas, Spain), Suzanne Carai (independent consultant), Peter Cegielski (US CDC), Shelly Chadha (WHO), Daniel Chemtob (National TB Programme, Ministry of Health of Israel), Stephen Connor (World Palliative Care Alliance/Soros Foundation), Stephanie Dagron (University of Zurich, Switzerland), Kelly Dooley (Johns Hopkins University School of Medicine, USA), Dennis Falzon (WHO), Bernard Fourie (University of Pretoria, South Africa), Inés García-Baena (WHO), Agnes Gebhard (KNCV, the Netherlands), Haileyesus Getahun (WHO), Chris Gilpin (WHO), Myriam Henkens (MSF), Timothy Holtz (US CDC), Tauhid Islam (WHO), Ernesto Jaramillo (WHO), Thomas Joseph (WHO), Joël Keravec (Stop TB Partnership), Salmaan Keshavjee (Harvard Medical School-Partners In Health, USA), Vaira Leimane (Riga East University Hospital, Riga, Latvia), Christian Lienhardt (WHO), Knut Lönnroth (WHO), Fuad Mirzayev (WHO), Carole Mitnick (Harvard Medical School-Partners In Health, USA), Linh Nguyen (WHO), Domingo Palmero (Hospital Muñiz, Buenos Aires, Argentina), Maria I. Quelapio (independent consultant), Andreas A. Reis (WHO), Michael L. Rich (Harvard Medical School-Partners In Health, USA), Sarah Royce (University of California, USA), Archil Salakaia (USAID/SIAPS, MSH), Michael Selgelid (Monash University, Australia), K Justine Seung (Harvard Medical School–Partners In Health, USA), Thomas M. Shinnick (US CDC), Jacques van den Broek (KNCV, the Netherlands), Wayne van Gemert (WHO), Francis Varaine (MSF), Fraser Wares (WHO), Diana Weil (WHO), Karin Weyer (WHO), Diego Zallocco (WHO).

Technical research and administrative assistants

Caoimhe Smythe (Partners In Health)
Anne Peruski (Partners In Health)
Tracy Mawer (WHO)
Henriikka Weiss (WHO)
Denisa Pohancanikova (WHO)

External expert reviewers

Charles Daley (National Jewish Health, USA), Dalene von Delft (TB-proof, South Africa), Dick Menzies (McGill University, Canada), Irina Vasilyeva (CTRI, Russian Federation), Wang Lixia (China CDC, China).

Funders

Funding from the United States Agency for International Development through USAID–WHO Consolidated Grants No. GHA-G-00–09–00003/ US-2013–0580 and No. GHA-G-00–09–00003/US-2012–0392 is gratefully acknowledged.

The co-authors, and the institutions where they work, contributed their time to the drafting of chapters, follow-up editing, and review of the final document; this support is also gratefully acknowledged.

Foreword

Resistance to tuberculosis (TB) drugs is a formidable obstacle to effective TB care and prevention globally. Multidrug-resistant TB (MDR-TB) is multifactorial and fuelled by improper treatment of patients, poor management of supply and quality of drugs, and airborne transmission of bacteria in public places. Case management becomes difficult and the challenge is compounded by catastrophic economic and social costs that patients incur while seeking help and on treatment.

In 2006, MDR-TB strains with additional resistance to second-line drugs were described as extensively drug-resistant TB (XDR-TB) strains, further compromising treatment options available to patients infected with these strains. Since then, clinicians in some settings have reported patients infected with strains in which virtually all treatment options have been exhausted. This rapidly evolving landscape is a clarion call to policy-makers and practitioners to respond with improvements in care delivery and introduction of innovative tools and approaches. In 2009, the 62nd World Health Assembly urged WHO Member States to provide universal access to care for drug-resistant TB patients. In that resolution, it was acknowledged that national TB programme managers, clinicians, nurses, all care providers and affected people themselves need guidance on how best to bring together different elements of health systems and services needed to effectively address the MDR-TB challenge. In 2014, the 67th World Health Assembly passed a resolution approving the new post-2015 Global TB Strategy, the *END TB strategy*, with its ambitious unprecedented targets and with its vision of ending the TB – as an epidemic disease – by 2035. Therefore, this Handbook has been developed for the purpose of describing ways to implement established WHO policies relevant for the management of MDR-TB. These WHO policy recommendations have been produced using the GRADE methodology for evidence assessment, as adopted by WHO in 2008.

While drug-resistant TB is today a major threat worldwide – and in some settings up to one third of new cases are multidrug-resistant at first diagnosis – it is important to remember that most patients are infected by drug-susceptible strains and can be cured with the standard six-month first-line regimen. Therefore, besides focusing on care for drug-resistant TB, the programmatic management of MDR-TB is premised upon keeping the number of cases with drug resistance to a minimum and treating those that have the condition with the best possible means available.

We trust that you will find this publication useful. WHO will continue working to keep pace with scientific advances in diagnostics, therapeutics and care delivery options so that it can respond effectively and in a timely manner to the needs of TB patients with drug resistance in all countries.

Dr Mario Raviglione
Director
WHO Global TB Programme

Executive summary

This *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* is intended to be a reference tool for use by national tuberculosis (TB) programme managers, clinicians and nurses, public health decision-makers and technical and implementing partners committed to the prevention, care, diagnosis and treatment of drug-resistant TB. It provides practical information on how to implement the relevant World Health Organization (WHO) policies, and provides expert opinion whenever there is, as yet, no WHO policy. Effective management of drug-resistant TB requires input from those responsible for activities related to prevention, case detection, care and treatment, surveillance, drug management, and monitoring and evaluation of a programme's performance. The coordination of all these activities at different levels of a national TB programme are referred to as the 'programmatic management of drug-resistant tuberculosis' (PMDT), and should be seen in the context of the legal and operational frameworks of local health care systems. Thus, the Handbook should be seen as an implementation guide that requires adaptation in the local context without departing from WHO's general policy guidance.

The introduction of new diagnostic and treatment tools for the management of drug-resistant TB is making a significant contribution to enable earlier diagnosis of multidrug-resistant TB (MDR-TB), and more effective treatment in cases were therapeutic options are very limited. Yet, they do not solve many of the major challenges that continue to make the programmatic management of MDR-TB a highly complex public health intervention.

Several important new policy areas in TB care and control have been developed by WHO in recent years. These have been incorporated into this new Handbook, making it a derivative product of the 2008 and 2011 editions of the WHO *Guidelines for programmatic management of drug-resistant tuberculosis*, and of subsequent WHO policy guidance on diagnostics and new anti-TB drugs. The section on diagnostics, for example, takes into account the revolutionary changes that occurred with the swift scale-up of reliable rapid molecular technologies, particularly the Xpert MTB/RIF assay since early 2011. WHO has developed updated policies given the fast emergence of new evidence on its use and incorporated them in this Handbook. Treatment regimens for MDR-TB consider the WHO guidelines of 2011 (which are based on a systematic review using the GRADE system) and growing experience reported from the field. The Handbook also takes into account the 2013 *WHO interim policy recommendations for the use of bedaquiline*, and the 2014 *WHO interim policy recommendations for the use of delamanid*. Bedaquiline and delamanid are the first drugs since the introduction of rifampicin in the late 1960s to be released specifically for the treatment of TB. Illustrative examples have been given in some sections to enable the user to weigh the different options, such as for deciding upon the composition of a drug regimen.

Specific mention is also made of other innovations added to the comprehensive response to MDR-TB care delivery, such as active surveillance for adverse effects of treatment. More space has been devoted to additional disciplines and innovations required for the comprehensive delivery of MDR-TB care. This includes pharmacovigilance, or the surveillance for the adverse effects of treatment, a discipline that is becoming crucially important as new TB drugs and regimens enter the market and 'off-label' use becomes a common practice for the treatment of extensively drug-resistant TB (XDR-TB) in view of the limited options.

The chapter (and annexes) on monitoring and evaluation have been revised completely with a focus on the indicator approach that national programmes are advised by WHO to adopt in order to assess their efforts to detect and successfully treat patients with rifampicin-resistant TB (RR-TB) or MDR-TB, which are being more easily identified since the introduction of molecular assays. The methods and options to deliver palliative/end-of-life care to patients in whom all treatment options are exhausted have been expanded, given that patients can experience relief from issues related to TB treatment and accompanying stigma and discrimination, and should be part of a comprehensive response to MDR-TB. A full chapter is devoted to access to drugs under development for compassionate use, and the ethics of diagnosis, treatment and care, which are increasingly important issues in the management of MDR-TB. Reference is also made to the role that electronic health (eHealth) tools can play to enhance different aspects of care, surveillance and programme management, taking advantage of the increased use of cellular phones and the expansion of Internet networks across the world.

Methods and process for developing the Handbook

To develop this Handbook, a prospective table of contents with the main topical areas being faced by clinicians, health care workers, and TB programme managers implementing WHO and national policies on drug-resistant TB was developed by the chief editors, with the input of members of the WHO Green Light Committee. This table was based heavily on the areas already covered in the 2008 emergency update of the *WHO guidelines for the programmatic management of drug-resistant tuberculosis*, and on emerging new policy areas developed by WHO after 2008. Two leading international clinical and public health practitioners were assigned to draft each chapter of the Handbook, drawing on the best practices reported in the literature and based on their professional experience. The corresponding draft chapters were subsequently reviewed by at least two external experts in the respective field. The final draft of the Handbook was reviewed by five external experts bringing together the perspective of patients, clinicians, researchers, TB programme managers and national TB policy-makers, all well experienced in their respective fields. The chief editors of the Handbook were responsible for the technical editing of the document, taking into account the feedback received from the reviewers and existing WHO policies. The most sensible and relevant expert opinions were presented in those instances where there was no approved WHO policy, albeit without *recommending* any specific course of action.

Declaration of interest forms were obtained from all non-WHO contributors and reviewers of the Handbook. The following potential conflicts of interest were declared:

- Charles Daley reported being chair of the data monitoring committee for clinical trials for delamanid (US$30 000 over five years).
- Dalene von Delft declared having received funding to cover flight, hotel and per-diem costs to attend meetings from AERAS, CPTR, Janssen Pharmaceuticals, TAG, and USAID.
- Maria I. Quelapio declared having worked until 2010 with the Tropical Disease Foundation, which had a contract with Otsuka for a clinical trial on delamanid, a new anti-TB drug.
- Salmaan Keshavjee declared that his employer has ongoing research grants from Eli Lilly Foundation (USD$2.5 million) and Janssen Pharmaceuticals (USD$2.5 million); and that he had a consultancy contract (US$3 900) with Johnson & Johnson.
- Michael L. Rich declared that since June 2014 he is the principal investigator of a project awarded by UNITAID (USD$ 60.4 million over five years) to a consortium in which his employer, Partners In Health, is a leading member. The goal of the project is to improve patient's access to new anti-TB drugs and to conduct research on shorter regimens for MDR-TB.

- Francis Varaine declared that since June 2014 he is the principal investigator of a project awarded by UNITAID (USD$ 60.4 million over five years) to a consortium in which his employer, Médecins Sans Frontières, is a member. The goal of the project is to improve patient's access to new anti-TB drugs and to conduct research on shorter regimens for MDR-TB.

The WHO Secretariat assessed the interests declared by each contributor to the Handbook. Potential conflict of interest was not identified to preclude Charles Daley, Dalene von Delft and Maria I Quelapio from contributing to the development of the Handbook, given that this document is not presenting new WHO policies, and they did not contribute to develop the annexes to this Handbook on how to use bedaquiline and delamanid, or to the chapter 5 on treatment of MDR-TB. Salmaan Keshavjee did not contribute to any chapter of this Handbook related with the use of bedaquiline, a new anti-TB drug developed by Janssen, a subsidiary of Johnson & Johnson. No conflict of interest was considered for the funding reported from the Eli Lilly Foundation by Salmaan Keshavjee, given that Eli Lilly Inc. is currently only producing cycloserine and capreomycin for the United States market (and not for any others). Potential conflict of interest was not identified to preclude Michael L. Rich and Francis Varaine from contributing to the development of this handbook given that this document is derivative of already established WHO policies for new drugs and shorter regimens.

CHAPTER 1

Prevention of drug-resistant tuberculosis

1.1 Introduction

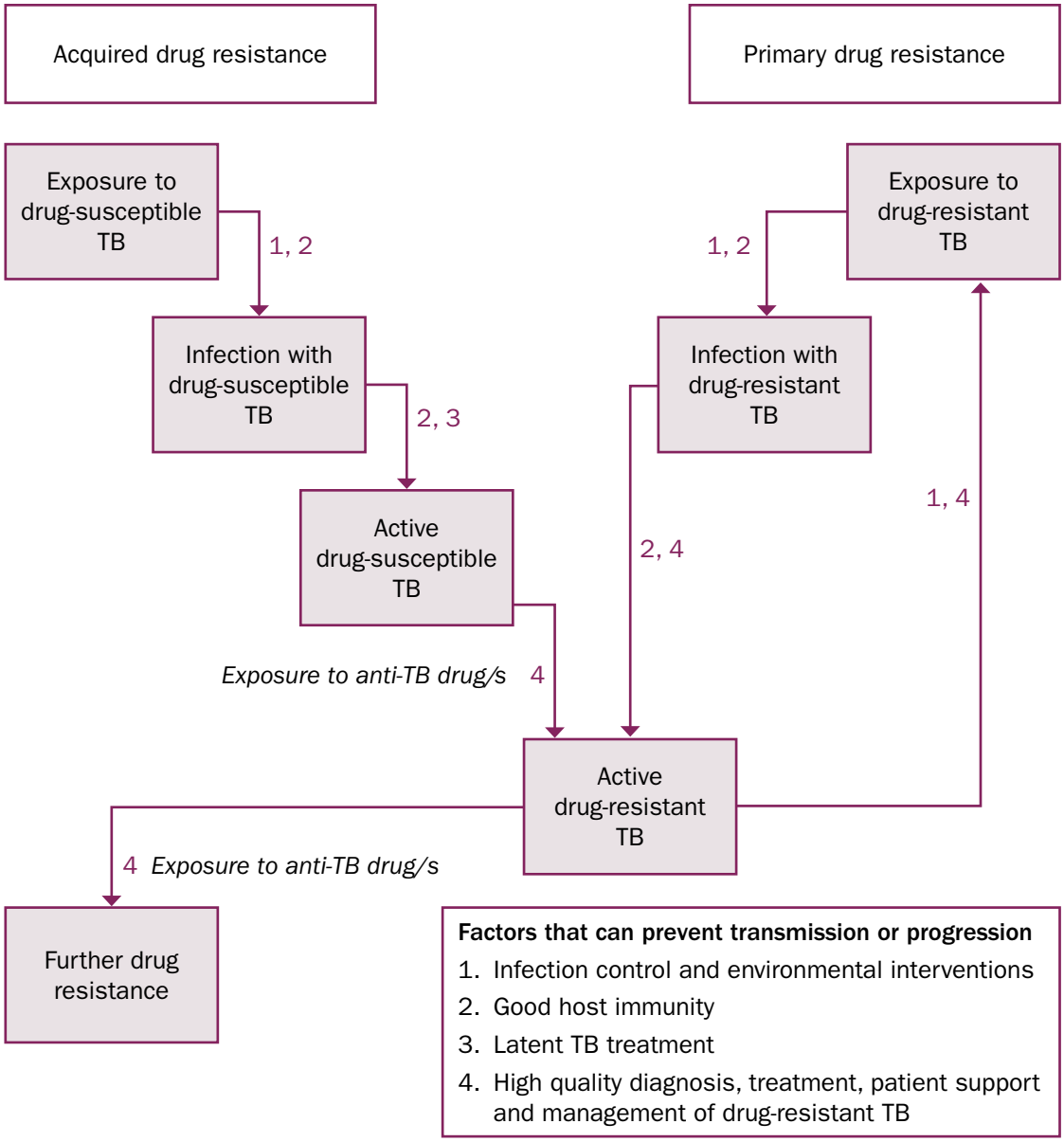
This chapter underscores that countrywide, comprehensive and effective implementation of the WHO-recommended Stop TB strategy (developed from the DOTS framework), is an important approach for preventing drug-resistant tuberculosis (TB) *(1)*. Drug-resistant TB requires an understanding of the causes and their effective response. Section two of this chapter describes the two pathways of development of drug-resistant TB and factors contributing to drug resistance. Section three outlines the main interventions that help prevent the development and spread of drug-resistant TB.

1.2 Causes of drug-resistant TB

1.2.1 Two pathways leading to drug-resistant TB

There are two principal pathways leading to the development of active drug-resistant TB: (i) acquired (secondary) drug resistance and (ii) primary drug resistance. These pathways are interconnected and have many contributing factors (Figure 1.1).

Figure 1.1 Two pathways leading to drug-resistant TB



Note: Pathways to development of drug-resistant TB. Arrows represent progression along the two pathways. Numbers represent factors that can contribute to the prevention of progression.

Acquired drug resistance. Acquired drug resistance is the result of inadequate, incomplete or poor treatment quality that allows the selection of mutant resistant strains. If drug-susceptible TB is treated with a regimen exclusively based on a single effective TB medicine, there is a risk that bacteria with drug-resistant mutations will be selected and multiply further during the course of treatment, eventually becoming the dominant strain. If a person infected with a strain, initially resistant to a specific medicine is treated with that medicine plus a new additional medicine, then there is a risk of developing resistance to the additional medicine. Step-wise additions of drugs may eventually lead to more severe patterns of drug resistance and eventually to untreatable forms of TB.

Simultaneous natural mutations in *Mycobacterium tuberculosis* resulting in resistance to more than one TB medicine are very rare. Therefore, appropriate treatment with a combination of several quality-assured TB medicines dramatically diminishes the risk of selection of resistant strains. This is the rationale for using a combination of quality-assured medicines when treating TB, while ensuring good adherence.

Poor treatment outcomes, including acquired drug-resistant TB, can be caused by inappropriate treatment; inadequate drug quality and supply; and patient factors hampering adherence and treatment responses (Table 1.1). Health system weaknesses and social determinants underpinning these factors are discussed below.

TABLE 1.1 **Factors contributing to poor TB treatment outcomes *(2)***

HEALTH CARE PROVIDERS: INAPPROPRIATE TREATMENT	DRUGS: INADEQUATE SUPPLY/QUALITY	PATIENTS: INADEQUATE DRUG INTAKE OR TREATMENT RESPONSE
Inappropriate guidelines	Poor quality medicines	Lack of information
Non-compliance with guidelines	Unavailability of certain medicines (stock-outs or delivery disruptions)	Lack of means to adhere to treatment (transportation, food, etc.)
Absence of guidelines	Poor storage conditions	Adverse effects
Poor training	Wrong dose or combination	Social barriers
Financial disincentives	Poor regulation of medicines	HIV
Poor patient education		Diabetes mellitus
No monitoring of treatment		Undernutrition
Poor management of adverse drug reactions		Malabsorption
Poor treatment support		Substance abuse/dependency
Poorly organized or funded TB control programmes		Psychiatric condition

Primary drug resistance. Primary or initial drug resistance means that a person has been infected with a drug-resistant TB strain. Transmission of drug-resistant TB occurs exactly in the same way as transmission of drug susceptible TB. High prevalence of drug-resistant TB in the community increases the risk of drug-resistant TB exposure in the community. Undiagnosed, untreated, or poorly treated drug-resistant TB contributes to sustained high drug-resistant TB prevalence, as well as high proportions of infectious drug-resistant TB cases among the community.

Environments conducive for TB transmission (such as crowding, poor ventilation and poor infection control practices in health facilities and other congregate settings), also contribute to transmission of drug-resistant TB. Infection control measures to prevent infection with drug-resistant TB are discussed in Chapter 14.

Similar to drug-susceptible TB, drug-resistant TB only progresses to active disease in a minority of those infected, and drug-resistant TB infection can remain latent for long periods of time. A poorly functioning immune system increases the risk of progression, and therefore factors that

can impair the immune system (e.g. HIV, under nutrition, diabetes, silicosis, smoking, alcohol abuse, a wide range of systemic diseases and treatments with immunosuppressant) are also risk factors for developing drug-resistant TB disease.

Bacillus Calmette–Guérin (BCG) vaccination prevents severe forms of TB in children and may have a protective effect against lung disease among children and adults (although estimates of efficacy for pulmonary disease greatly vary). It is unclear if the protective effect of the BCG vaccine has an overall effect on mitigating TB as a problem for the general population. This efficacy of vaccination is the same for drug-susceptible and drug-resistant TB *(3)*.

1.2.2 Cross-cutting factors contributing to the spread of drug-resistant TB

Health system weaknesses. Poorly functioning general health systems contribute to poor TB diagnosis and treatment outcomes that may lead to the development and spread of drug-resistant TB. Fundamental aspects of a good health care system include: sufficient health financing and universal health coverage; government stewardship and regulation; a well-developed health-care infrastructure; well-trained and motivated workforce; uninterrupted supply and good management of medicines; diagnostics and other commodities; and a well-functioning health information system, including disease surveillance.

Challenges exist for all of the aforementioned fundamentals within many health systems, but they are particularly pronounced in low- and middle-income countries. TB-specific programmatic solutions can be pursued to some extent by national TB control programmes (NTPs) and partners to improve financing for TB services, TB drug management, delivery of services, and human resource development for TB as discussed in Part 2 of this publication. However, the solutions are likely to be sub-optimal and temporary unless linked to broader health system strengthening.

Underlying risk factors and social determinants. People belonging to poor socioeconomic background and other vulnerable groups are at increased risk of being exposed to poor living/working conditions and immunocompromising conditions (such as HIV, undernutrition, smoking, and drug and alcohol abuse), and having poor access to diagnosis and treatment. Poor adherence due to social and economic constraints, as well as poverty and socioeconomic inequalities are determinants that cut across all levels of the two pathways to drug-resistant TB (Figure 1.1).

Specific social structures (or lack thereof) also contribute to increased risk of drug-resistant TB in a society. Weak or absent social support and protection may contribute to poor access to TB services, as well as poor adherence to TB treatment. Poor policies and practices within the penitentiary system, which lead to poor living conditions and poor access to quality health services for prisoners, increase the risk of transmission and acquisition of additional resistance. Furthermore, weak immigration policies and inability of health systems to cope with a large influx of migrants during complex emergency situations may lead to poor access to quality health services and poor living conditions among refugees and other migrants.

In very poor settings, access to TB drugs may be (or may have been in the recent past) limited. Therefore, drug-resistant TB rates are still low as people have not yet been sufficiently exposed to inappropriate TB treatment. Drug-resistant TB prevalence rates tend to be high in middle-income countries and more usually affect the poor and vulnerable groups within those settings. Resource-limited countries scaling up TB diagnosis and treatment face the risk of an emerging drug-resistant TB epidemic if the risk factors for drug-resistant TB are not addressed.

1.3 Interventions to prevent drug-resistant TB

There are five principal ways to prevent drug-resistant TB:

1. Early detection and high quality treatment of drug-susceptible TB.
2. Early detection and high quality treatment of drug-resistant TB.
3. Effective implementation of infection control measures.
4. Strengthening and regulation of health systems.
5. Addressing underlying risk factors and social determinants.

For these interventions to be effective, countries would have to adopt and implement the WHO-recommended TB strategy (see Chapter 16).

1.3.1 Early detection and high quality treatment of drug-susceptible TB

In all settings, regardless of the drug-resistant TB prevalence rate, the development of drug-resistant TB in patients with drug-susceptible TB should be prevented. This key drug-resistant TB prevention measure can be achieved by ensuring that drug-susceptible TB is properly diagnosed, treated and managed.

Ensuring early detection of TB involves the introduction or strengthening of interventions to improve access and utilization of high-quality TB services established across the health system, including in the private sector. Specific interventions include: suitable diagnostic methods to ensure early detection of TB comprising screening of risk groups and inclusion of household contacts of infectious TB patients; placing patients on effective treatment with treatment follow-up; and minimizing barriers to health care access.

In every setting, specific challenges for treatment adherence should be assessed and support packages designed accordingly. Moreover, the adverse social and financial consequences for people with TB, arising from the disease itself as well as from its diagnosis and treatment, should be analysed. Appropriate mechanisms should then be put in place to mitigate the consequences.

WHO guidelines on TB diagnosis *(4–7)* and treatment *(8,9)* provide specific recommendations on best practices. Additionally, special guidelines are also available on infection control *(10)*. The WHO handbook *Implementing the WHO Stop TB strategy (11)* provides guidance on the implementation of all elements of the Stop TB strategy *(12),* in conjunction with the international standards of TB care *(13)*.

1.3.2 Early detection and high quality treatment of drug-resistant TB

In settings where treatment of drug-susceptible TB is of sufficient quality, i.e. where the rate of acquired resistance is relatively low, most incident drug-resistant TB cases may still be generated through the transmission of drug-resistant TB from the pool of prevalent drug-resistant TB cases. In such settings, the most important element of drug-resistant TB prevention is to ensure proper diagnosis, as well as treatment and management of drug-resistant TB. Early diagnosis and prompt, effective treatment are among the strongest actions to curb the drug-resistant TB epidemic.

The proportion of drug-resistant TB in new cases is typically lower than in retreatment cases. However, the absolute number of new TB cases may be much higher than the number of retreatment cases. Therefore, many countries have a higher absolute number of drug-resistant TB in new cases, rather than in retreatment cases.

Presently, in most low- and middle-income countries, drug susceptibility testing (DST) is done only in a fraction of all cases. If done routinely, it is often only done in retreatment cases. This leads to a large number of undetected drug-resistant TB cases, or severely delayed diagnosis of the majority of drug-resistant TB cases.

(Strategies for early detection of drug-resistant TB are discussed in Chapter 4, while its effective treatment is discussed in Chapter 5. Investigation of close contacts of people with drug-resistant TB is discussed in Chapter 15.)

1.3.3 Infection control

TB infection control is a combination of measures aimed at minimizing the risk of TB transmission within populations. Infection control policies should be well formulated and implemented at every level of health delivery (public and private), in congregate settings, such as correctional facilities, military barracks, homeless shelters, refugee camps, boarding schools and nursing homes, and at the household level. Community campaigns can focus on how to minimize the exposure of TB in general and how households that have a TB patient within them can help prevent transmission. Societal level infection control involves improved general living and working conditions, thus creating environments that are less conducive to TB transmission. Drug-resistant TB infection control is addressed in Chapter 14 and there are comprehensive recommendations on TB infection control that have been produced by WHO *(10)*.

1.3.4 Health system strengthening and regulation

Assessing health system barriers and opportunities is an essential part of planning TB control interventions. Such assessments should identify bottlenecks that could be addressed both through TB-specific programmatic interventions (see Part 2 of this publication) and interventions that need to be pursued beyond the purview of the NTPs. Opportunities for integration of service delivery, sharing of resources and joint actions to improving human resource development, diagnostic capacity, and drug management with other public health programmes should be explored. TB-specific interventions that risk disrupting or distorting overall health system operations and prioritizations should be avoided to the extent possible.

WHO has provided guidelines for NTPs on how they can contribute to general health system strengthening *(14)*.

A health system element of particular importance for drug-resistant TB prevention is regulation of diagnostics and drugs, which is further discussed in Chapter 22. Quality and availability of both first- and second-line medicines need to be assured, such that regulation of registration, import and manufacturing of TB drugs is addressed. A large proportion of TB drugs are used outside of NTPs and NTP-affiliated facilities, notably in the private sector where prescription practices and treatment management is often of very poor quality. This is an important contributor to drug-resistant TB development in many settings. Some countries have successfully restricted the use of first-line TB medicines to NTP-affiliated facilities, which is an effective method to help keep the drug-resistant TB prevalence low. It is essential to regulate the availability of both first- and second-line TB medicines and restrict use to those facilities where quality of prescription and treatment management can be ensured. In particular, banning over-the-counter sales of TB medicines should be strictly enforced. Private and public providers not linked to the NTP, including those providing drug-resistant TB diagnosis and treatment without following international standards and programmatic management of drug-resistant TB (PMDT) principles, can be engaged through public–private mix approaches, allowing access to free quality-assured TB medicines upon adherence to national guidelines *(15)* (see Chapter 17).

Another important regulatory intervention is to make TB a notifiable disease and enforce regulation. This concept is key to both enabling proper surveillance of TB as well as identifying where TB (including drug-resistant TB) is being diagnosed and managed. These monitoring strategies will help ensure that quality and treatment outcomes can be assessed across the whole health system.

1.3.5 Addressing underlying risk factors and social determinants

Optimal diagnosis and treatment of known TB cases are essential, however, they are not sufficient to manage or prevent drug-resistant TB. The most critical and immediate social intervention for prevention of drug-resistant TB is to assess social and financial barriers to access and adherence to health-care services and to address them accordingly. While this includes providing all TB diagnostic and treatment services free of charge to the patients, it must also minimize the cost to patients for other related clinical services (such as managing comorbidities, notably HIV infection which may have a negative impact on TB treatment outcomes, see Chapters 7 and 8), as well as minimize the indirect costs of care (for example, those related to transport and loss of income). Indirect costs of TB care are often catastrophic, even when TB diagnosis and treatment is provided free of charge. Access to available social protection schemes, including sickness/disability funds and other cash transfers, should be ensured for people with TB. If such schemes are not fully developed or if people with TB are not eligible, the NTP should advocate for the development/adaptation of social protection schemes. Such interventions are critical for both drug-susceptible and drug-resistant TB patients in order to reduce the risk of poor treatment outcomes leading to acquired/amplified resistance and transmission of drug-resistant TB. They may also contribute to poverty alleviation on a household level, with medium- to long-term preventive effects. (See Chapter 12 for details on adherence and social support interventions).

Addressing risk factors and social determinants of drug-resistant TB when people have already fallen ill and try to seek care is necessary, but not sufficient. For long-term and sustainable TB control – drug-resistant TB control included – the underlying vulnerabilities of TB-affected communities need to be reduced. Neither structural interventions for poverty and inequality reduction, nor public health interventions to diminish the prevalence of important risk factors (e.g. HIV, undernutrition, diabetes, smoking, alcohol/drug abuse) can be pursued by NTPs alone. However, the NTP should assess what risk factors are most important and collaborate with others to address them, within and outside of the health sector.

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CHAPTER 2

Monitoring the detection, enrolment and treatment outcomes of drug-resistant TB patients

2.1 Introduction

This chapter explains the parameters and activities necessary for monitoring interventions in tuberculosis (TB) patients infected with drug-resistant TB strains, including patient care, programme supervision, as well as planning and measurement of progress toward universal access. It explains the definitions in use to identify, register and assign outcomes to drug-resistant TB patients who require second-line anti-TB medication. Following extensive consultations since 2010, the definitions and minimal reporting requirements included in this chapter have been updated from the ones in the *WHO 2008 Guidelines for the programmatic management of drug-resistant tuberculosis (1)*. An attempt has been made to simplify methods,

to introduce indicators on coverage of drug susceptibility testing (DST) and to adapt the monitoring parameters to address today's fast-changing landscape in TB care. The advent of novel diagnostic technologies and the release of new anti-TB drugs make this particularly relevant. The outcome definitions have been revised in 2013 and can be applied to both second-line TB regimens recommended by WHO (which are on average about 20 months long) and to regimens that are substantially shorter *(2,3)*. The minimum indicators to monitor multidrug-resistant TB (MDR-TB) patients, which were released in 2010 *(4)*, have been adapted in this chapter to accommodate testing centres relying on Xpert MTB/RIF[1] for the diagnosis of rifampicin-resistant TB (RR-TB).

2.2 Implementing an effective information system

The organization of information on drug-resistant TB cases facilitates the:

- standardization of patient data for registration;
- assignment of appropriate treatment regimens;
- monitoring of detection, patient enrolment and treatment outcomes between different units and over time; and
- surveillance of drug resistance.

In common with other health information systems, those used to manage data for drug-resistant patients are usually composed of several distinct parts. These include components to collect data from different sources and process that data into interpretable indicators for management and decision-making. These functionalities are organized very differently among countries and usually involve interplay of paper and electronic methods.

The main features of many information systems used for drug-resistant TB have historically evolved from those elaborated much earlier for DOTS programmes and intended primarily to treat drug-susceptible TB patients. As a result a number of data elements are common between the systems. The format of treatment cards, request forms, registers and reports, as well as the way that they are routed in the programme, are similar for the two streams of TB patients. Much of the drug-resistant TB recording and reporting up to now has been managed on paper-based systems. Aggregation of data at the provincial level before they are reported to the central level is commonplace, although a number of countries have a patient-based dataset even at the central level for MDR-TB cases. As patient numbers increase, the heavy requirements in data management make an electronic system particularly desirable. Very often electronic patient records are based on the content of the treatment card or the Second-line TB treatment register. Once such individual patient records are entered into a system, the generation of indicators becomes easier. Information quality also improves as checks can easily be programmed at the time of data entry or at a later phase; and transcription and computation errors can be reduced. When adopting electronic systems it becomes important to employ standard formats for data elements which may need to be linked, such as registration numbers, district names, treatment unit codes, dates, patient names and identifiers.

[1] A molecular-based rapid test from Cepheid Inc. for TB diagnosis. It can simultaneously detect *M. tuberculosis* complex DNA and mutations associated with rifampicin resistance directly from sputum specimens in less than two hours

Many programmes need to decide when and how to computerize their systems. In 2012, WHO and its technical partners produced guidance on the electronic recording and reporting of TB in terms of the necessary organization, scope, capabilities, resources and infrastructure *(5)*. These guidelines help the managers go through the critical steps leading to such decisions. The document also provides guidance on how to commission a system from an external provider. A set of requirements in human resources, infrastructure and information technology have to be met to ensure a functional system. The system should ideally fit into any overall "eHealth" framework that the country may have *(6)*.

BOX 2.1 eHEALTH

Electronic health or "eHealth" entails the use of information and communication technologies for health to, among others, treat patients, pursue research, educate, track diseases and monitor public health. There are different domains in which eHealth utilities can benefit TB programmes and patients. It has an important role in facilitating the management of data and electronic systems that are today becoming indispensable in programme monitoring. The electronic management of patient medical records makes the storage of data and access to them more efficient and permits the rapid analysis for response to treatment and for pharmacovigilance. This is also important for operational research. Moreover, computerized databases can provide programme managers with up-to-date information on stocks of drugs and other consumables and the physical distribution of patients and their contacts using geographical coordinates. Mobile health (mHealth), a sub-type of eHealth, is also expanding rapidly as cellular phones become more widely available. For instance, patients may receive reminders on their mobile phones to follow prescribed care and adherence may be rewarded through incentives (e.g. conditional cash transfers or as mobile phone credit). Patients may also use their mobile phones to alert their carers to adverse drug reactions. The Internet now provides huge opportunities to improve patient and carer information on drugs and their safety as web access steadily penetrates even very remote areas.

The proper functioning of any system depends very much on the vision and the motivation of the workers who use it. The system should be a tool to help people deliver their work better rather than to cut down on manpower requirements. Any information that is not going to be used by the system should not be included. Once a system is implemented, the users will require training and supervision in their work. Regular meetings with staff from different levels are also very helpful in ensuring long-term success.

2.3 Definitions for cases and treatment outcomes

2.3.1 Patterns of drug resistance

The confirmation of drug resistance depends on a laboratory diagnosis. The conventional method is to show that strains of *Mycobacterium tuberculosis* grow on culture media in the presence of one or more anti-TB drugs (phenotypic testing). Newer genotypic (molecular)

techniques are now available to detect mutations, which are associated with resistance to certain drugs (see Chapter 3 for further information on laboratory methods).

Different patterns of drug resistance carry different implications for treatment and management. For the purposes of monitoring, drug-resistant cases are classified in categories based on DST in clinical isolates confirmed to be *M. tuberculosis* (note, the categories are NOT mutually exclusive):

- **Mono-resistance:** resistance to one first-line anti-TB drug only.
- **Poly-resistance:** resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin.
- **Multidrug resistance (MDR):** resistance to at least both isoniazid and rifampicin.
- **Extensive drug resistance (XDR):** resistance to any fluoroquinolone, and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.
- **Rifampicin resistance (RR):** resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR.

MDR-TB and extensive drug-resistant TB (XDR-TB) are also included when enumerating rifampicin resistance (RR). While it has been the practice until now to limit the definitions of mono-resistance and poly-resistance to first-line drugs only, future drug regimens may make it important to classify patients by their strain resistance patterns to fluoroquinolones, second-line injectable agents as well as any other anti-TB drug for which reliable DST becomes available. In this chapter, the emphasis is on monitoring of patients with RR-TB or MDR-TB. Patients placed on second-line anti-TB medications usually belong to one of the following groups:

- **Confirmed RR-TB or MDR-TB.**
- **Presumptive RR-TB or MDR-TB.** Patients may be registered and started on second-line anti-TB treatment on the basis of significant risk for drug resistance and before laboratory confirmation of resistance, or on the basis of a rapid molecular result (see Chapters 3 and 4).
- **Poly-/mono-resistant TB without rifampicin resistance.** Some of these cases may have second-line anti-TB drugs added to their treatment (see Chapter 6).
- **XDR-TB (confirmed or presumptive).** Patients may be started on XDR-TB treatment on the basis of a laboratory diagnosis or, in its absence, because of significant risk.

2.3.2 Treatment outcomes

Standardized definitions have been in use for several years to assign treatment outcomes to drug-resistant TB patients *(7)*. In 2013, the definitions were revised following broad consultation and piloting in different settings *(8)*. The categories *Cured* and *Treatment failed* were simplified to facilitate their use prospectively. The previous category *Defaulted* has been renamed to *Lost to follow-up*. While the previous category *Transferred out* – referring to a patient who moved to another treatment centre but whose definitive outcome at the end of treatment was not established – may inform the health-facility programme manager about patient mobility, it

has no significance at the national or global level. As a result it is no longer being included as one of the final outcome categories (see also under Section 2.5 below). Such cases should be considered *Not evaluated* or *Lost to follow-up* depending on the circumstances under which the patient separated from the services.

The revised treatment outcome definitions now make a clear distinction between two types of patient groups ("cohorts"):

1. Patients treated for rifampicin-susceptible TB; and
2. Patients treated for RR-/MDR-TB using combination second-line drug treatment, which includes drugs other than the first-line medicines in Group 1 *(1)*.

The two groups are mutually exclusive. Any patient found to have RR-/MDR-TB **and** placed on second-line treatment is removed from the rifampicin-susceptible TB treatment cohort. RR-/MDR-TB patients who were not started on a MDR-TB regimen are assigned an outcome from those for rifampicin-susceptible TB (see Table A.2.1 in *(8)*). This means that the Basic Management Unit (BMU) TB register and the Second-line TB treatment register need to be coordinated to ensure proper accounting of treatment outcomes.

The revised definitions for patients with drug resistance are as provided in Table 2.1.

If the clinician changes two or more anti-TB drugs during the intensive phase because of lack of response or adverse drug reactions, then the case is not considered a *Treatment failure* and the same treatment episode needs to be monitored for outcomes. However, if such a change or termination of regimen occurs during the continuation phase for reasons given in Table 2.1, then the *Treatment failure* outcome is fulfilled.

The sum total of *Cured* and *Treatment completed* is commonly used as an indicator of favourable outcome, or *Treatment success*. The outcome *Cured* is restricted to pulmonary bacteriologically confirmed TB cases only.

TABLE 2.1 **Definitions of treatment outcomes for drug-resistant patients *(8)***

TREATMENT OUTCOME	DEFINITION
Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.[a]
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.[a]

Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: • Lack of conversion[b] by the end of the intensive phase[a]; or • Bacteriological reversion[b] in the continuation phase after conversion[b] to negative; or • Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs; or • Adverse drug reactions.
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for two consecutive months or more.
Not evaluated	A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown).
Treatment success	The sum of *Cured* and *Treatment completed.*

[a] For *Treatment failed*, lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of the intensive phase applied by the programme. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between intensive and continuation phases, a cut-off eight months after the start of treatment is suggested to determine when the criteria for *Cured, Treatment completed* and *Treatment failed* start to apply.

[b] The terms 'conversion' and 'reversion' of culture as used here are defined as follows:

Conversion (to negative): Culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative Culture is used as the date of conversion.

Reversion (to positive): Culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining *Treatment failure*, reversion is considered only when it occurs in the continuation phase.

2.3.3 Bacteriology and sputum conversion

Bacteriological examinations in patients with drug-resistant TB include sputum smear microscopy, culture and DST as well as molecular techniques such as Xpert MTB/RIF and line-probe assay (LPA). The mainstays for testing patient response to treatment are sputum smear microscopy and culture. Xpert MTB/RIF and LPA are recommended for diagnostic testing for the presence of *M. tuberculosis* and detection of mutations associated with rifampicin resistance; molecular tests are not recommended for treatment monitoring (also see Chapter 3 for further information on Xpert MTB/RIF and molecular tests). DST may be used during treatment to assess for any acquisition of additional resistance or reinfection (also see Chapter 10 for more information on monitoring response to treatment and recommended frequency of DST during treatment). Given that decisions on the treatment of patients depend to an important degree on the bacteriological findings, it is crucial that the tests are performed in conformity to international standards *(9)*.

For a patient to be considered bacteriologically confirmed at the start of second-line treatment, the following criteria must be met:

1. At least one pre-treatment specimen was positive on sputum smear microscopy, Xpert MTB/RIF or culture.
2. The collection date of the sample on which the laboratory examination was performed was less than 30 days before or seven days after the initiation of second-line treatment.

Examinations are required at the start of treatment to confirm the diagnosis of TB, and to determine the infectiousness of the patient. Patients with positive sputum smear are the most infectious. Both smear and culture should be used to monitor patients throughout the therapy. At least one sputum sample should always be cultured at the time of start of second-line TB treatment. The monitoring of sputum culture is important for decisions on changes in treatment.

2.4 Registration of information on drug-resistant TB cases

Four key forms are used for the purposes of registration and are described below (see Part 4 for templates of these forms):

Form 01. Second-line TB treatment card;
Form 02. Second-line TB treatment register;
Form 03. Request for examination of biological specimen for TB;
Form 04. Laboratory register for culture, Xpert MTB/RIF and drug susceptibility testing (DST).

Form 01. Second-line TB treatment card

Information relevant to the start and continuation of second-line treatment in a TB patient is entered on the patient's Treatment card (Form 01). The card is usually kept at the treatment centre or with the health care worker providing directly-observed therapy. A daily record of the administration of drugs is kept on the treatment card. The card, or a copy of it, must always follow the patient (e.g. from a specialized hospital to an ambulatory facility).

Much of the data and suggested layout of the treatment card are similar to those used for basic TB. The card is usually opened after a decision is taken to start the patient on treatment and s/he is registered in the Second-line TB treatment register (Form 02; see below). It is the primary source of information to update this register.

Information on the Second-line TB treatment card is organized in a number of blocks:

The section on **patient information** includes demographic and clinical details: *Patient name, Address/telephone, Sex, Date of birth (or Age), Initial weight* and *Site of disease*. *Site of disease* is denoted as "pulmonary" and "extrapulmonary" in the same way as for basic TB management. This section also includes the *Second-line TB treatment registration number* (the unique register number assigned at start of treatment) and the *Date of registration*.

Registration group: Patients are assigned to a registration group based on the most recent treatment history at the time of collecting the biological specimen that was used to confirm MDR-TB or RR-TB.

- **New.** A patient who has received no or less than one month of anti-TB treatment (see below).
- **Relapse.** A patient who was previously treated for TB and whose most recent treatment outcome was *Cured* or *Treatment completed*, and who is subsequently diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).
- **Treatment after loss to follow-up.** A patient who had previously been treated for TB and was declared *Lost to follow-up* at the end of the most recent course of treatment. (This was previously known as *treatment after default.*).
- **After failure of first treatment with first-line drugs.** A patient who has received first-line drug treatment for TB and in whom treatment has failed.
- **After failure of retreatment regimen with first-line drugs.** A previously treated TB patient who has received a retreatment regimen with first-line drugs and in whom the retreatment has failed.
- **Other previously treated patients**. A previously treated TB patient whose outcome after the most recent course of treatment is unknown or undocumented.

Patients with unknown previous TB treatment history do not fit into any of the groups listed above.

For the purposes of registration on second-line treatment for MDR-TB, patients are considered *New* if DST was performed within one month of the start of treatment, even if they had received more than one month of **first-line drug treatment** for TB by the time that the DST results returned and they were registered for second-line TB treatment.

Treatment failure of a first-line treatment regimen is defined as a sputum smear or culture that is positive at five months or later during treatment *(8).* The identification of MDR-TB at any point during a first-line treatment is no longer automatically assigned a *Treatment failure* outcome, considering that effective second-line treatment may be immediately available.

If the patient is transferred-in from a different second-line treatment centre, it is indicated here with the name of the original centre. To simplify recording in the Second-line TB treatment register, *Transfer in* is included as one of the Registration groups (see also note under Form 02 below).

Previous tuberculosis treatment episodes: Any anti-TB regimen received in the past for one month or more, whether first- or second-line. The previous BMU TB register number (if first-line) or Second-line TB treatment register number and the respective date of registration; as well as the outcome of treatment should be recorded. A previous treatment for TB using second-line drugs for more than one month, with or without use of first-line drugs, is considered as previous second-line treatment.

HIV information. This section summarizes information on testing for any MDR-TB patient and the details on the start of antiretroviral treatment (ART) and co-trimoxazole preventive therapy for those found to be HIV-infected. Some programmes choose not to include this information on the treatment card for patient confidentiality or to place it on a back page.

Meetings of the review panel. Dates and decisions (treatment start, stop or change) of the authority responsible for treatment, variably called the medical commission, selection committee, or *consilium*.

Sputum smear microscopy and culture. The date of sputum collection, sample number in the laboratory register and result of smear and culture are registered according to the month of treatment. The notation of results is indicated in the treatment card.

Drug susceptibility testing results. The date that the specimen (usually sputum) is collected, sample number and the results for both first- and second-line anti-TB drugs. If molecular methods are used for testing, this is recorded near the results. If drugs other than those listed were tested, the rows labelled 'Other' can be changed to specify the name of the drugs tested.

Second-line treatment regimen. The date treatment is started, changed or stopped, along with the dosage (mg) of each drug. Changes of a drug-dosage or changes to the regimen may be noted in the comments column.

Administration of drugs. This is essentially maintained as a diary of drug administration. Each row corresponds to a calendar month, the first one being the first month of treatment. Daily treatment administration is indicated by tick marks under the date. If split doses are used, the upper left half is used to mark the morning dose and the lower right for the evening dose. The tick mark notation is indicated in the card. The last column is for key comments on the body weight, biochemistry and chest radiography.

A more detailed manner of recording the doses administered is to have one block devoted to one month of treatment, with the individual drugs in a regimen listed down the first left-hand column and the daily record of treatment indicated in the subsequent columns. This method would necessitate that the treatment card pages are organized as a booklet.

Comments. This is the place to enter remarks that cannot be placed elsewhere but which are important for the patient's treatment. It includes details of medical conditions such as diabetes and opportunistic infections, and notes on adverse events (date, description and suspected drug(s)).

Outcome of treatment. The final outcome is recorded as defined above, with the date on which the outcome was met. *Lost to follow-up* is recorded after two consecutive months of interruption and the date when the interruption started is recorded.

Form 02. Second-line TB treatment register

The Second-line TB treatment register is primarily intended to keep a record of those data that are important for generating indicators and reports among patients placed on second-line regimens. It is also commonly used to follow, at a glance, the adequacy of testing and treatment decisions. The register should not contain information that is beyond this scope. The Second-line TB treatment register should be updated regularly from individual Second-line TB treatment cards and from the laboratory registers. Patients are recorded in the register consecutively by their date of registration.

As MDR-TB treatment is of longer duration than first-line regimens, the register is typically much wider than the BMU TB register (previously referred to as the District TB register) used for basic TB programmes (DOTS programmes) *(8)*. The register is generally kept at the centre responsible for registration. This may be peripheral if services are decentralized or combined with basic TB care ('mainstreaming'). If the services for drug-susceptible and drug-resistant TB are combined, both the BMU TB register and the Second-line TB treatment register would need to be located in the same treatment unit. The BMU TB register should contain the records of all TB patients eligible for treatment, including the multidrug-resistant ones, regardless of whether treatment was actually started or not. In order to enhance the process of registration and reporting, a few modifications to the information in the current format of the BMU TB register are suggested.

- Any patient who fits one or more risk categories for RR-TB or MDR-TB and who should undergo DST for rifampicin ± isoniazid according to the national policy, should be highlighted. This will simplify the calculation of the *Detection indicators* (see below).
- Space to record DST should be added, including the date of collection of the sample and the drugs that are being tested.

If culture and Xpert MTB/RIF are being done (in addition to smear microscopy) in a substantial number of cases, dates of collection and results should be added to both the initial testing, and for culture, the follow-up columns. A patient who is switched to a second-line drug regimen because of RR-TB or MDR-TB should have this change noted in the space for outcome in the BMU TB register. This case is included only in the calculation of final outcomes of the second-line drug treatment cohort and not in the one for basic TB outcome cohorts. If a second-line drug treatment programme is unavailable, the case would be a *Treatment failure* as per definition (see above).

It is generally recommended to register patients in the Second-line TB treatment register only if they are embarking on a full MDR-TB regimen. Patients bearing strains resistant to first-line drugs and who are not on a full MDR-TB regimen should be kept in the BMU TB register only (any modified regimen can be noted in the Comments section, especially if it contains second-line anti-TB drugs). Some patients may be registered and started on second-line TB treatment based on the presumption of RR-TB or MDR-TB (empiric treatment). If these are later found not to be RR-TB/MDR-TB cases, and are switched back to a first-line regimen, the row bearing the record should be crossed out and the follow-up recorded in the BMU TB register. Such cases, as well as those started on an XDR-TB treatment and later found not to have XDR-TB, are enumerated for the scopes of *Enrolment indicator* reporting (see below). Only confirmed RR-TB and MDR-TB are counted for cohort reporting of interim results and final outcomes.

The information in the Second-line TB treatment register is largely aligned to the data on the treatment card (see Form 01 in Part 4). The notes below refer to the data to be entered in the registers (from the first column in the left to the right):

Unique Second-line TB treatment register no.: An individual code assigned to the patient who is starting a second-line TB treatment. The code may be composite and include an identifier of the treatment centre and year in which the treatment was started.

Date entered in Second-line TB treatment register: The day when the health staff enters the patient in the register. In some countries, it may be the date when the review panel decided to register the patient.

The section on patient information: The demographic details (name, sex, age/date of birth, and address) and clinical data (site of disease and previous history of second-line drugs received) are identical to those in the treatment card (see above). These also include the date and registration number of previous entries in the BMU TB register. The Registration Groups differ from the ones on the card in that they also include *Transfer in* as an option. This is done to simplify recording but programmes may opt to have a separate column to denote patients transferring in and thus also retain information on any previous treatment they may have had in this register (as per the BMU TB register; see page 16 in reference *(8)*).

Result of DST: The DST recorded in this space is the one that resulted in the patient being registered for second-line TB treatment. The date that the sample was collected from the patient is recorded. If the DST is performed in a staged manner (e.g. rifampicin and isoniazid first, and then second-line drugs in case the patient is RR-/MDR-TB), the results can be completed as they become available so long as the sample is the one taken before start of treatment, which is used for registration. Any follow-up DST results are recorded in the Treatment card but not in the register.

Reasons for registering on second-line TB treatment: The patient may be a laboratory-confirmed or else a presumptive case of RR-/MDR-TB. In the case of a patient with poly-resistance without RR-TB who is registered on treatment, a note "not applicable" may be entered to ensure the case is not enumerated in cohort outcome monitoring.

Second-line TB treatment: The initial second-line TB treatment regimen using the drug abbreviations and date of start of this regimen.

Smear (S), culture (C) or Xpert MTB/RIF (X) results: The register column should record the type of test, the date the sample was taken, and the result. The Xpert MTB/RIF result taken at Month 0 (start of treatment) is to be recorded. If more than one smear or culture or Xpert test is done in a given month, the most recent positive result is registered.

Final outcome: The patient is assigned an outcome at the end of treatment according to the standard categories above. The date that the outcome is met is also recorded.

TB/HIV activities: This section reproduces the same details on the treatment card (see above).

Comments: This column may be used to record any notes on the patient, such as if they move or if their place of treatment or intermediate outcomes change. Also, indicate here if a patient is found not to need second-line TB treatment and is transferred back to the BMU TB register.

Form 03. Request for examination of biological specimen for TB

This request form accompanies the biological specimen to the laboratory. It contains information required for both patient management, and when matched with other information about the number of presumptive RR-/MDR-TB cases, can be used to evaluate testing coverage (see also Form 05, and *Detection indicator 2*). When the laboratory analysis is completed the same form will combine information on the patient (including the reason for testing) and the outcome of the testing making it a key document for decision-making in patient care and to monitor adherence to diagnostic algorithms. If different analyses are requested, the results from the laboratory should be sent to the requestor step-wise as they become available. It is therefore practical for the programme to have the request forms reproduced as booklets with self-carbonating paper. As for other forms mentioned in this publication it is expected that programmes tailor this form according to their needs. For instance it may be expedient to have two Request forms used, one for microscopy and Xpert MTB/RIF at peripheral laboratories and another for culture, DST and molecular tests (including LPA) for higher level laboratories. The upper portion of the request form is completed only by the requestor. It includes basic demographic and contact details of the patient being tested. The coordinates of the requestor are recorded lower down.

The form is similar to the one used in DOTS programmes *(8)*. The reason for examination – diagnostic or follow-up – is needed to allow the laboratory to register the different type of requests received and to help the health staff record the results in the Second-line TB treatment card and the register in the correct location. In the case of diagnostic testing, previous TB treatment history is indicated as yes, no or unknown. The form may also accommodate more details on previous treatment history if these are reliably available to the requestor and felt to be necessary. Space is provided to indicate if the testing is done upon suspicion of RR-/MDR-TB. For follow-up specimens, the month of treatment should be indicated if known. Information about the patient's HIV status may be useful to evaluate the testing algorithms; if it is felt to be too sensitive to record on the form the programme may opt to omit this from the form.

If the sample is not sputum, the type of specimen is specified. The requestor then indicates what analysis is being requested from the laboratory. Depending on the type of analysis demanded, the date of collection of the sample is also entered in the lower part of the form. The person responsible for the test result needs to be identifiable and a signature should be placed against the result.

Form 04. Laboratory register for culture, Xpert MTB/RIF and drug susceptibility testing (DST)

The second-line TB treatment programme needs to have access to laboratories that can perform sputum smear microscopy, culture and DST for initial diagnostic and monitoring purposes. The implementation of Xpert MTB/RIF is now becoming more widespread and the registration of diagnostic results from this testing are to be recorded in the Laboratory register alongside those for culture and DST. The information entered in the Laboratory register should correspond to that in the Request for examination of biological specimen for TB. The details should be limited to those necessary to process the sample and to record the result properly. The register is used to generate programme indicators (see below). Its contents should

be compared regularly with the Second-line TB treatment register to identify confirmed RR-/MDR-TB cases who have not been started on treatment. The frequency of cross-checking depends on the volume of testing in a particular site but could vary from weekly to monthly.

As for the other forms included in this publication, the register formats proposed are meant primarily to standardize the method to collect the essential data elements. Local adaptations **will** be needed, for example, the programme may decide not to register information on HIV status. In the case of a laboratory which will only undertake culture but not DST or will only undertake Xpert MTB/RIF, for example, the register columns may be modified as relevant.

2.5 Minimum indicators for monitoring drug-resistant TB programmes

Four sets of indicators for programme management are described in this publication (see Part 4 for suggested templates on how to aggregate the necessary data, and Annex 5 for a summary of these indicators in spreadsheet format).

Form 05. on detection;
Form 06. on enrolment;
Form 07. on interim results;
Form 08. on final outcomes.

These data also form the basis of annual reporting on TB by countries to WHO (see **www.who.int/tb/data**).

Form 05. Six-monthly report on detection of TB cases with rifampicin resistance (RR) and multidrug resistance (MDR)

Early detection of resistance to rifampicin and isoniazid is intended to ensure initiation of appropriate drug regimen from the start, increase the likelihood of treatment success and prevent the acquisition of additional resistance. Where resources permit, DST is offered to all TB cases. Limited resources however often result in DST being reserved for patients considered at increased risk of drug resistance (see Chapter 4). Groups to be targeted for DST vary by national policy, but WHO generally recommends as a minimum to offer DST to all previously treated patients and contacts of MDR-TB cases. In some settings, eligibility for DST may be broader if there are other factors known to increase the risk of infection with resistant strains or the vulnerability of patients – especially those with HIV-infection – to unfavourable prognosis should they develop drug resistance. DST for fluoroquinolones and second-line injectable anti-TB medication is important in the case management of MDR-TB patients *(9)*.

The five indicators for detection measure the progress toward universal access of TB patients to diagnosis of drug resistance, a key indicator for the programmatic management of drug-resistant TB (PMDT) (see Box 2.2 below). The first two indicators are calculated for all cases tested and as many risk categories that exist in the national policy. These include all TB patients previously treated for TB, contacts of a confirmed MDR-TB case, or other individuals considered to be at risk of drug resistance. The third indicator is usually calculated only on

the total number of confirmed MDR-TB cases and the fourth on those among them with an XDR-TB diagnosis. The delay in testing and the frequency of MDR-TB among individuals in different risk categories are also evaluated. These parameters are important for the programme manager because they are needed to evaluate how the targeting and timeliness of DST, as well as the yield of MDR-TB cases, vary by the risk category of the patient targeted. In addition, national programme managers need to keep in perspective how the number of MDR-TB cases detected relate to those estimated to occur among the notified TB cases in the country, based on the most recent drug resistance surveillance data *(10)*. In sites testing with Xpert MTB/RIF alone in particular, the *Detection indicators* 1, 2 and 5 should include all cases with a rifampicin test result and the main object for detection changed to a case with RR-TB rather than MDR-TB.

The suggested period of assessment is six calendar months. This is usually counted from January to end-June and July to end-December. Indicators are measured three months after the end of the six-month period. All data can usually be extracted from the BMU TB register, the Second-line TB treatment card and the Laboratory register.

BOX 2.2 CALCULATION OF DETECTION INDICATORS

Detection indicator 1:[1] **TB patients with result for isoniazid and rifampicin DST**

Numerator: Number of TB cases with DST result for **both** isoniazid and rifampicin by each risk category specified in the national policy during the period of assessment.

Denominator: Number of TB cases identified in each respective risk category during the period of assessment.

Data source: Numerator data are available from the Laboratory register; denominator data from the Basic TB register and treatment cards. For some risk categories (e.g. contacts of MDR-TB) the information may not be in the treatment card and has to be traced from elsewhere in their medical records.

Detection indicator 2:[1] **Confirmed MDR-TB cases detected among TB patients tested for susceptibility to isoniazid and rifampicin**

Numerator: Number of confirmed MDR-TB cases by each risk category specified in the national policy during the period of assessment.

Denominator: Number of TB cases in each risk category with DST result for **both** isoniazid and rifampicin during the period of assessment.

Data source: Numerator data are available from the Laboratory register; the denominator is identical to the numerator of Detection indicator 1.

[1] In sites testing with Xpert MTB/RIF alone, the numerator in *Detection indicator 1* and denominator in *indicator 2* can be modified to include all cases with a rifampicin test result, while the numerator in *indicator 2* would also include all rifampicin-resistant (RR-TB) cases (see Form 05). Likewise *Detection indicator 5* can be adapted for use when testing for RR-TB.

***Detection indicator 3*: Confirmed MDR-TB cases tested for susceptibility to any fluoroquinolone and any second-line injectable drug**

Numerator: Number of confirmed MDR-TB cases tested for susceptibility to a fluoroquinolone and a second-line injectable anti-TB medication during the period of assessment.

Denominator: Number of confirmed MDR-TB cases during the period of assessment.

Data source: Numerator data are available from the Laboratory register; the denominator is identical to the (non-disaggregated) numerator of Detection indicator 2.

***Detection indicator 4*: Confirmed XDR-TB cases detected among MDR-TB patients tested for susceptibility to any fluoroquinolone and any second-line injectable drug**

Numerator: Number of confirmed XDR-TB cases detected during the period of assessment.

Denominator: Number of confirmed MDR-TB cases tested for susceptibility to a fluoroquinolone and a second-line injectable anti-TB medication during the period of assessment.

Data source: Numerator data are available from the Laboratory register; the denominator is identical to the numerator of Detection indicator 3.

***Detection indicator 5*:[1] Interval between presumption of RR-/MDR-TB and DST results**

Definition: The duration in days between the date when the TB patient was identified as being in a risk category as per the national policy and the dates of the DST results for isoniazid and rifampicin as recorded in the Laboratory register. The first date is determined by type of risk category. This date may correspond to when TB is diagnosed if universal DST is practised, or when a laboratory result indicates treatment failure or persistent sputum smear positivity during the course of TB treatment, or when HIV-associated TB is detected. In the case of a contact with TB, this would be when the laboratory confirms MDR in the source case, which may precede or occur after the diagnosis of TB in the contact (information as in the Laboratory register). In sites testing with Xpert MTB/RIF alone, the indicator can be modified to include all cases with a rifampicin test result and the date of the first result showing rifampicin resistance is used, regardless of whether the same patient was confirmed to be MDR-TB or not subsequently.

The calculation is done on all cases with DST results for isoniazid and rifampicin (sensitive or resistant) entered in the Laboratory register during the six-month period of assessment. The difference in days between the two dates is summed up for all patients and divided by the number of cases with test results. The indicator is expressed as the arithmetic mean number of days with the minimum and maximum ranges for the episodes included in the calculation. The number of episodes included in the calculation should be indicated.

Form 06. Six-monthly report on enrolment of TB cases with rifampicin resistance (RR) and multidrug resistance (MDR) on second-line TB treatment

The programme manager is responsible to ensure that all patients in whom MDR-TB is detected are placed on appropriate treatment in the shortest time possible. This may also apply to patients at risk of drug resistance but who are not confirmed (presumptive). In sites testing with Xpert MTB/RIF alone, the indicators shown in this section can be modified to include all cases with rifampicin-resistance and the main object for detection changed from MDR-TB to a case with RR-TB. Much of the benefit of detecting drug resistance early is lost unless the patient is started on an appropriate drug regimen. Four minimum indicators are included to assess the coverage of enrolment of TB patients on second-line TB treatment, with separate stratifications for children and females, who may encounter differential access to care in certain settings. An additional sub-grouping for HIV-positive RR-/MDR-TB patients assesses the proportion of them placed on antiretroviral therapy (ART). A comparison between newly enrolled and identified RR-/MDR-TB cases gives an indication of access to care although patients started on treatment may have been detected prior to the period of assessment (see Box 2.3 below).

BOX 2.3 CALCULATION OF ENROLMENT INDICATORS

Enrolment indicator 1:[2] **RR-/MDR-TB cases (presumptive or confirmed) enrolled on MDR-TB treatment**

Definition: Number of RR-/MDR-TB cases (presumptive or confirmed) registered **and** started on a prescribed MDR-TB treatment regimen during the period of assessment.

Comparator: Number of RR-/MDR-TB cases (presumptive or confirmed) eligible for second-line drugs treatment during the period of assessment.

Data source: The number of RR-/MDR-TB cases (presumptive or confirmed) is obtained from the Second-line TB treatment register; the comparator data are sourced from the Basic TB register and Laboratory register for culture, Xpert MTB/RIF and DST (for confirmed cases the date of DST result is used; other cases are defined by the date when they are presumed to have RR-/MDR-TB e.g. patients whose treatment failed are defined when sputum smear remains positive). This indicator is computed for (i) all cases, (ii) cases aged <15 years, and (iii) females.

Enrolment indicator 2:[2] **Confirmed RR-/MDR-TB cases enrolled on MDR-TB treatment regimen**

Definition: Number of confirmed MDR-TB cases registered **and** started on a prescribed MDR-TB treatment regimen during the period of assessment.

Comparator: Number of confirmed MDR-TB cases detected during the period of assessment.

[2] In sites testing with Xpert MTB/RIF alone, the indicators can be modified to also enumerate RR-TB cases started on a second-line TB treatment and compare them to RR-TB cases, presumptive or confirmed.

Data source: The number of confirmed MDR-TB cases on treatment is obtained from the Second-line TB treatment register; the comparator data are sourced from the Laboratory register for culture, Xpert MTB/RIF and DST (using the date of DST result).

This indicator is computed for (i) all cases, (ii) cases with HIV on ART, and (iii) cases with HIV but not known to be on ART.

***Enrolment indicator 3*: Confirmed XDR-TB cases enrolled on XDR-TB treatment regimen**

Definition: Number of confirmed XDR-TB cases registered **and** started on a prescribed XDR-TB treatment regimen during the period of assessment.

Comparator: Number of confirmed XDR-TB cases detected during the period of assessment.

Data source: The number of confirmed XDR-TB cases on treatment is obtained from the Second-line TB treatment register; the comparator data are sourced from the Laboratory register for culture, Xpert MTB/RIF and DST (using the date of DST result).

***Enrolment indicator 4*: Interval between RR-/MDR-TB diagnosis and start of MDR-TB treatment**

Definition: The duration in days between the date of RR-/MDR-TB confirmation (DST results showing resistance to both isoniazid and rifampicin in the Laboratory register) and the date when the patient started a prescribed second-line drug regimen as per the Second-line TB treatment register; in sites testing with Xpert MTB/RIF alone, the indicator is modified to include all confirmed RR-TB cases and the date of the first result showing rifampicin resistance is used regardless of whether the same patient was confirmed with MDR-TB or not subsequently (i.e. the date when the patient was first found to be eligible for a MDR-TB regimen).

The calculation is done on all confirmed RR-/MDR-TB cases recorded on the Second-line TB treatment register during the six-month period of assessment. The difference in days between the date of confirmation and start of treatment is summed up for all patients and divided by the number of treatment episodes. The indicator is expressed as the arithmetic mean number of days with the minimum and maximum ranges for all episodes included in the calculation. If treatment was started before the confirmatory DST was reported then the interval is marked as zero days. The number of episodes included in the calculation should be indicated.

The suggested period of assessment is six calendar months, the first usually counted from January to end-June and the second from July to end-December. Indicators are measured in the month following the end of the six-month period. All data can be extracted from the basic TB register, the Second-line TB treatment register and the Laboratory register for culture, Xpert MTB/RIF and DST. Some programmes keep a separate listing of patients with MDR-TB (presumptive or confirmed) who are not on second-line TB treatment: such a list, if well maintained, could be a valuable resource for the programme.

Form 07. Quarterly report on interim results of TB cases with rifampicin resistance (RR) and multidrug resistance (MDR-TB) on second-line TB treatment

Treatment for MDR-TB typically takes 20 months or more and final outcomes can thus only be assessed two to three years after enrolment. The programme manager often needs an indication of how patients are faring before that. This is particularly important when a drug-resistant TB treatment component of a programme is starting. Assessing culture conversion to negative (for confirmed pulmonary cases) in month six and death by six months is widely used as an indicator of treatment response. Information on loss to follow-up by six months is helpful. It is also useful to know how many patients started on second-line drugs for MDR-TB turned out not to have MDR-TB (and likewise for XDR-TB). This evaluates the effectiveness of the treatment algorithm in treating patients who really need second-line regimens and avoiding a potentially toxic regimen in patients who do not.

The period of assessment is three calendar months (one quarter), usually counted from (i) January to end-March, (ii) April to end-June, (iii) July to end-September, and (iv) October to end-December. All patients registered **and** starting treatment during the period of assessment are included in the calculation. In sites testing with Xpert MTB/RIF alone, the first four enrolment indicators can be modified to include all cases with RR-TB started on a MDR-TB regimen. Only laboratory confirmed RR-TB, MDR-TB and XDR-TB cases who have started treatment are counted for reporting of Interim results. When calculating the proportion of cases with negative culture by six months, all patients started on treatment remain in the denominator, including patients who died or were lost to follow-up before six months. If a patient is lost to follow-up and then dies by six months, then the result retained will be *Lost to follow-up*, having been the first outcome met.

Indicators are measured nine months after the end of the quarter of assessment (see Box 2.4 below). This gives sufficient time for culture results at month six to be issued and retrieved. All data can be extracted from the Second-line TB treatment register.

Form 08. Annual report of final outcomes of TB cases with rifampicin resistance (RR), multidrug resistance (MDR) and extensive drug resistance (XDR) on second-line TB treatment

The Final outcome is the most important direct measurement of the effectiveness of the MDR-TB control programme. All confirmed MDR-TB patients entered in the treatment register should be assigned one of six mutually exclusive outcomes at the end of their therapy (see Table 2.1 above and Box 2.5 below). In sites testing with Xpert MTB/RIF alone, the indicators need to be modified to also include RR-TB cases started on a MDR-TB treatment regimen (see Chapter 6). Cases that are not evaluated due to transferring out, treatment still not completed at the time of final assessment or missing information are grouped together under *Not evaluated for outcome*. A patient who transfers in does not get enumerated in the cohort of the receiving treatment centre but only in the outcome cohort of the centre where treatment was started. All patients should be assigned the first outcome they experience for the treatment being evaluated. The outcome *Cured* is restricted to bacteriologically confirmed pulmonary TB cases. The period of assessment is 12 calendar months, usually counted from

BOX 2.4 CALCULATION OF INTERIM RESULTS INDICATORS

Interim results indicator 1:[3] **RR-/MDR-TB cases on MDR-TB treatment regimen with negative culture by six months.**

Numerator: Number of confirmed pulmonary RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment with negative results for culture in month six of their treatment.

Denominator: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment.

Interim results indicator 2:[3] **RR-/MDR-TB cases on MDR-TB treatment regimen who died by six months.**

Numerator: Number of confirmed RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment who died of any cause by the end of month six of their treatment.

Denominator: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment.

Interim results indicator 3:[3] **RR-/MDR-TB cases on MDR-TB treatment regimen who were lost to follow-up by six months.**

Numerator: Number of confirmed RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment who were lost to follow-up by the end of month six of their treatment

Denominator: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment.

Interim results indicator 1 only applies to pulmonary cases. To simplify, the denominator for all indicators is all cases started on treatment. The three indicators should include XDR-TB cases started on prescribed treatment with second-line drugs.

Interim results indicator 4:[3] **Patients on MDR-TB treatment regimen found not to have RR-/MDR-TB.**

Definition: Number of patients started on a prescribed MDR-TB treatment regimen during the period of assessment and later found not to have RR-/MDR-TB.

***Interim results indicator 5*: Patients on XDR-TB treatment regimen found not to have XDR-TB.**

Definition: Number of patients started on a prescribed XDR-TB treatment regimen during the period of assessment and later found not to be XDR-TB.

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[3] In sites testing with Xpert MTB/RIF alone, the indicators also enumerate RR-TB cases started on a second-line MDR-TB treatment who are assigned an interim result, or, in the case of *Interim results indicator 4*, were prescribed a second-line MDR-TB treatment regimen which was not warranted.

January to end-December, and referred to as an annual cohort. All patients registered **and** starting treatment during this period are included in the calculation. Only laboratory confirmed RR-TB, MDR-TB and XDR-TB cases are counted for cohort reporting of Final outcomes.

Indicators are measured 24 months after the end of the year of assessment. This gives sufficient time for most patients to complete their treatment and for the final culture results to be issued and recorded. All data can be extracted from the Second-line TB treatment register.

2.6 Using indicators to monitor programme performance

2.6.1 Rationale and interpretation

This publication emphasizes the generation of programme indicators, rather than the production of standard reports. The forms described in the previous section are intended to help derive these indicators. The implementation of an indicator-based monitoring system will require training of health caregivers on how to derive and use the indicators, as this approach may be novel to them. WHO has developed self-training modules with answers on the minimum indicators (see: www.who.int/tb/challenges/mdr/tools). A toolkit has also been developed to assist programmes on how to use indicators for PMDT *(12)*. Supervisory visits from the programme provide an opportunity to reinforce proper, regular use of the indicators to improve programme performance.

The indicator sets and the recommended periodicity at which they are generated should allow the manager to compare detection, enrolment and outcome between different units and over time (see also Annex 5). Low detection may point to problems with laboratory diagnosis, referral of patients, or poor retrieval of data. Alignment between diagnosis and treatment can be assessed by the enrolment indicators – a value of enrolled-to-identified >1 may indicate that a backlog of cases diagnosed with RR-TB or MDR-TB in the past but not started on treatment (e.g. lack of drugs or adequate support services) is being tackled. When this is sustained over time it may point to a situation where empiric treatment is common or where detection and enrolment statistics are not linked and data collection on diagnosis is incomplete. A value consistently <1 may indicate lack of drugs or difficulties to have cases return to start treatment after diagnosis. The interim results should uncover early problems in case-holding, mortality and sputum conversion; they are to be considered provisional and for quick assessment. Final outcomes provide the ultimate proof of the effectiveness of interventions.

Adaptations to the detection indicators will be needed given that the choice of risk-groups for whom to monitor DST coverage differs between national policies. This set of indicators in particular may require more work to derive than others. In order to measure the coverage of DST and the interval until result there will be a need to cross-reference the information located in the BMU TB register on which TB patients are at-risk and require DST with requests and results in the Laboratory register.

Under conditions in which DST coverage in certain sub-groups – such as previously treated TB patients – is close to complete, the first four indicators in the detection set provide the basis for routine surveillance of drug-resistance patterns *(13)*. The assessment of yield of RR-/

BOX 2.5 CALCULATION OF OUTCOME INDICATORS

***Outcome Indicators 1–6*: RR-/MDR-TB cases on MDR-TB treatment regimen with an outcome:**

1. Cured
2. Treatment completed
3. Treatment failed
4. Died
5. Lost to follow-up
6. Not evaluated for outcome

Numerator: The number of confirmed RR-/MDR-TB cases registered for MDR-TB treatment during the period of assessment assigned one of the six outcomes.

Denominator: Number of confirmed RR-/MDR-TB cases registered for treatment and starting a prescribed MDR-TB treatment regimen during the period of assessment.

This indicator is expressed as the percentage of persons in each of the mutually exclusive outcomes.

Programmes having the capacity to differentiate XDR-TB from other MDR-TB cases, particularly those where XDR-TB cases represent >5% of MDR-TB, should report outcomes for non-XDR MDR-TB (including other RR-TB) and XDR-TB cases separately. MDR-TB patients found to have XDR-TB anytime in the course of their second-line TB treatment would be taken out of the non-XDR MDR-TB cohort and enumerated in the XDR-TB treatment cohort.

Outcome indicators in HIV-infected patients should be computed separately for cases with positive HIV status in countries where HIV prevalence is ≥1% in pregnant women or ≥5% in TB patients (4,11).

MDR-TB cases by different risk groups can also guide the programme on how to prioritize the use of DST. This is feasible in systems that capture routine diagnostic testing information. If this is not practicable, drug-resistance surveillance needs to rely on well-designed surveys conducted periodically.

The indicators in this publication should be viewed as a minimum. Programmes may prefer more frequent feedback or more information about certain sub-populations. They may also wish to monitor disease recurrence or relapse one year after successful completion of treatment, particularly if shorter regimens are being introduced. Programmes will certainly want to monitor aspects of their managerial activities other than patient flows, such as stocks of pharmaceuticals, laboratory reagents, radiographs and other consumables; associated costs; human resources and training requirements. For this, other monitoring components will be required.

Interim results indicators 4 and *5* are meant to give the manager a sense of how many patients may be getting second-line treatment needlessly. The adverse drug reactions associated with these regimens can lead to a TB patient interrupting treatment before completion, and thus contribute to morbidity, treatment failure, reduced quality of life or death. Pharmacovigilance,

or the surveillance of adverse effects of treatment, is particularly relevant to PMDT. The projected global scale-up in MDR-TB treatment will expose more people of different ages and diverse ethnic mix to complex combinations of second-line anti-TB drugs. HIV and other co-morbidities necessitate the concomitant use of other medications increasing the risk of drug interactions. New TB drugs are in the pipeline and they will be used in combination with existent second-line anti-TB drugs, creating a potential for previously unrecognized adverse drug reactions. In 2012, WHO produced a handbook on pharmacovigilance for TB *(14)*. Programmes are encouraged to reinforce systems of spontaneous reporting of adverse drug reactions and also to consider more targeted approaches and active surveillance under certain circumstances (see Chapter 11 and Annex 10).

2.6.2 Deriving and reporting the indicators

The methods for calculating the indicators using the standard registration tools as data sources have been detailed in the previous section. The method by which a national programme collects information to produce these indicators is specific to each setting. Standardized tabulations are often used to aggregate information on TB patient flows. Paper reporting to the central level has been the mainstay in many places. In many countries, drug-resistant TB patients are treated in only a few specialized centres and data are therefore aggregated in one step at the central level. Forms 05–08 in Part 4 of this publication provide templates to guide programmes on how this can be done for the minimum indicators. These would need to be adapted to their local settings. With the decentralization of drug-resistant TB care there may be opportunities to integrate the indicators for both basic TB and drug-resistant TB on a single form. This will require some creative work by the manager to determine how essential indicators for both forms of the disease can be reported alongside each other and to successfully coincide different periods of assessment on the same sheet, particularly when reporting treatment outcomes. There is now a trend to move towards electronic record keeping, which can introduce dramatic improvements in the aggregation of data, minimization of computational errors, flexibility when reporting parameters and periods of assessment, and the speed by which information can be transmitted. A computerized system, which integrates data from the laboratory and from both the basic and drug-resistant TB registers, would greatly facilitate the more difficult computations, particularly detection delays.

Whereas the BMU TB register is expected to contain records for all patients diagnosed with TB and eligible for TB treatment, the Second-line TB treatment register has only been used for those patients for whom a decision has been made to actually start treatment. As a result there may be many patients without access to treatment who will not be recorded. With the recent drive to provide universal access to MDR-TB care *(15–17),* it is important to assess progress towards this goal, and certain indicators – particularly *Detection indicators 1* and *3*, and *Enrolment indicators 1* and *2* – are specifically there for this purpose. Moreover, comparison of cases detected and started on treatment with those estimated to occur is also important to assess the impact of programme efforts on the burden of drug-resistant TB cases *(10)*.

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CHAPTER 3

Laboratory

3.1 Introduction and general considerations

Definitive diagnosis of drug-resistant TB requires that *Mycobacterium tuberculosis* bacteria be detected and resistance to anti-TB drugs determined. This can be done by isolating the bacteria by culture, identifying it as belonging to the *M. tuberculosis* complex (MTBc), and conducting drug susceptibility testing (DST) using solid or liquid media or by performing a WHO-endorsed molecular test to detect TB DNA and mutations associated with resistance *(1)*.

Early detection of drug resistance allows the use of appropriate treatment regimens for patients, which has an important impact on improved TB control. The development of rapid methods for DST is crucial due to increasing rates of multidrug-resistant TB (MDR-TB) worldwide and the emergence of extensively drug-resistant TB (XDR-TB), with very high reported HIV-associated mortality. Spread of drug-resistant TB strains and the management of patients diagnosed with drug-resistant disease are among the most formidable obstacles faced by national TB control programmes. This is compounded by a critical lack of appropriate diagnostic tools and vastly inadequate laboratory capacity.

Conventional culture and DST methods require prolonged lengths of time to confirm mycobacterial growth and detect drug resistance, during which patients may be inappropriately treated, drug-resistant strains may continue to spread, and amplification of resistance may occur. Early and rapid diagnosis of TB and drug resistance will therefore have obvious benefits for patient and public health, including better prognosis, increased survival, prevention of acquisition of further drug resistance, and reduced spread of drug-resistant strains to vulnerable populations.

This chapter describes standards for laboratory services needed to diagnose and treat drug-resistant TB in the context of existing laboratory capacity and technological constraints *(1–18)*. It is built on existing laboratory standards outlined in guidelines by WHO and other authorities and incorporates recommendations from current WHO policies on diagnostic methods *(6–29)*.

3.2 General definitions for laboratory and DST

The following are definitions of the laboratory aspects discussed in this chapter.

- **Phenotypic DST (conventional DST).** Phenotypic testing determines if an isolate is resistant to an anti-TB drug by evaluating growth (or metabolic activity) in the presence of the drug *(5,6,10)*.
- **Genotypic DST (molecular DST).** Genotypic testing detects mutations in the TB genome associated with specific drug resistance. (Note: genotypic testing is also used to identify *M. tuberculosis* by detecting the presence of TB-specific mycobacterial DNA).
- **Direct testing.** Direct testing refers to testing directly from a clinical sample (most commonly a sputum specimen). In direct DST, processed clinical samples are directly inoculated onto media with and without drugs, or processed for molecular testing.
- **Indirect testing**. Indirect testing refers to testing performed on cultured isolates of *M. tuberculosis (11)*.
- **Critical drug concentration.** This is the lowest concentration of a drug that inhibits growth of 95% of *M. tuberculosis* strains isolated from patients who have never been treated with/exposed to that drug (i.e. presumably susceptible isolates), while at the same time not inhibiting growth of strains isolated from patients non-responsive to therapy with that drug (i.e., presumably resistant to that drug). For some drugs, such as ethambutol, there is no optimal drug concentration that meets this definition. For such drugs, the concentration that shows the greatest difference between presumably susceptible and presumably resistant

isolates is used in phenotypic DST. Typically, isolates of *M. tuberculosis* are tested against only the critical concentration of a drug.

- **Reproducibility**. The ability of a test to be accurately reproduced or replicated, under independent conditions. Intra-operator reproducibility relates to the agreement of test results when a sample is tested multiple times independently by the same operator. Inter-operator reproducibility relates to the agreement of test results across different operators or laboratories.
- **Reliability**. The reliability of a test depends on both the accuracy and reproducibility of the test. Accuracy is defined by comparing the test results with a gold standard and is usually expressed in terms of sensitivity and specificity, or in terms of positive and negative predictive values.
- **Validity.** The validity of a test refers to whether a test is measuring what it is supposed to be measuring. Ideally, a drug susceptibility test result should predict clinical efficacy.
- **Cross resistance.** Mutations that confer resistance to one anti-TB drug may also confer resistance to some or all of the members of the same drug family, and less commonly, to members of different drug families.

3.3 Essential laboratory services and infrastructure

Optimal management of drug-resistant TB requires both mycobacteriology and clinical laboratory services. Culture capacity remains essential for monitoring drug-resistant TB patients' response to therapy. Capacity to reliably identify *M. tuberculosis* and detect resistance to rifampicin and isoniazid remains a minimum requirement in any drug-resistant TB programme and along with mycobacteriological examinations, clinical laboratory services should also provide basic haematology, biochemistry, serology and urine analysis, required for adequate evaluation of patients and treatment monitoring (see Chapters 9 and 10).

In addition to diagnostic and clinical services, laboratories supporting drug-resistant TB control programmes have an important role in the surveillance of drug resistance patterns, which is essential for providing information on the magnitude and trends in drug resistance, for developing appropriate treatment modalities, and for evaluating the impact of control programme interventions. DST for first-line anti-TB drugs other than rifampicin and isoniazid is not essential. However, laboratories serving populations and patients with significant previous exposure to second-line drugs should develop capacity to perform DST against specific second-line agents as a priority (Figure 3.1). Nevertheless, routine DST for second-line drugs is not recommended for clinically-based decision-making unless the required laboratory infrastructure and competence have been established, quality assurance is in place and sustained high proficiency has been demonstrated.

During the initial phase of implementing a drug-resistant TB programme, it may be necessary to outsource DST for second-line drugs while building capacity, expertise and proficiency under mentorship from a member of the WHO/Global Laboratory Initiative (GLI) TB Supranational Reference Laboratory (SRL) Network. A collaboration agreement with an SRL is therefore strongly recommended for drug-resistant TB control programmes also in order to establish and maintain quality assured DST, as outlined in Section 3.4 below.

Laboratory-acquired TB infection, including MDR-TB and XDR-TB, is a well-recognized risk for laboratory workers *(14)*. Specific precautions, good microbiological practices, engineering controls, proper training and containment measures are needed to ensure safe handling of *M. tuberculosis* at all levels of the laboratory network (see Section 3.9).

In order to ensure quality and reliability of laboratory results as well as safe working conditions in the TB laboratory, it is necessary for laboratories to implement a quality management system (QMS) to ensure that all aspects of laboratory diagnostic services (including pre-analytical, analytical and post-analytical phases) are performed properly and allow for the detection of any laboratory errors. These systems must include standard operating procedures (SOPs), and both internal quality control (QC) and external quality assessment (EQA) protocols for all performed laboratory techniques, which are necessary to ensure accurate detection of drug resistance for subsequent treatment decisions and avoid false diagnoses. All DST laboratories should be covered with documented QMS systems. In addition, documented first-line DST proficiency, preferably by one of the SRLs, is strongly recommended for drug-resistant TB control programmes. Details on quality assurance are given in Section 3.10.

Establishing and maintaining laboratory networks is demanding, complex and expensive. Adequate resource allocation (human and financial) is therefore essential to ensure availability of sufficient, qualified and trained laboratory staff and for the functioning of the laboratory infrastructure with appropriate level of biosafety, well-maintained equipment and sufficient consumables.

3.4 Organization of the TB laboratory network

In many resource-limited or high-burden settings, TB laboratory networks have a pyramidal structure with a large number of peripheral laboratories (Level I) accessible to all individuals presumed or known to have TB, a moderate number of intermediate laboratories (Level II) that are usually located in mid-sized population centres and health facilities, and a single (or more than one in large countries) central laboratory (Level III) at the provincial, state or national level. This chapter concentrates on the activities of Level III laboratories usually responsible for DST as outlined in Table 3.1.

The organization and operation of Level I and II laboratories are well described in other publications *(2,3,12)*. Different levels of biosafety precautions are needed depending on the type of procedure being performed, the risk of generation of infectious aerosols and the concentration of TB bacilli in the aerosols. The most hazardous procedures are those related to manipulating positive cultures for identification and for performing DST and hence are often restricted to the central laboratory level.

The current target in the *Global Plan to Stop TB 2011–2015* for both culture and DST capacity (to at least rifampicin and isoniazid) is one laboratory per 5 million population *(30)*. However, establishing and maintaining this many laboratories is difficult to achieve and is not sustainable in many resource-limited settings due to the cost of establishing and maintaining facilities but also the challenge of developing the technical expertise of staff required to perform the tests. The Xpert MTB/RIF assay achieves an equivalent sensitivity for the detection of TB as culture

on solid media and reliably detects rifampicin resistance. Adoption of Xpert MTB/RIF in decentralized lower level laboratories therefore provides an opportunity to increase and expand access to accurate TB diagnostics without the need for additional sophisticated infrastructure needed for TB culture and DST facilities. The implementation of new rapid molecular methods, notably line probe assays (LPAs) and the Xpert MTB/RIF assay have been used by several countries at different laboratory levels to allow adequate population coverage with DST service for first-line anti-TB drugs.

As the Xpert MTB/RIF assay is a DNA-based assay it cannot be used as a replacement for smear and culture for monitoring the response of drug-resistant TB patients to therapy. As a minimum, culture facilities must be established at least at the central TB laboratory with appropriate equipment and laboratory infrastructure. In resource-limited settings, the use of culture facilities should be prioritized for monitoring drug-resistant TB patients' response to treatment. Current requirements for monitoring patient treatment response are for monthly cultures during the intensive phase followed by quarterly cultures during the continuation phase. Furthermore, culture facilities are needed to grow isolates of *M. tuberculosis* from drug-resistant TB patients for performing DST against second-line drugs.

A systems approach should be used also to ensure access to culture for monitoring drug-resistant TB patient treatment and for performing DST for second-line anti-TB drugs. As a general rule, countries and territories with small drug-resistant TB patient populations may find it more practical to send specimens for DST to neighbouring countries or to one of the SRLs rather than to establish national capacity, while countries with larger patient populations should aim as a priority to build sustainable DST capacity in the country. This will require implementation of appropriate (i.e. rapid, reliable and safe) referral and transport mechanisms of properly selected specimens to a central mycobacteriology laboratory, balanced with a testing volume sufficient to ensure technical proficiency (details on specimen collection and transport of infectious substances are given in Section 3.5).

Since 1994, the WHO/GLI TB SRL Network has been a driving force in strengthening national and central level laboratories globally, providing long-term technical assistance to countries under the framework of collaborative agreements. The network comprising more than 30 laboratories covering all six WHO regions is also instrumental in supporting drug resistance surveys, providing quality assurance through proficiency testing and validating DST data. Central reference laboratories supporting drug-resistant TB control programmes should therefore establish formal links with one of the SRLs to ensure adequate expert input on infrastructure development, diagnostic algorithms development, budgeting and training for the TB laboratory network.

3.5 Specimen collection and transport of infectious substances

Good quality specimens are essential for proper laboratory diagnosis of TB and drug-resistant TB. However, collecting sputum, the most frequent specimen for TB testing, represents a significant hazard as coughing produces potentially infectious aerosols. Therefore, specific measures must be taken to minimize exposure. Wherever possible, sputum specimens should

be collected in open air where infectious droplets are rapidly diluted and UV rays can rapidly inactivate TB bacilli.

Sputum specimens should not be collected in laboratories, toilets, waiting rooms, reception rooms, or any other enclosed space not specifically conceived, organized and equipped as a sputum collection area. Ventilated sputum collection rooms, correctly used and maintained, are a safe alternative when available. Collecting a good specimen in a safe manner also requires staff trained to provide the patient with effective instructions as well as with adequate material and procedures, using wide-mouthed containers that are sterile, clear and leak-proof (with screw caps).

Specimens containers should be promptly transported to the laboratory using appropriate packaging for safe transport of infectious materials, i.e. surrounded by absorbent material, protected by a secondary packaging and then placed in a shock-resistant outer packaging labelled according to national and international regulations for the transport of infectious materials *(13,14)*.

Specimens should be submitted to the laboratory and processed for culture within 24 hours from collection. If transport delays are anticipated, specimens should be kept refrigerated at 4°C and transported to the laboratory in a cool box. The quality of sputum specimens submitted to the laboratory is critical in obtaining reliable results for rapid molecular tests, as with other tests, although contamination of specimens due to inappropriate storage and long transport times of specimens to the laboratory is less of a concern than with conventional culture-based approaches. A reliable specimen transport system will ensure that full benefit is gained from use of a rapid assay, by reducing diagnostic delay times.

International organizations such as the Universal Postal Union (UPU), the International Civil Aviation Organization (ICAO) and the International Air Transport Association (IATA) have developed strict guidelines and procedures to facilitate the safe shipment of infectious substances *(13)*. International shipment of *M. tuberculosis* cultures (e.g. for diagnostic DST, re-testing, or proficiency testing) is subject to international regulations as well as national import and export regulations specific to individual countries.

TABLE 3.1 **Functions and responsibilities of the different levels of TB laboratory services**

LEVEL I: THE PERIPHERAL LABORATORY
• Receipt of specimens • Preparation and staining of smears for Ziehl-Neelsen or LED fluorescence microscopy • Xpert MTB/RIF for use as the initial diagnostic test in individuals suspected of having MDR-TB • Recording and reporting of results • Maintenance of laboratory registers • Cleaning and maintenance of equipment • Management of reagents and laboratory supplies • Internal quality control • Participation in an external quality assessment programme such as blinded re-checking or panel testing

LEVEL II: THE INTERMEDIATE (OFTEN REGIONAL) LABORATORY

- All the functions of a Level I laboratory
- Line-probe assays (LPA) for direct detection of resistance mutations in acid-fast bacilli (AFB) smear-positive processed sputum samples
- Digestion and decontamination of specimens and inoculation into cultures
- Isolation by culture and identification of *M. tuberculosis*
- Training of microscopists and supervision of peripheral-level staff with respect to microscopy and Xpert MTB/RIF assay
- Preparation and distribution of reagents for microscopy to peripheral laboratories
- Proficiency testing and quality improvement of microscopy at peripheral laboratories

LEVEL III: THE CENTRAL (OFTEN NATIONAL) LABORATORY

- All the functions of Level I and II laboratories
- Close collaboration with the central level of the national TB control programme
- Provides strategic oversight for the management, quality and efficient use of the TB laboratory network balanced with all available TB diagnostics
- DST of *M. tuberculosis* isolates (first- and second-line anti-TB drugs)
- Molecular tests for TB and rifampicin resistance determination (alone or in combination with isoniazid) from positive cultures and identification of mycobacteria other than *M. tuberculosis*
- Organization of a specialist to periodically perform the technical control of and repair services for laboratory equipment
- Updating and dissemination of laboratory manuals, including guidelines on diagnostic methods, on care and maintenance of equipment, on training and supervision, and on quality assurance
- Distribution of reagents and consumables when requested by intermediate or peripheral TB laboratories (optional)
- Supervision of intermediate laboratories regarding bacteriological methods and their implementation, as well as their performance monitoring activities of the peripheral laboratories
- Quality assurance of all procedures performed at intermediate laboratories including microscopy, culture and DST
- Training of intermediate-level laboratory staff
- Organization of anti-TB drug resistance surveillance
- Operational and applied research relating to the laboratory network, coordinated with the requirements and needs of national TB control programmes

Note: Xpert MTB/RIF should also be available at the central laboratory for screening of MDR-TB suspects so that the laboratory can become sufficiently competent with the technology to provide support for its use in Level I and II laboratories, and also to decrease the load of full diagnostic DST needed in MDR-TB suspects.

3.6 Mycobacteriology laboratory services for drug-resistant TB programmes

Detailed information on laboratory methods can be found in the WHO manuals *Laboratory Services in Tuberculosis Control, Parts I, II and III (2,12,15)*.

3.6.1 Microscopy

Smear microscopy is a low-cost and frontline tool for TB (but not drug-resistant TB) diagnosis. The introduction of light emitting diode (LED) fluorescence microscopy is recommended by WHO and has increased test sensitivity without increasing overall costs: rather, it has reduced the turnaround time required allowing the screening of a larger number of slides at the peripheral level *(31)*. The main purposes of microscopy for drug-resistant TB are to assess initial bacterial load, specimen triage to different diagnostic algorithms, monitor response to therapy, and to confirm the presence of AFB rather than contaminants in the culture media, before proceeding to rapid identification tests.

Microscopy for AFB cannot distinguish viable from non-viable organisms nor differentiate between drug-susceptible and drug-resistant *M. tuberculosis* bacteria, or between different species of mycobacteria. Its usefulness in drug-resistant TB treatment monitoring is therefore limited: samples showing AFB by smear microscopy but negative to culture suggest that bacilli are not viable (caution is nonetheless warranted for these patients to be considered as possibly infectious); while samples showing AFB by smear microscopy but negative by molecular tests are likely to harbour non-tuberculous mycobacteria (NTM).

Among persons at risk of drug-resistant TB, WHO recommends the use of Xpert MTB/RIF® as the initial diagnostic test rather than microscopy, culture and DST.

3.6.2 Xpert MTB/RIF

In 2010, WHO endorsed the Xpert MTB/RIF assay, a cartridge-based fully automated molecular diagnostic assay that uses real-time PCR to identify *M. tuberculosis* complex DNA and the mutations associated with rifampicin resistance directly from sputum specimens, in less than two hours. The assay has similar sensitivity, specificity and accuracy as culture on solid media and has been recommended by WHO as the initial diagnostic test among people at risk of MDR-TB (see Chapter 4). A policy update was issued at the end of 2013 and the key policy recommendations are given below. Detailed guidance on the introduction of Xpert MTB/RIF® at country level is available *(9,27)*.

Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in adults and children suspected of having MDR-TB or HIV-associated TB.

Xpert MTB/RIF may be used as a follow-on test to microscopy in adults and children where MDR-TB and HIV is of lesser concern, especially in further testing of smear-negative specimens.

Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all adults suspected with TB.

3.6.3 Line probe assays

Molecular LPAs allow rapid detection of resistance to rifampicin (alone or in combination with isoniazid) and were endorsed by WHO in 2008, with detailed policy guidance on their introduction at country level *(7)*. LPA is a high through put technology, typically allowing for 12 specimens to be processed simultaneously and enabling several batches of tests to be done per day.

Currently available LPAs are suitable for use with AFB smear-positive sputum specimens or on *M. tuberculosis* isolates grown by conventional culture methods. LPAs are suitable for use at the central or national reference laboratory level, with potential for decentralization to regional level if the appropriate infrastructure can be ensured (three separate rooms are required).

3.6.4 Culture of *M. tuberculosis*

Culture in liquid media is the current reference method for bacteriological confirmation of TB. However, good quality specimens, prompt transport to the laboratory and quality of laboratory processing (appropriate digestion and decontamination, as well as good quality culture media and incubation conditions) are essential to optimize the yield of culture. Laboratory errors, such as mis-labelling or cross-contamination between specimens during aerosol-producing procedures, may lead to false-negative or false-positive results. Therefore, laboratory findings should be always correlated with the patient's clinical condition and any diagnostic test should be repeated if necessary.

The advantages and disadvantages of different culture media and techniques are discussed in published references, including guidance on the use of liquid culture in middle- and low-resource countries *(2,3,5,12,15–17)*. In general, the recovery of tubercle bacilli is higher and the time to detection is shorter with liquid culture than with solid culture methods. However, liquid culture media being a more sensitive culture system has higher contamination rates than solid media. NTM are more frequently isolated with liquid media than with solid media. It is therefore essential to differentiate *M. tuberculosis* isolates from other mycobacteria.

3.6.5 Identification of *M. tuberculosis*

All mycobacterial isolates from solid or liquid cultures must be identified to allow differentiation of the *M. tuberculosis* complex from NTM. In countries with a high burden of TB, the vast majority of mycobacterial isolates will be *M. tuberculosis.* However, the prevalence of NTM varies among countries and can be more common in patients infected with HIV. There are a number of ways to identify *M. tuberculosis*: the tests can be phenotypic (the most common being the nitrate reduction and niacin tests), immune-chromatographic, or genotypic (which analyses species–specific DNA sequences). Their full description is beyond the scope of this chapter and can be found in the literature.

In summary, clinicians must be aware that genotypic assays provide faster and generally more reliable identification results than phenotypic tests and that, unless the species is confirmed as *M. tuberculosis*, mycobacterial isolates appearing phenotypically resistant to first-line drugs may represent infection with NTM and not drug-resistant TB. At a minimum, laboratories

supporting drug-resistant TB control programmes should be able to conduct identification tests for *M. tuberculosis* complex that follow international guidelines.

3.6.6 Drug susceptibility testing

DST plays an important role in most strategies to identify and treat patients with, or at high risk of drug-resistant TB (see Chapter 4). NTPs should develop the capacity to provide access to DST for any patient for whom resistance is considered likely. This recommendation is consistent with the international standards of TB care endorsed by the WHO and other partners *(18)* and with the TB resolutions endorsed by the World Health Assembly in 2007 and 2009, which call for universal access to DST by 2015 *(19,20)*.

Phenotypic DST (conventional DST). A number of techniques are available for phenotypic DST, which typically involves culturing of *M. tuberculosis* bacteria in the presence of anti-TB drugs to detect inhibition of growth. Phenotypic methods allow the detection of drug resistance regardless of the mechanism or molecular basis and can be performed as direct or indirect tests on solid media or in liquid media. In the direct test, a set of drug-containing and drug-free media is inoculated directly with portions of a decontaminated and concentrated specimen. An indirect test requires the growth of a pure culture from the specimen; dilutions of the isolate are then inoculated into drug-containing and drug-free media. Indirect phenotypic tests have been extensively validated and are currently regarded as the reference standard. The most commonly used methods for solid media are the proportion, absolute concentration, and resistance ratio methods; and for liquid culture systems, the proportion method. The details of these methods have been described in numerous textbooks and reviews *(21–26)*. Good concordance is seen between these methods for DST against first-line anti-TB drugs.

Several non-commercial culture and DST methods have been developed that are aimed for use in laboratories with limited resources as an interim solution pending capacity development for genotypic DST. Among these methods, microscopic observation of drug susceptibility (MODS), colorimetric redox indicator (CRI) methods, and the nitrate reductase assay (NRA) have shown to be inexpensive methods. These noncommercial methods have similar biosafety precautions to conventional culture and DST and are therefore only suitable for use at the central or regional level laboratories.

For second-line DST, broth or liquid methods and the proportion method on solid medium give similar results. The absolute concentration and resistance ratio methods for second-line DST have not been validated, and neither have any of the non-commercial methods. The current status of DST methods, consensus on reliability and reproducibility, and critical concentrations for different methods for second-line DST are given in Table 3.3.

Genotypic DST. Molecular tests detect the genetic determinants of resistance rather than the resistant phenotype. The available technologies can amplify either DNA or RNA, polymerase chain reaction (PCR) being the most common method of amplification. Among these technologies, nucleic acid amplification technology, the most common genotypic DST, holds promise for significant gains in speed and performance for DST.

Molecular LPA and the Xpert MTB/RIF are currently the only two molecular technologies endorsed by WHO for the genotypic detection of rifampicin resistance. In most settings, particularly where fixed-dose combination (FDC) first-line anti-TB drugs are used, resistance to rifampicin is strongly associated with resistance to isoniazid. Detection of rifampicin resistance therefore serves as a reliable (though not complete) proxy for MDR-TB. The advantages of rapid rifampicin testing include prompt screening of patients at risk of MDR-TB, earlier identification of patients on inappropriate first-line regimens, and allows for early interruption of MDR-TB transmission.

The use of molecular tests for rapid detection of MDR-TB does not eliminate the need for conventional culture and DST capability. Culture is primarily required for monitoring MDR-TB patient's response to therapy and for performing second-line DST.

For detection of XDR-TB only one molecular test is commercially available which is not currently recommended for use by WHO. Assessment of the available evidence by an Expert Group in 2012 found that while the specificity of the Genotype MTBDR*sl*/LPA for the detection of resistance to fluoroquinolones and second-line injectable drugs was high, its sensitivity was sub-optimal, and the assay results cannot identify the most appropriate fluoroquinolone or injectable drug to be used in a tailored treatment regimen (since the mutations detected are shared between the different groups of drugs). At present, phenotypic DST techniques are considered the reference methods for detecting XDR-TB. Commercial liquid culture is considered the fastest and is a reliable method for second-line DST.

3.6.7 Limitations of DST

The reliability of DST (performed under optimal circumstances) varies with the drug tested *(5–9,17)*.

- First-line DST
  - Most reliable for rifampicin and isoniazid.
  - Less reliable and reproducible for streptomycin, ethambutol and pyrazinamide (pyrazinamide testing can only be performed on liquid media after appropriate pH adjustment).
- Second-line DST
  - Has good reliability and reproducibility for second-line injectable drugs (amikacin, kanamycin, capreomycin) and fluoroquinolones.
  - Data on the reproducibility and reliability of DST for the other second-line drugs are limited, and for several of them methods have not been established or standardized; in addition, data correlating DST results to the clinical outcome are still insufficient.

For rifampicin resistance there is not complete concordance between phenotypic and genotypic detection methods. Emerging evidence suggests that DNA sequencing of the rpoB gene (the gold standard method for genotypic DST) may be a better although not perfect reference method than the phenotypic DST. WHO continues to collect and evaluate emerging data on this issue and will formally review the accuracy of phenotypic resistance standards for DST once sufficient data becomes available.

3.6.8 Cross-resistance

Cross-resistance and lack of understanding of the molecular mechanisms underlying TB drug resistance further confound the interpretation of DST results. Emerging evidence shows a clear association between phenotypic drug resistance and specific molecular mutations for most drugs; however, not all mutations conferring resistance to second-line drugs have been described, neither have the underlying molecular mechanisms for the detected mutations been elucidated. Table 3.2 is a summary of known cross-resistance between anti-TB drugs.

TABLE 3.2 **Summary of known cross-resistance between anti-TB drugs** *(29,30)*

Rifamycins	All rifamycins (rifampicin and rifabutin) have high levels of cross-resistance.
Isoniazid	There is high cross-resistance between isoniazid and ethionamide if the *inhA* mutation is present.
Aminoglycosides and polypeptides	Amikacin and kanamycin have (very) high cross-resistance. Amikacin/kanamycin and capreomycin can have cross-resistance, which is associated with the *rrs* mutation (clinical implications are not clear). Streptomycin has low cross-resistance with amikacin/kanamycin and capreomycin.
Fluoroquinolones	Fluoroquinolones are believed to have variable cross-resistance between themselves, with in vitro data suggesting that later-generation fluoroquinolones (levofloxacin, gatifloxacin, moxifloxacin) remain effective when lower generation fluoroquinolones (ofloxacin) are demonstrating resistance. It is unknown if the in vitro data translates into clinical relevance. When levofloxacin (a third generation fluoroquinolone) is demonstrating resistance, it is not known if fourth generation quinolones (moxifloxacin and gatifloxacin) remain effective, and their use in such cases is not standardized. It is not known if cross-resistance is complete between fourth generation fluoroquinolones (i.e. between moxifloxacin and gatifloxacin), but is generally considered complete in vitro studies. Laboratories should test isolates for resistance to each fluoroquinolone used by their TB programme (i.e. if a TB programme uses levofloxacin in the standardized regimen the fluoroquinolone DST of choice for the programme is levofloxacin, not ofloxacin as is often being done).
Thiamides	Prothionamide and ethionamide have 100% cross-resistance.

3.7 Rational use of DST in drug-resistant TB programmes

Maintaining proficiency in DST requires good laboratory technique and infrastructure, as well as an adequate workload (numbers of specimens) to be tested. In many settings, this implies centralization of laboratory services for DST. Overall, for drug-resistant TB programmes with small numbers of patients, consideration may be given to outsourcing DST services, for example, to a neighbouring country or one of the laboratories of the SRL network.

Current WHO policy guidance on DST is as follows *(6)*:

- Laboratory capacity to reliably detect rifampicin resistance and/or MDR-TB through molecular tests and/or quality-assured DST of isoniazid and rifampicin resistance is a minimum requirement for drug-resistant TB programmes.
- Formal links with one of the laboratories of the SRL network is needed to ensure appropriate infrastructure for the procedures being performed and proper diagnostic algorithms and quality assurance mechanisms in place.
- Strategies for laboratory services in support of drug-resistant TB programmes should follow a systems approach (see Figure 3.1) and take into account the DST limitations outlined above. DST should be focused on those drugs for which reliable and reproducible methods are available.
- DST methods for the second-line injectable drugs (amikacin, kanamycin, capreomycin) and fluoroquinolones are accurate and reproducible. However, routine DST for second-line drugs should not be performed unless the required laboratory quality and biosafety standards are met, infrastructure and capacity have been established, rigorous quality assurance is in place, and sustainable high proficiency has been demonstrated for isoniazid and rifampicin testing. In order to retain proficiency and expertise, it is recommended that second-line DST only be performed if at least 200 specimens are tested per year.
- At present, routine DST for Group 4 drugs (ethionamide, prothionamide, cycloserine, terizidone, para-aminosalicylic acid) and for Group 5 drugs (bedaquiline, delamanid clofazimine, amoxicillin/clavulanate, clarithromycin, linezolid, imipenem, meropenem, thioacetazone) is not recommended as accuracy and reproducibility of laboratory testing cannot be guaranteed.
- Strains should be tested for resistance to the fluoroquinolone(s) used in a programme's treatment strategy. Cross-resistance is not complete between older- and newer-generation fluoroquinolones (see Chapter 5 for more details on cross resistance).

TABLE 3.3 **DST methods and critical concentrations for first- and second-line DST**

DRUG GROUP[a]	DRUG	STANDARDIZED DST METHOD AVAILABLE	DST CRITICAL CONCENTRATIONS (µg/ml)			
			Löwenstein-Jensen[b]	Middlebrook 7H10[b]	Middlebrook 7H11[b]	MGIT960
Group 1	Isoniazid	Solid, liquid	0.2	0.2	0.2	0.1
First-line oral anti-TB agents	Rifampicin[c]	Solid, liquid	40.0	1.0	1.0	1.0
	Ethambutol[d]	Solid, liquid	2.0	5.0	7.5	5.0
	Pyrazinamide	Liquid	-	-	-	100.0
Group 2	Streptomycin[e]	Solid, liquid	4.0	2.0	2.0	1.0
Injectable anti-TB agents	Kanamycin	Solid, liquid	30.0	5.0	6.0	2.5
	Amikacin	Solid, liquid	30.0	4.0	-	1.0
	Capreomycin	Solid, liquid	40.0	4.0	-	2.5
Group 3	Ofloxacin[f]	Solid, liquid	4.0	2.0	2.0	2.0
Fluoroquinolones	Levofloxacin	Solid, liquid	-	1.0	-	1.5
	Moxifloxacin[g]	Solid, liquid	-	0.5/2.0	-	0.5/2.0
	Gatifloxacin[h]	Solid	-	1.0	-	-
Group 4[i]	Ethionamide	Solid, liquid	40.0	5.0	10.0	5.0
Oral bacteriostatic second-line anti-TB agents	Prothionamide	Solid, liquid	40.0	-	-	2.5
	Cycloserine	Solid	30.0	-	-	-
	Para-aminosalicylic acid	Solid, liquid	1.0	2.0	8.0	4.0

Group 5[i]	Clofazimine	Liquid	-	-	-	-
Anti-TB agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)	Amoxicillin/clavulanate	None	-	-	-	-
	Clarithromycin	None	-	-	-	-
	Linezolid	Liquid	-	-	-	1.0

[a] WHO *Guidelines for the programmatic management of drug-resistant TB*.

[b] Indirect proportion method recommended. Other solid media methods (resistance ratio) have not been adequately validated for second-line drugs. Concentrations for the absolute concentration method were not evaluated.

[c] Rifampicin borderline resistance more frequently missed by mycobacteria growth indicator tube (MGIT). Prevalence and geographical distribution of borderline resistance not clear, and final Löwenstein-Jensen (LJ) interpretations should be made after 6 weeks

[d] Ethambutol 5µg/ml in mgIT is not equivalent to other methods. Ethambutol testing in 7H11 not equivalent to 7H10. There is insufficient evidence to recommend a change in concentration for any method

[e] Streptomycin has a bimodal distribution of MIC values. There is insufficient evidence to recommend a change.

[f] Ofloxacin concentration in LJ media increased to 4.0ug/ml. There is insufficient data to extrapolate change in 7H10 or 7H11 methods.

[g] Moxifloxacin. Two concentrations are proposed. In programmes using both ofloxacin/levofloxacin and moxifloxacin, possible testing is for moxifloxacin only at both concentrations OR test ofloxacin/levofloxacin and moxifloxacin at higher concentration. In programmes using ofloxacin/levofloxacin only test only these drugs. In programmes using only moxifloxacin, test at higher concentration of moxifloxacin only.

[h] Use of gatifloxacin should always be appropriately monitored (see Chapter 11).

[i] Routine DST for Group 4 and 5 drugs is not recommended. Linezolid suitable for testing in mgIT only.

Figure 3.1 Systematic approach to implementation of DST under routine programmatic conditions *(6)*

Priority of programmatic development of laboratory DST

HIGH PRIORITY

Implement DST to H and R

Implement wide access to Xpert MTB/RIF as the initial diagnostic test in individuals suspected of MDR-TB (adults and children)

High proficiency in DST to H and R should be a priority for the correct identification of patients to be placed on second-line anti-TB drug regimens.

Conventional DST to H and R can be done at a central laboratory while fast detection by Xpert TB/RIF should be widely available, as programmatically relevant.

Expand phenotypic DST to other drugs

Group 2: **Second-line injectable agents: amikacin, kanamycin, capreomycin**

Group 3: **Fluoroquinolones**

In settings where XDR is a concern, DST to second-line injectable agents and fluoroquinolones will be needed to rapidly allow the identification of XDR-TB patients.

Given the variability in cross-resistance reported for the aminoglycosides and polypeptides, it is recommended that testing for kanamycin, amikacin and capreomycin is done.

Selection of the most appropriate fluoroquinolone (among the new generation molecules) for DST is based on treatment strategy (because cross-resistance is not complete between older and newer generations of fluoroquinolones, it cannot be assumed that resistance to one confers resistance to all fluoroquinolones).

LOW PRIORITY

Expand phenotypic DST to Group 4 and Group 5 drugs

Group 4 DST is not recommended for routine testing for individual patient care. When performed in proficient laboratories, it may provide surveillance data information for empiric MDR regimen design. DST for Group 5 drugs is not yet standardized.

Note. H: isoniazid; R: rifampicin.

3.8 Testing and reporting: turnaround time

Growth detection and identification of *M. tuberculosis* may take 3–8 weeks on solid media and 1–3 weeks in liquid media. DST of a *M. tuberculosis* isolate takes an additional 2–4 weeks in solid media and 7–10 days in liquid media. Molecular test results can be available in less than two hours with Xpert MTB/RIF), and within two days with LPA. To ensure rapid diagnosis of *M. tuberculosis* and drug-resistant TB, laboratories should define standard turnaround times, which should be strictly followed. A summary of TB diagnostic methods and DST methods and turnaround times are provided in Table 3.4.

TABLE 3.4 **Summary of TB diagnostic and DST methods (non-WHO endorsed tests are not included) and turnaround time**

DIAGNOSTIC PLATFORM	TEST NAME	TURNAROUND TIME	DESCRIPTION AND COMMENTS
Smear microscopy	Conventional light microscopy – Ziehl-Neelsen	2 hours	Less sensitive than fluorescent/LED microscopy.
	Conventional fluorescence microscopy		Requires a quartz-halogen or high-pressure mercury vapour lamp. Sensitivity is improved over light microscopy, observation time is reduced. Expensive.
	Light emitting diode (LED) fluorescence microscopy		LED microscopes improve sensitivity by 10% over conventional light microscopy. Observation time is similar to conventional fluorescence microscopy. LED conversion kits for light microscopes are available.
Solid culture	Lowenstein–Jensen	3 weeks smear positive 4–8 weeks smear negative	Egg-based medium, inexpensive.
	Middlebrook and Cohn 7H10		Agar based medium. Less prone to contamination than Lowenstein–Jensen but more expensive.
Automated liquid culture		8 days smear positive 2–6 weeks smear negative	Liquid culture systems. Fully automated systems that use either fluorimetric or colourimetric detection.

DIAGNOSTIC PLATFORM	TEST NAME	TURNAROUND TIME	DESCRIPTION AND COMMENTS
Non-commercial WHO endorsed culture and DST techniques	Media-based microscopic observation drug susceptibility (MODS)	2–21 days direct 3–4 weeks indirect	MODS is a manual liquid technique that uses basic laboratory equipment (including an inverted microscope). Colonies are observed through the bottom of a sealed plastic container. Allows for H and R DST. MODS requires additional staff skills and a containment laboratory.
	Nitrate reductase assay (NRA)	6–9 days direct 7–11 weeks indirect	NRA is a colourimetric test using solid media. Allows for H and R DST. TB cells are cultured for 10 days and Greiss reagent is added, which indicates the presence of growing cells.
	Colourimetric redox indicator (CRI)	3–5 weeks	CRI is an indirect colourimetric test using liquid media. TB cell are cultured in the presence of a dye. Allows for H and R DST.
Molecular testing	Line probe assay (LPA)	1–2 day (direct on smear positive specimen only)	Two LPA have been developed to detect *M. tuberculosis* resistant to R and H either directly or indirectly. DNA targets are amplified by PCR and hybridized to immobilized oligonucleotide targets. Results are visualized colourimetrically. If it is a smear negative specimen, culture must be grown first.
	Xpert MTB/RIF	2 hours	A fully automated test working in a dedicated platform performing detection of MTB and R resistance, using real-time PCR. Results are available in less than two hours.

Note. H: isoniazid; R: rifampicin.

3.9 Laboratory biosafety

The relative hazards of TB as infectious microorganisms handled in the laboratory are no longer classified by WHO according to their risk of causing human disease, the potential for laboratory spread, and whether effective treatment and prevention measures are available ("risk group classification") (*14*) but are now based on the assessment of the risks associated with the different technical procedures performed in the different types of TB laboratories ("risk assessment"). For laboratories conducting TB testing, the most important risk is the generation of infectious aerosols, because infection with *M. tuberculosis* occurs primarily by the inhalation of infectious aerosols (although it can also occur by direct inoculation or by ingestion). Therefore, depending mainly on the probability of infectious aerosols being generated and on the number of bacteria in the material handled, the relative risk of laboratory-acquired

TB infection varies according to the procedures performed in the laboratory, with the lowest risk being associated with direct smear and Xpert TB/RIF preparation and highest risk being associated to processing of liquid cultures and performing DST *(14)*.

Published guidelines for safely working with samples containing *M. tuberculosis* bacteria should be rigorously followed and expert engineering consultation sought when establishing laboratory facilities for DST *(14)*.

Safety in the TB laboratory requires essential measures be in place and enforced:

- Appropriate layout of the laboratory in line with the techniques implemented: facilities (e.g. containment rooms) and engineering controls (e.g. biosafety cabinets, aerosol-containment centrifuges, ventilation systems providing directional airflow) that are well designed and functioning as designed to prevent or contain aerosols. Effective and specific administrative controls should be enforced (e.g. standard operating procedures, waste management procedures, accident management plans, health monitoring of the staff, etc.).
- Proper practices and procedures for general laboratory safety (including physical, electrical and chemical safety) must be in place: workers should be technically proficient in good microbiological practices and in the use of safety equipment, and should be supervised by experienced laboratory professionals.
- Personal protective equipment appropriate for the techniques being performed should be used.

TB containment laboratories (high-risk TB laboratories) should have the minimum design features necessary to safely manipulate TB cultures and to perform phenotypic DST as well as LPA testing *(6,14)*. They require the strengthening of laboratory operations and safety programmes, specifically those related to laboratory design, the use of specialized equipment to prevent or contain aerosols and health surveillance of laboratory staff.

Health and medical surveillance of laboratory personnel handling specimens or cultures containing tubercle bacilli is strongly recommended. Surveillance should include a detailed medical history, targeted baseline health assessment, monitoring of respiratory signs and symptoms, and appropriate plan for proactive medical investigations when indicated. Routine BCG vaccination is not recommended as a means of preventing drug-resistant TB in laboratory workers. The use of infection control measures is discussed in more detail in Chapter 14. Laboratory workers who choose to disclose their status as HIV-infected should be offered safer work responsibilities and should be discouraged from working with drug-resistant TB specimens. Pregnant women should be reassigned until after childbirth and lactation.

3.10 Quality assurance

A diagnosis of drug-resistant TB has profound implications for the individual patient; therefore, accuracy of the laboratory diagnosis is crucial and a comprehensive laboratory quality assurance (QA) programme must be in place to ensure accuracy, reliability and reproducibility of DST results. Internal quality control (QC) and external quality assessment (EQA) procedures and monitoring of performance indicators should be an integral part of laboratory operations.

Procedures for quality assessment of microscopy, culture and DST (phenotypic and genotypic) are described in detail in other documents *(2,3,9,12,15–17,27)*. To help in ensuring the quality of laboratory services and the validation of DST results, central reference laboratories supporting drug-resistant TB programmes should also establish formal links with an SRL for external quality assessment and technical assistance, which should include: (i) an initial assessment to evaluate the laboratory facilities and operations, with corrective action as required; (ii) proficiency testing with an adequate number of coded isolates; and (iii) periodic visits and re-checking of isolates obtained within the DR-TB programme. Proficiency testing by the SRL involves regular distribution of panels of coded *M. tuberculosis* strains with predefined drug resistance profiles. As a minimum performance indicator, laboratories should correctly identify resistance to isoniazid and to rifampicin in more than 95% of samples, and in two out of three recent rounds of panels. Panels including isolates with second-line drug resistance are also available through the SRL Network, as well as EQA panels for molecular methods.

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CHAPTER 4

Case finding for drug-resistant TB

4.1 Background

This chapter describes effective strategies for case finding and diagnosis of patients with drug-resistant TB, including rifampicin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). The choice of approaches for case finding and enrolment in drug-resistant TB control programmes should take into consideration country- or setting-specific epidemiology, as well as the human and financial capacity available. Included in this chapter are appropriate strategies for testing patients for drug-resistant TB in adults and children, and when to use DST for first- and second-line drugs.

Case finding for drug-resistant TB refers to the process of:

- identifying individuals who may have drug-resistant TB;
- evaluating them appropriately;
- diagnosing drug-resistant TB; and
- recording and reporting any drug-resistant TB diagnosed according to standardized criteria (see Chapter 2).

The detection of drug-resistant TB requires medical workers (doctors, nurses, medical assistants, clinical officers) to be able to assess individuals for risk of drug-resistant TB and

be aware of when to test for drug resistance; have access to reliable laboratory diagnosis of drug-resistant TB (including a referral network); and be able to perform proper medical evaluations on patients presumed to have drug-resistant TB. This is a complex set of activities and behaviours, and failure at any stage in this process can cause misses and delays in diagnoses of drug-resistant TB.

4.2 Epidemiological data and drug resistance surveillance

The epidemiological context of TB and drug resistance must be taken into account to optimize case detection strategies for drug-resistant TB. Data from drug resistance surveillance and surveys are crucial to help determine the probability (or risk) of an individual patient or groups of patients having drug-resistant TB *(1–3)*, which is needed for establishing effective strategies for targeted DST (see Section 4.3).

All programmes should have representative drug resistance surveillance data on at least rifampicin, isoniazid and second-line drugs (from the groups of fluoroquinolones and second-line injectable drugs) most commonly used in the country. These data should be stratified by patient-group and TB treatment histories – new patients, different categories of retreatment patients (patients who failed a new regimen with first-line anti-TB drugs, patients who failed a retreatment regimen with first-line anti-TB drugs, patients who relapsed or returned after loss to follow-up) and high-risk groups (including for example, drug-resistant TB patient contacts or prisoners). In countries where routine drug resistance surveillance data are not available, are outdated or are not representative of the population or sub-groups of TB patients, a drug resistance survey should be organized periodically every four to five years.

While rifampicin resistance is a reliable proxy for MDR-TB in patient groups in many countries *(9–14)*, country-specific data should be obtained on the frequency of concomitant isoniazid resistance when rifampicin resistance is present. For patients who are diagnosed with rifampicin resistance using Xpert MTB/RIF (which is not able to detect isoniazid resistance), understanding the frequency of MDR-TB among rifampicin-resistant patients may be useful for designing initial treatment regimens with or without isoniazid. Rifampicin mono-resistance is managed in the same way as MDR-TB, with the exception of including isoniazid; see Chapters 5 and 6.

Drug resistance surveillance data also enable programmes to estimate the number of patients who could be detected and enrolled in the drug-resistant TB programme, which in turn greatly facilitates strategy planning and long-term drug procurement.

4.3 High-risk groups and targeted DST

Ideally, testing for drug resistance should be provided for all identified TB patients before the start of TB treatment, so that the most appropriate therapy for each individual can be determined. However, the goal of universal access to DST has not yet been realized for most of the world's TB patients, and in many areas only patients considered at high risk for drug-resistant TB have access to DST. Targeted DST allows for the most drug-resistant TB patients to be detected with the resources available. This requires careful risk assessment of patients.

Risk for drug-resistant TB is determined by patient history combined with epidemiological data from drug resistance surveillance or surveys, which can help identify high-risk groups. The prevalence of resistance in specific risk groups is reviewed in Table 4.1; it can vary greatly across different countries and settings. Therefore, programmes should examine drug resistance surveillance data available from the different patient groups, and targeted DST should be performed for groups determined to be at higher risk for drug-resistant TB.

In some high-burden TB countries, the absolute number of TB patients with drug-resistant TB may actually be higher among the large group of patients who have no prior history of TB treatment, i.e. with no apparent risk factor for drug-resistant TB. Therefore, in order to effectively control drug-resistant TB, all countries must aim to build universal access to DST.

Specific elements of a patient's history that suggests an increased risk for drug resistance are listed in Table 4.1. Stronger risk factors are placed higher on the table. Risk factors for XDR-TB are discussed separately in Section 4.6.

TABLE 4.1 **Target groups for DST**

RISK FACTORS FOR DRUG-RESISTANT-TB	COMMENTS
Failure of retreatment regimens with first line anti-TB drugs (SHREZ)[a] (previously known as chronic TB cases)	Patients who are still sputum smear-positive at the end of a retreatment regimen have perhaps the highest MDR-TB rates in any group, often approaching 90% *(5)*.
Exposure to a known drug-resistant TB case	Most studies have shown that close contacts of MDR-TB patients have very high rates of MDR-TB. Management of drug-resistant TB contacts is described in Chapter 15.
Failure of new TB regimens (HREZ)	Patients who, while on treatment, are sputum smear-positive at month five or later during the course of treatment are at elevated risk for drug-resistant TB. Not all patients in whom a regimen fails have drug-resistant TB, and the percentage may depend on a number of factors, including whether rifampicin was used in the continuation phase and whether directly observed therapy was used throughout treatment.
Failure of anti-TB treatment in the private sector	Anti-TB regimens from the private sector can vary greatly. A detailed history of drugs used is essential. If both isoniazid and rifampicin were used, the chances of MDR-TB may be high. Sometimes second-line anti-TB drugs may have been used, and this is important information for designing the retreatment regimen.
Patients who remain sputum smear-positive at month two or three of a first-line anti-TB drug regimen	Many programmes may choose to perform culture and DST on patients who remain sputum smear-positive at months two and three. This group of patients is at risk for drug-resistant TB, though rates can vary considerably.

RISK FACTORS FOR DRUG-RESISTANT-TB	COMMENTS
Relapse and return after loss to follow-up, without recent treatment failure	Evidence suggests that most relapse cases and those that return after loss to follow-up (without recent treatment failure) do not have drug-resistant TB. However, certain patient histories may point more strongly to possible drug-resistant TB; for example, erratic drug use or early relapses.
Exposure in institutions that have drug-resistant TB outbreaks or a high drug-resistant TB prevalence	In many countries, patients who frequent homeless shelters, prisoners and health care workers in clinics, laboratories and hospitals can have high rates of drug-resistant TB *(2,3)*.
Residence in areas with high drug-resistant TB prevalence	Drug-resistant TB rates in many areas of the world can be high enough to justify routine DST in all new cases.
History of using anti-TB drugs of poor or unknown quality	The percentage of drug-resistant TB caused by use of poor-quality drugs is unknown but considered significant. All drugs should comply with acceptable international quality assurance standards.
Treatment in programmes that operate poorly (especially with recent and/or frequent drug stock-outs)	These are usually programmes with poor drug management and/or distribution systems.
Co-morbid conditions associated with malabsorption or rapid-transit diarrhoea	Malabsorption may result in selective low serum drug levels and may occur in either HIV-negative or HIV-positive patients.
HIV in some settings	Data from the Global Project on Anti-TB Drug Resistance Surveillance *(2)* suggest an association between HIV and MDR-TB in some parts of the world, and numerous drug-resistant TB outbreaks have been documented in HIV-positive patients. Data are still limited and specific factors involved in this association may be country-specific. Even if HIV is not considered to be a risk factor for drug-resistant TB in a country, it is strongly recommended that all individuals with HIV-associated TB have DST to rule out drug-resistant TB and to avoid high rates of mortality due to unrecognized drug-resistant TB in these patients.

[a] S=streptomycin; H=isoniazid; R=rifampicin; E=ethambutol; Z=pyrazinamide.

After analysis of the risk groups, programmes should define their diagnostic algorithms indicating those categories of patients that will undergo DST at the start of treatment. Programmes with limited access to rapid DST or limited drug resistance surveillance data should, at a minimum, strive toward performing rapid DST in the following groups.

- Any patient before the start of a retreatment regimen (those having failed a regimen, relapsed, or returned after loss to follow-up).
- All close contacts of drug-resistant TB patients who have been diagnosed with active TB.

- Patients not responding to first-line anti-TB treatment (remaining sputum smear-positive at month two or three).
- HIV-positive patients with active TB.
- Any TB patient coming from a group determined by the programme to have a significant risk for drug-resistant TB.

4.4 Recommendations regarding conventional and molecular DST for drug-resistant TB detection

Establishing the presence of drug-resistant TB is done through DST using conventional (phenotypic) or molecular (genotypic) tests described in Chapter 3.

The best strategy for detection of drug-resistant TB, and the WHO recommended strategy, is to use rapid DST. The WHO 2011 update of *Guidelines for the programmatic management of drug-resistant tuberculosis,* specifically states:

> **Rapid drug susceptibility testing (DST) of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis of TB, subject to available resources (conditional recommendation, very low quality evidence)** *(1)*

Using rapid DST, patients can be started on an appropriate treatment regimen sooner and infection control measures implemented if needed, improving treatment outcomes while also decreasing transmission of infection to others.

Current WHO-recommended rapid technologies are described in Chapter 3.

4.4.1 Interpreting rifampicin resistance results from molecular testing

As described in Chapter 3, WHO-recommended molecular testing methods (Xpert MTB/RIF and line probe assays) have been found to have a high sensitivity and specificity for detection of rifampicin resistance. Molecular methods do not have perfect concordance with phenotypic culture-based DST methods (see Chapter 3) and patient details such as treatment history and risk factors for drug-resistant TB should always be taken into account when interpreting laboratory results.

WHO-recommended molecular methods detect mutations in the *rpoB* region of *M. tuberculosis* DNA, which are responsible for >95% of rifampicin-resistant strains. Given the resultant high sensitivity of molecular methods, a negative result generally excludes rifampicin resistance and no further testing to confirm negative results is required. In rare instances, when a patient is strongly presumed to have RR-TB even after a negative molecular test, follow-up testing using phenotypic culture-based DST may be used to test for rifampicin resistance resulting from a small number of mutations occurring outside the *rpoB* region.

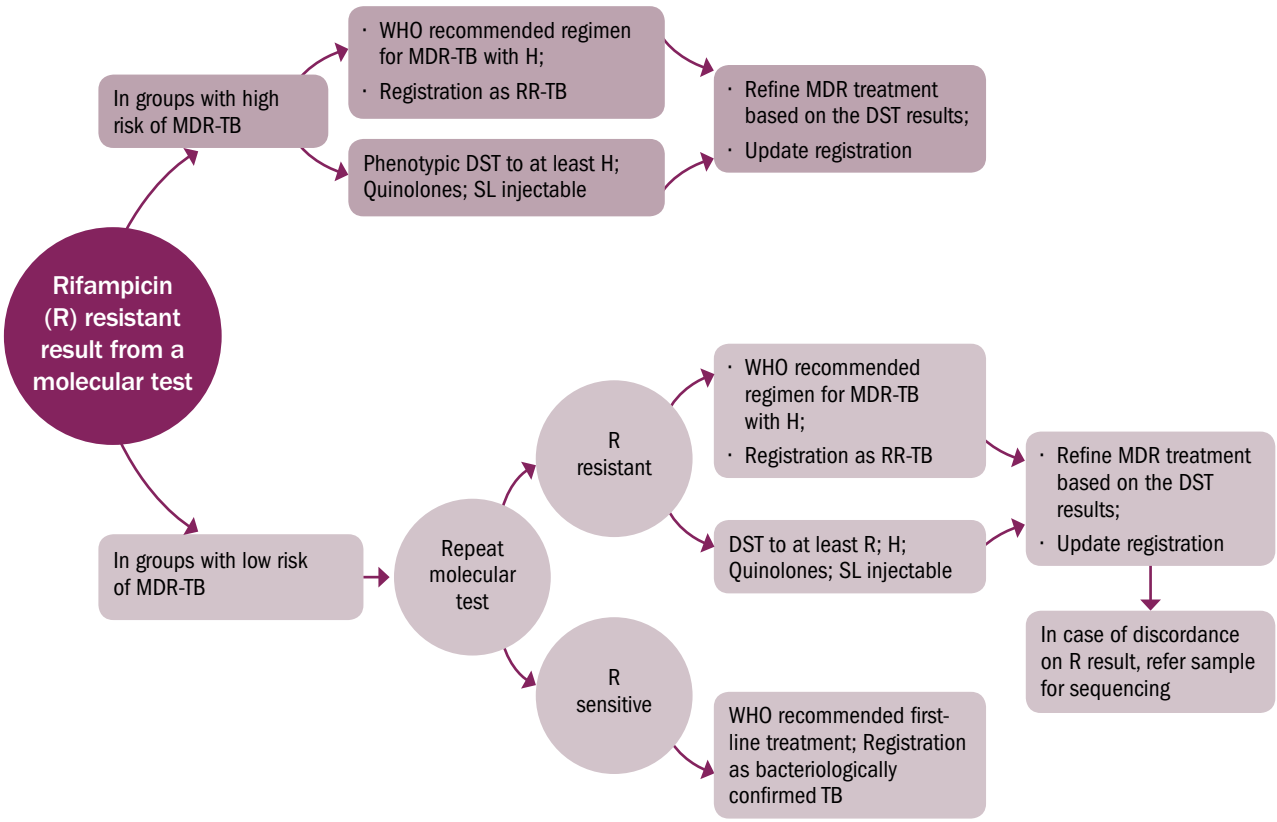
WHO-recommended molecular methods also have very high specificity for detection of rifampicin resistance. Nevertheless, any diagnostic test with a specificity of less than 100% when used in a population with a low prevalence of the condition can result in a lower positive

predictive value, which means that a number of false-positive results are present among those diagnosed as having the condition. Increasing evidence, however, is showing that the occurrence of ostensibly false-positive rifampicin resistance detected by Xpert MTB/RIF compared to phenotypic culture-based DST methods may be linked to the detection by molecular methods of strains that are truly resistant to rifampicin, yet are not detected by culture-based DST. Such strains appear to have clinically-relevant mutations in the *rpoB* region conferring resistance to rifampicin, causing disease that is likely to fail first-line treatment. A recent study has shown that an epidemiologically-significant proportion (close to 10%) of rifampicin-resistant strains in first failure and relapsed patients are missed by phenotypic DST *(35)*.

The interpretation of molecular results and follow-on steps will depend on the result itself as well as on the patient group from which the patient originated. All patients identified by molecular methods should be initiated on an appropriate WHO-recommended treatment regimen as soon as possible. Prompt treatment initiation will have a positive effect on patient outcomes, while the treatment regimen can be refined when additional testing results become available.

The recommended algorithm for interpretation of results from molecular methods is depicted in Figure 4.1.

Figure 4.1 Algorithm for interpretation of results from molecular methods



When a molecular method detects rifampicin resistance, the decision on further steps depends on the patient's risk of having drug-resistant TB:

- In patients originating from a group **at high risk of MDR-TB**, a WHO-recommended regimen for MDR-TB with the addition of isoniazid should be initiated (when susceptibility to isoniazid is not known). The patient should be registered as having bacteriologically confirmed RR-TB, and another sputum sample (taken immediately, prior to treatment onset) should be sent for phenotypic or another genotypic DST to isoniazid. The sample should be subjected to phenotypic DST against fluoroquinolones and second-line injectable agents (see Chapter 3). Confirmatory testing of rifampicin resistance using another technology is not necessary in such cases. When DST results are available, the MDR-TB treatment regimen should be refined based on the results and patient registration updated accordingly. Treatment modifications may include dropping isoniazid if resistance was shown, adding an appropriate fluoroquinolone or second-line injectable agent or, in case of XDR-TB, placing the patient on an appropriately designed regimen including Group 5 drugs. Accordingly, the registration of the patient should be modified reflecting this new information and be notified as per national regulations.
- In patients originating from a group **at low risk of MDR-TB**, this result may be considered unexpected and further follow-up is required. While this unexpected result may be attributed to test specificity not being 100% for detection of rifampicin resistance, it may also result from the non-systematic or random errors at pre- or post-analytical stages of the testing that are relatively frequent even in quality-assured laboratories. These include clerical errors when recording specimen information or test results, or administrative errors that result in specimens being mixed up, etc. While not addressing the test's specificity, **an immediately repeated test on a fresh sample can be useful** in improving a clinician's confidence when deciding on the treatment to be prescribed.

When the result of a second test shows rifampicin susceptibility (an unsurprising result in an individual at low risk of MDR-TB), a WHO-recommended first-line regimen should be prescribed, and the patient should be registered as having susceptible, bacteriologically confirmed TB.

When the result of a second test is in accordance with the initial finding of rifampicin resistance, a WHO-recommended regimen for MDR-TB with the addition of isoniazid should be started without any further delay. Such a patient should be registered as having bacteriologically confirmed RR-TB, and an additional sample should be taken for phenotypic or genotypic DST to confirm resistance to rifampicin and also test for susceptibility to isoniazid, fluoroquinolones and second-line injectable agents. When DST results become available, the MDR-TB treatment regimen and patient registration should be refined, if appropriate. Treatment modifications may include dropping isoniazid from the regimen if resistance was found, adding an appropriate fluoroquinolone or second-line injectable agent or, in the case of detection of XDR-TB, placing the patient on an appropriately designed regimen including Group 5 drugs. Accordingly, the registration of the patient should be modified to reflect this new information and be notified as per national regulations.

In case of discordance in rifampicin resistance results between a molecular method and phenotypic DST or another molecular method, the available culture isolate should preferably be referred for DNA sequencing in a reference laboratory (e.g. one of the SRLs), and in the meantime a clinical decision should be made on whether the MDR-TB regimen should be continued. Emerging data show that Xpert MTB/RIF detects some rifampicin-resistant strains that are susceptible on phenotypic DST. Sequencing of these discordant results usually resolves in favour of Xpert MTB/RIF, and patients with rifampicin resistance missed by phenotypic DST often harbour mycobacteria with clinically relevant mutations in the region conferring resistance to rifampicin, causing disease that is likely to fail first-line treatment.

Molecular methods are not suitable for monitoring of treatment response. Results can stay positive for *M. tuberculosis* by detection of DNA in dead organisms after viable bacteria have been eliminated, resulting in false-positive results. Therefore, culture remains the preferred method for monitoring patient response to drug-resistant TB therapy.

Details of the technical operation and 'how-to' practical considerations of Xpert MTB/RIF are provided elsewhere *(8)*.

4.5 Presumptive MDR-TB when rapid genotypic DST is not available

When rapid DST is not available, there are selected groups of patients where the risk of MDR-TB is so high that a presumptive diagnosis of MDR-TB would apply and patients can be directly enrolled on empiric MDR regimens. The MDR-TB regimen should be adjusted when conventional phenotypic DST results become available as described in Chapter 5. The groups eligible for the presumptive diagnosis of MDR-TB and direct enrolment into an MDR regimen include:

- **Failures of retreatment regimens with first-line drugs** *(5,21)*. Patients in whom retreatment with first-line drugs has failed in national TB control programmes often have MDR-TB. If the quality of the drugs in the TB control programme is uncertain or if the quality of directly observed therapy is poor or unknown (i.e. if regular ingestion of medicines is uncertain), retreatment regimens may fail for reasons other than drug resistance.
- **Close contacts of drug-resistant TB cases that develop active TB disease.** These patients can be enrolled for treatment with MDR regimens, pending DST results. See Chapter 15 for a description on the management of contacts of drug-resistant TB patients.
- **Failures of new regimens with first-line anti-TB drugs in some settings.** Since the prevalence of drug-resistant TB in this group of patients may vary greatly *(21–25)*, the drug-resistant TB rate in this group must be documented through appropriate testing and analysis before deciding whether empiric treatment for MDR-TB is justified and to determine which drugs should be included in empiric treatment (see Chapter 5).

For all patients started on empiric MDR-TB regimens, the standard of care is to receive DST to confirm the diagnosis *(6)*. However, it should be noted that:

- **In settings where DST results are not yet routinely available to guide the management of individual patients, empiric regimens will continue throughout the course of treatment** *(7)*. *Remark:* If DST results become available, regimens should be adjusted appropriately.
- **National TB programmes should obtain and use their country-specific drug resistance surveillance data on failure, relapse and loss to follow-up patient groups to determine the levels of MDR** *(7)*.

4.6 Diagnosing XDR-TB

All patients diagnosed with MDR-TB should preferably be tested for XDR-TB. In areas where second-line DST is limited, patients with risk factors for XDR-TB should be tested for XDR-TB at the very least. In areas where no capacity for second-line DST exists, partnering with a Supranational Reference Laboratory (SRL) that has the capacity is advised.

The two strongest risk factors for XDR-TB are:

1. failure of an MDR-TB treatment regimen, which contains second-line drugs including an injectable agent and a fluoroquinolone; and
2. close contact with an individual with documented XDR-TB or with an individual for whom treatment with a regimen including second-line drugs is failing or has failed.

All individuals presumed to have XDR-TB should have DST to isoniazid, rifampicin, the three second-line injectable agents (kanamycin, amikacin, and capreomycin) and the fluoroquinolone(s) used in the country (see Chapter 3). XDR-TB is diagnosed through conventional phenotypic DST. The reliability and reproducibility of second-line anti-TB DST is discussed in Chapter 3. A WHO Expert Group reviewed the utility of the molecular line probe assay for the detection of second-line drug resistance and concluded that the test is not sensitive enough to reliably rule out XDR-TB. In addition, given the cross-resistance between second-line drugs, the test cannot be used to identify the individual drugs to be used for treatment *(26)*.

Concomitant HIV-infection in an individual with either of the above XDR-TB risk factors requires urgent action because of the high risk of rapid death associated with HIV and XDR-TB co-infection. The actions include an assessment for the risk of second-line drug resistance, and (if XDR-TB is likely) the starting of an empiric XDR regimen while awaiting conventional phenotypic DST results.

4.7 Management of specimens and results

For Xpert MTB/RIF or line probe assay examination, one sputum specimen for diagnostic testing is collected. If phenotypic culture and DST are chosen as part of the case finding strategy, two sputum specimens should be cultured, and DST should be performed on the specimen that produces the best culture (e.g. the one with more colonies or highest reading on liquid culture, and confirmed as *M. tuberculosis* complex). DST does not need to be carried out in duplicate.

Procedures for collecting and managing specimens for culture and DST are described in Chapter 3, Section 3.5, which also addresses different techniques, limitations, quality assurance requirements and other issues of culture and DST.

Infection control measures for sputum collection must be in place so as not to risk infecting others (see Chapters 3 and 12).

All parts of the diagnostic process, including sample collection, processing, testing and reporting, as well as the clinical follow-up, can contribute to significant delays in starting the appropriate treatment. Therefore, specimens must be transported to the laboratory as soon as possible. When possible, specimens should be processed the same day they are collected (see Chapter 3 for sputum transportation and processing recommendations). Results of any test performed should be reported as soon as they become available, ideally through electronic means of communication *(28–30)*. Once the results are received at the facility or by the health care provider, the patient should have an immediate follow-up medical visit to initiate appropriate treatment.

Previously treated patients may have had DST in the past, but previous DST results may no longer reflect the resistance pattern of the patient's strain at the time of starting treatment for drug-resistant TB. Programmes giving individualized treatment (see Chapter 5) should repeat DST at the start of treatment to obtain the most accurate DST results on which to base treatment.

4.8 Drug-resistant TB case finding in paediatric patients

Paediatric cases require exceptional diligence in diagnostic testing. Diagnostic criteria and indications for treatment may require adjustments. Most young children will not be able to produce adequate sputum specimens upon request. Sputum induction with nebulized hypertonic saline may facilitate collection of tracheobronchial secretions, especially in children who have a dry cough or no cough.

Nebulization may often also be unsuccessful in young children. In this situation, gastric lavage is the most common procedure for collecting specimens for Xpert MTB/RIF or culture and DST. Children (like adults) swallow their tracheobronchial secretions so gastric lavage specimens may contain respiratory secretions, especially early in the morning before the child has had anything to eat or drink. Of note, gastric lavage should not be used if only smear microscopy is being done (because of the low yield, it is not worth the distress caused to the child); gastric lavage should be used for examination by Xpert MTB/RIF or culture *(31–33)*.

In settings with appropriate facilities and technical expertise, fibre-optic bronchoscopy may be the best next step if gastric aspirates fail.

In cases where the anatomic location of disease includes sites outside the pulmonary parenchyma, fine needle aspiration or biopsy should be considered. Specimens obtained by aspiration or biopsy may also need to be sent to the pathology laboratory for examination, in addition to the microbiological testing to rule out other diseases (also see Section 4.9).

Special attention should be given to maintenance of the equipment used for specimen collection.

In 2013, WHO updated its policy guidance, issuing the following recommendations for the use of Xpert MTB/RIF in detection of TB and rifampicin resistance in children *(18)*:

1. Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in children suspected of having MDR-TB or HIV-associated TB (strong recommendation, very low-quality evidence).

2. Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all children suspected of having TB (conditional recommendation acknowledging resource implications, very low-quality evidence).

Children suspected of having pulmonary TB but with a single Xpert MTB/RIF-negative result should undergo further diagnostic testing, and a child with high clinical suspicion for TB should be treated even if an Xpert MTB/RIF result is negative or if the test is not available.

Because of the seriousness of drug-resistant TB and toxicity plus the limited efficacy of second-line drugs, additional efforts to obtain appropriate specimens are not only justifiable, but also recommended in appropriate settings. Many health care providers believe erroneously that attempting to diagnose TB microbiologically in children is futile and do not attempt diligent diagnostic evaluations. This creates a self-defeating cycle in which children systematically become victims of poor medical practice. After thorough diagnostic testing, if Xpert MTB/RIF and culture results are negative (resulting in no specimen available for DST), such children with active TB who are close contacts of patients with MDR-TB can be started on MDR regimens (see Chapter 15 on managing drug-resistant TB contacts for more information).

4.9 Drug-resistant TB case finding among extrapulmonary TB patients

Drug-resistant extrapulmonary TB (EPTB) can be detected using Xpert MTB/RIF or conventional culture and DST.

In 2013 WHO updated its policy guidance on use of Xpert MTB/RIF, issuing the following recommendations for the use of Xpert MTB/RIF in detection of EPTB *(18)*.

- Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing **cerebrospinal fluid specimens** from patients presumed to have TB meningitis (strong recommendation given the urgency of rapid diagnosis, very low quality of evidence).
- Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of specific non-respiratory specimens (**lymph nodes and other tissues**) from patients presumed to have extrapulmonary TB (conditional recommendation, very low quality of evidence).

At the time of formulation of the updated WHO recommendations in 2013, not enough data were available on the utility of Xpert MTB/RIF for detecting extrapulmonary TB and rifampicin resistance in stool, urine or blood. If no DST diagnosis can be made, a strong history of TB failure or contact with an MDR-TB patient may warrant an empiric MDR regimen.

4.10 Drug-resistant TB case finding in HIV-infected patients

The diagnosis of TB in HIV-infected people is more complex and may be confused with other pulmonary or systemic infections. PLHIV are more likely than HIV-negative persons to have smear-negative TB or extrapulmonary TB. WHO recommends Xpert MTB/RIF as a primary diagnostic test in the following individuals *(18)*: (i) all adults and children living with HIV who have signs or symptoms of TB, (ii) those seriously ill and suspected of having TB regardless of HIV status, and (iii) those with unknown HIV status presenting with strong clinical evidence of HIV infection in HIV-prevalent settings.

Because unrecognized drug-resistant TB is associated with very high mortality in HIV-infected patients, all patients diagnosed with HIV-associated TB should receive a rapid molecular test, including Xpert MTB/RIF or line probe assay *(26)*, for the detection of potential drug resistance. Programmes without facilities or resources to test all HIV-positive patients suffering from TB for drug-resistant TB should put significant efforts into establishing such capacity, especially if drug-resistant TB rates are moderate or high.

HIV-infected patients with MDR-TB or rifampicin resistance should be tested for second-line anti-TB drug resistance (see Section 4.6).

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CHAPTER 5

Treatment strategies for MDR-TB and XDR-TB

5.1 Introduction

This chapter provides guidance on the strategies for the treatment of multidrug- and extensively drug-resistant TB (M/XDR-TB), with emphasis on regimen design. The treatment of mono- and poly-drug-resistant TB is addressed in Chapter 6. The strategies described in this chapter are largely based on the recommendations from the 2011 update of *Guidelines for the programmatic management of drug-resistant tuberculosis,* which underwent systematic review and analysis of the evidence for best treatment practice *(1)*.

5.2 Essential assessments prior to designing a programmatic treatment strategy

Access to quality-assured DST is a critical component of TB treatment. It is critical for drug-resistant TB programmes to be familiar with the prevalence of drug resistance in new patients, as well as in different groups of retreatment cases (failure in a new patient using first-line anti-TB regimen, failure in a previously treated patient with first-line anti-TB drugs, relapse, return after loss to follow-up, and others). This data is often obtained from an analysis of a country's drug resistance surveillance (DRS) data.

In addition, it is essential to determine which and with what frequency second-line anti-TB drugs have been used within a given area served by a programmatic strategy. Some second-line anti-TB drugs may have been used only rarely and will likely be effective in drug-resistant TB treatment regimens, while others may have been used extensively, and therefore, have a high probability of ineffectiveness in a large proportion of drug-resistant TB patients.

It is recognized that some drug-resistant TB programmes may have to design strategies based on limited data, as treatment for many patients cannot wait until full assessment DRS and other information are available. In these cases the programme can still follow the basic principles put forth in this chapter on how to design an effective regimen and continue to collect the information needed to design the most optimal treatment strategy.

5.3 Definitions of terms used to describe treatment strategies

The following are definitions of terms often used to describe treatment strategies.

- **Standardized treatment:** DRS data from representative patient populations are used to as the basis for regimen design in the absence of individual DST. All patients in a defined group or category receive the same regimen (see Chapter 4 for risk groups for MDR-TB). Suspected MDR-TB should be confirmed by DST whenever possible.
- **Individualized treatment**: Each regimen is designed based on the patient's past history of TB treatment and individual DST results.

TB programmes often use a combination of standardized and individualized approaches. However, in situations where DST is unavailable or limited to only one or two first-line drugs, programmes will most commonly use a purely standardized approach. These strategies are

discussed in more detail in Section 5.9, which addresses using these strategies in programme conditions.

This Handbook uses the term '**empiric**' to refer to the initiation of treatment prior to determination of a firm diagnosis of drug-resistant TB. Empiric regimens can be used for both standardized and individualized treatment strategies. For example, an empiric XDR regimen refers to the use of a regimen designed to treat XDR-TB before the diagnosis of XDR-TB is made.

5.4 Classes of anti-TB drugs

The classes of anti-TB drugs have traditionally been divided into first- and second-line anti-TB drugs with isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin being the primary first-line anti-TB drugs. While this classification is used in this document, it also uses a system that classifies the drugs into five different groups. The five-group system is based on efficacy, experience of use, safety and drug class. WHO will be reviewing this five-group system in the next update of the guidelines for the management of MDR-TB in view of the new drugs being introduced and the emerging evidence on its safety and efficacy. The different groups are shown in Table 5.1. Not all drugs in the same group come from the same "drug class" or have the same efficacy or safety. For more information, see individual descriptions of each group in this section. Individual detailed drug information for all anti-TB drugs is provided in the drug information sheets of Part 3.

TABLE 5.1 **WHO recommended grouping of anti-TB drugs**

GROUP NAME	ANTI-TB AGENT	ABBREVIATION
Group 1. First-line oral agents	Isoniazid	H
	Rifampicin	R
	Ethambutol	E
	Pyrazinamide	Z
	Rifabutin[a]	Rfb
	Rifapentine[a]	Rpt
Group 2. Injectable anti-TB drugs (injectable agents or parental agents)	Streptomycin[b]	S
	Kanamycin	Km
	Amikacin	Am
	Capreomycin	Cm
Group 3. Fluoroquinolones (FQs)[d]	Levofloxacin	Lfx
	Moxifloxacin	Mfx
	Gatifloxacin[c]	Gfx
Group 4. Oral bacteriostatic second-line anti-TB drugs	Ethionamide	Eto
	Prothionamide	Pto
	Cycloserine	Cs
	Terizidone[e]	Trd
	Para-aminosalicylic acid	PAS
	Para-aminosalicylate sodium	PAS-Na

GROUP NAME	ANTI-TB AGENT	ABBREVIATION
Group 5. Anti-TB drugs with limited data on efficacy and/or long term safety in the treatment of drug-resistant TB (This group includes new anti-TB agents)	Bedaquiline	Bdq
	Delamanid	Dlm
	Linezolid	Lzd
	Clofazimine	Cfz
	Amoxicillin/ clavulanate	Amx/Clv
	Imipenem/cilastatin[f]	Ipm/Cln
	Meropenem[f]	Mpm
	High-dose isoniazid	High dose H
	Thioacetazone[g]	T
	Clarithromycin[g]	Clr

[a] Rifabutin and rifapentine have similar microbiological activity as rifampicin. Rifabutin is not on the *WHO list of essential medicines*, however it has been added here as it is used routinely in patients on protease inhibitors in many settings. Rifapentine is part of a latent TB infection and active TB treatment in some countries but to date is not part of any WHO endorsed treatment regimens.

[b] There are high rates of streptomycin resistance in strains of MDR-TB; therefore, streptomycin is not considered a second-line anti-TB injectable agent.

[c] Gatifloxacin can have severe side-effects including serious diabetes (dysglycaemia). The drug has been removed from the market of a number of countries as safer alternatives whenever possible are available for the diseases for which the drug is labeled. Safer alternatives are discussed below in the section of Group 5 drugs.

[d] Ofloxacin is considered a weaker agent with less activity against TB than other fluoroquinolones and has been removed as a choice in Group 3 drugs (see section below on Group 3 – Fluoroquinolones for more information).

[e] Terizidone has limited programme data and effectiveness data as compared to cycloserine.

[f] Clavulanate (Clv) is recommended as an adjunctive agent to imipenem/cilastatin and meropenem.

[g] Limited data on the role of thioacetazone and clarithromycin in MDR-TB treatment has resulted in many experts not including these drugs as options for Group 5.

Group 1: First-line oral agents. Group 1 anti-TB drugs, the most potent and best tolerated, should be used if there is good laboratory evidence **and** clinical history that suggests that a drug from this group is effective. For patients with strains resistant to low concentrations of isoniazid but susceptible to higher concentrations, the use of high-dose isoniazid may have some benefit (when isoniazid is used in this manner it is considered a Group 5 drug, see below). The newer rifamycins, such as rifabutin, have very high cross-resistance to rifampicin.

Pyrazinamide is routinely added to MDR regimens unless there is a reasonable clinical contraindication for its use (hepatotoxicity or other serious adverse effect). DST to pyrazinamide is not reliable and for this reason it is considered an acceptable practice to use pyrazinamide in a regimen even when a laboratory result demonstrates resistance.

Ethambutol is not routinely added to MDR regimens, however, it can be added if the criteria of it being a likely effective drug are met (see Section 5.7 for criteria of a likely effective drug). Due to difficulties in testing, ethambutol is never considered a key drug in an MDR regimen, even if the strain is found susceptible.

Group 2: Injectable anti-TB drugs. All patients should receive a second-line Group 2 injectable agent in the intensive phase of MDR-TB treatment unless resistance is documented or highly suspected. Either kanamycin, amikacin or capreomycin can be used as a first choice if all meet the criteria of "likely to be effective". Given the high rates of streptomycin resistance in patients with MDR-TB (greater than 50% is some countries) and extensive use as a first-line agent in many countries, streptomycin is not often used in MDR regimens, even if DST shows susceptibility to it. Kanamycin and amikacin have lower costs than capreomycin, have less toxicity than streptomycin and have been used extensively for the treatment of drug-resistant TB throughout the world. Amikacin and kanamycin are very similar in structure, and they have a high frequency of cross-resistance between them. Amikacin has a lower minimum inhibitory concentration and may be the most efficacious of the two *(2)*, however, clinical comparison is lacking. Capreomycin may have cross-resistance with amikacin/kanamycin if the rrs gene mutation is present, but the clinical implications of this are not well understood. Limited evidence suggests that capreomycin has less ototoxicity than aminoglycosides *(3)*. If an isolate is resistant to both streptomycin and kanamycin, or if DRS data show high rates of resistance to amikacin and kanamycin, then capreomycin is suggested as the injectable of choice. In cases where the strain is resistant to all the second-line injectable drugs (amikacin, kanamycin and capreomycin) except streptomycin, streptomycin should be considered, as there is little cross-resistance between streptomycin and the other injectable agents.

All Group 2 drugs are given intramuscularly – most commonly injected deeply into the upper outer quadrant of the gluteal muscle. Additionally, Group 2 drugs can be given intravenously, however, they must be given slowly (over 60 minute period) using this method. Full dosing instructions are given in Part 3. In view of the pain caused by the intramuscular injection of kanamycin, some programmes prefer to install a catheter for daily delivery of the drug (a peripherally inserted central line is often required as it is not possible to rotate a standard intravenous catheter for such a long time. However, standard peripheral IV catheters can be used to give patients short breaks from the intramuscular injections). This method of delivery is usually better accepted by the patient but comes with additional costs and requires an expertise that is not readily available in all settings.

There is limited experience in delivering injectable drugs via nebulizers for TB control and no recommendations can be made on this delivery mechanism at this stage.

Group 3: Fluoroquinolones. Fluoroquinolones are often the most effective anti-TB drugs in an MDR-TB regimen. There are two important recommendations regarding fluoroquinolone use from the 2011 update of the *Guidelines for the programmatic management of drug-resistant tuberculosis (1)*.

- **In the treatment of patients with MDR-TB, a fluoroquinolone should be used (strong recommendation, very low quality evidence).**
- **In the treatment of patients with MDR-TB, a later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (conditional recommendation, very low quality evidence).**

In a meta-analysis of MDR-TB treatment *(1,2,4)*, fluoroquinolones were significantly associated with cure and the effect was more pronounced in later-generation fluoroquinolones. In the analysis, "later generation" quinolones were moxifloxacin and levofloxacin, which were compared against ofloxacin. However, ofloxacin is considered to be a second-generation fluoroquinolone, levofloxacin a third-generation, and moxifloxacin and gatifloxacin are considered fourth-generation fluoroquinolones *(5)*. The analysis did not do a comparison of levofloxacin (third generation) versus moxifloxacin (a fourth generation).

Levofloxacin is the l-isomer and more active component of the racemic ofloxacin (racemic = composed of dextrorotatory and levorotatory forms of a compound in equal proportion). Levofoxacin can be considered to have approximately twice the activity against TB than ofloxacin. In one study, levofloxacin had better efficacy against ofloxacin-resistant strains than did ofloxacin, and provides some evidence that levofloxacin can overcome ofloxacin resistance (*6*). In theory, the weaker activity of ofloxacin could lead to fluoroquinolone resistance quicker. There is little reason for programmes to choose ofloxacin in standardized regimens, and it is likely in the future that ofloxacin will be removed as a choice for TB regimens.

Ciprofloxacin has weaker efficacy against TB than other fluoroquinolones and is not recommended as an anti-TB drug *(7)*.

Gatifloxacin has been associated with serious side-effects, such as hypoglycaemia, hyperglycaemia and new onset diabetes *(8)*. Until more valid data clarifies the safety profile of gatifloxacin in treatment of MDR-TB, moxifloxacin or levofloxacin are the preferred fluoroquinolones.

Fluoroquinolones are known to prolong the QT interval. QT interval prolongation predisposes to torsades de pointes, which may result in sudden death. There is variability between the fluoroquinolones in this effect; however, the prolongation is considered minimal. Additional cardiac monitoring is required when used with drugs that prolong the QT interval (see Chapter 11). Moxifloxacin and gatifloxacin have more effect of QT prolongation than do levofloxacin and ofloxacin *(9)*

Thus, for the fluoroquinolones, it is suggested that unless there is a strong indication for not doing so, all MDR-TB patients should be treated using 'later-generation' fluoroquinolones – levofloxacin or moxifloxacin.

Group 4: Oral bacteriostatic second-line anti-TB drugs. Both ethionamide and prothionamide are prodrugs that need activation by mycobacterial enzymes. There is no clear advantage of ethionamide over prothionamide; efficacy and side-effects also appear similar. Thus, the term 'ethionamide/prothionamide" is used throughout this Handbook to indicate that either one can be used. Of the Group 4 drugs, ethionamide/prothionamide performed the best in the meta-analysis of MDR-TB treatment conducted to update the 2011 guidelines *(1,4)*. However, it should be noted that inhA gene mutation in TB bacteria has been associated with cross-resistance with low-level isoniazid resistance and high-level ethionamide resistance *(10)*. If the inhA gene mutation is present, ethionamide/prothionamide can still be included in an MDR regimen, but it should not be counted as a "likely effective second-line anti-TB drug". Cycloserine and/or para-aminosalicyclic acid (PAS) should be included in MDR

regimens. Both PAS and cycloserine share no cross-resistance to other anti-TB drugs. Since the combination of ethionamide/prothionamide and PAS often causes a high incidence of gastrointestinal side-effects and hypothyroidism, these agents are usually used together only when three Group 4 agents are needed. Whether terizidone (containing two molecules of cycloserine) is equally efficacious as cycloserine was unknown at the time of this writing. The drugs in Group 4 may be started at a low dose and escalated over three to 10 days to reduce frequency or severity of side-effects (known as dose-ramping) *(11)*.

Group 5. Group 5 drugs are not recommended by WHO for routine use in MDR-TB treatment. Although all of them have demonstrated some activity at least *in vitro* or in animal models, the quality of the evidence of their efficacy and safety in humans for the treatment of drug-resistant TB varies. Most of these drugs are, with the exception of bedaquiline and delamanid, not registered for treatment of MDR-TB making their use 'off-label.'[5] In some cases the drugs are quite costly and require intravenous administration (imipenem and meropenem). However, they remain as options in cases where adequate regimens are impossible to design with medications from Groups 1–4. If a situation requires the use of Group 5 drugs, often experts will recommend using two to three drugs from the group given the limited knowledge of efficacy. Of note, there are currently no data on the simultaneous use of bedaquiline and delamanid in the same patient. Until such data become available, WHO cannot make a recommendation on the joint administration of these two medicines (see Annexes 4.1 and 4.2 for more details). The following is information that may help choose which Group 5 drugs to use when indicated (for full drug information see Part 3 – Individual Drug Prescribing Information).

- ***Bedaquiline*** – See Annex 4.1 for description of bedaquiline including its indications and safety monitoring requirements.
- ***Delamanid*** – See Annex 4.2 for descriptions of delamanid including its indications and safety monitoring requirements
- ***Linezolid*** – Linezolid has shown good activity *in vitro* and in animal studies. There are also a number of cases of off-label use in M/XDR-TB; it has recently been demonstrated to improve outcomes in XDR-TB *(12,13)* Of the Group 5 drugs it is considered one of the most effective against TB and is often a key drug in XDR treatment regimens (also see Section 5.15 and Box 5.4). It has numerous severe side-effects including: myelosupression (anaemia, leucopenia, thrombocytopenia and pancytopenia), peripheral neuropathy and lactic acidosis. When serious adverse effects arise the drug often needs to be stopped (in some cases the adverse effect can be managed by decreasing the dose (usually from 600 mg daily to 300 mg daily). While 300 mg dosing is associated with fewer side-effects, it is not known if the lower dosing is as effective or if it will lead to a higher chance of resistance amplification, though some clinical experts have found that the lowering of the dosing due to anaemia quite often coincides with culture conversion, which increases the chance to keep the drug in the treatment regimen.
- ***Clofazimine*** – A significant amount of experience with clofazimine in MDR-TB treatment exists *(14–16)*, and it has been included in 9- to 12-month regimens and reported to have

[5] **Off-label use** is the practice of prescribing a drug to treat a medical condition for which a stringent drug regulatory body has not approved the indication. It may also include using the drug in an age group not yet approved for or in a dosage or form of administration different from the original approval.

very good outcomes *(17)*. However, the efficacy of clofazimine against TB remains unclear. Clofazimine is often added to regimens for XDR-TB. In relation to adverse effects, skin pigmentation occurs in 75% to 100% of patients within a few weeks; reversal can take months to years after the treatment.

- ***Amoxicillin/clavulanate*** – Generally, beta-lactam antibiotics are not regarded as very useful drugs against TB, but the addition of the beta-lactamase inhibitor makes them active in vitro against TB. There is limited evidence of in vivo bactericidal activity *(18)*. While amoxicillin/clavulanate is probably a relatively weak anti-TB drug, it is often included within regimens because it is available, inexpensive and with few side-effects.
- ***Imipenem/cilastin and meropenem.*** Imipenem and meropenem belong to the drug class carbapenem, given only intravenously. Due to cost and difficulty in intravenous administration these drugs are commonly used in resource-constrained settings. Meropenem is preferred for use in children and adults with central nervous system disease, as there is less association with seizure. Given that imipenem is rapidly degraded by renal proximal tubule dipeptidases, it is marketed in combination with the dipeptidase inhibitor, cilastatin. Conversely, meropenem is stable to renal dipeptidases and requires no cilastatin *(19)*. Since it is in the beta-lactam class of antibiotics it is likely that these imipenem/cilastin and meropenem can benefit from the addition of clavulanate 125 mg every 8–12 hours. Clavulanate was added to merpenem in one study of XDR-TB patients with reasonably good outcome results *(13)*. (Clavulanate is not readily available alone and some give it as amoxicillin/clavulanate 500 mg/125 mg oral tablet).
- ***High-dose isoniazid***. Many experts feel that high-dose isoniazid can be used against strains resistant to low concentrations of isoniazid but susceptible to higher doses *(20)* (>1% of bacilli resistant to 0.2 mcg/ml but susceptible to 1 mcg/ml of isoniazid), whereas, isoniazid is not recommended for high-dose resistance (>1% of bacilli resistant to 1 mcg/ml of isoniazid). Some experts give 900 mg three times a week *(21)* in adults while others use as high as 16–20 mg/kg/day *(22)* Good data are not available on the safety of high-dose isoniazid and there may be possible associated higher rates of peripheral neuropathy, hepatitis and other unforeseen adverse effects. Experts also recommend not using isoniazid if the strain is documented to have a katG gene mutation. The katG mutation is detected by line probe assay tests available today.
- ***Thioacetazone.*** While thioacetazone is a drug with known efficacy against TB, it is placed in Group 5 because its role in drug-resistant TB treatment is not well established. Overall, a weak bacteriostatic drug, thioacetazone has cross-resistance with ethionamide *(23)* and isoniazid *(24,25)*. Thioacetazone is contraindicated in HIV-infected individuals *(26)* due to a serious risk of adverse reaction that can result in Stevens-Johnson Syndrome and death. The drug is also not well-tolerated in persons of Asian origin. For all these reasons, this drug is rarely added as a Group 5 drug. Until there is more information on its role in MDR-TB therapy, most experts advise drug-resistant TB programmes not to include thioacetazone, especially if HIV status is unknown.
- ***Clarithromycin.*** Clarithromycin is included in Group 5, but its activity against *M. tuberculosis* is uncertain. Some studies suggest that clarithromycin may have a synergistic effect with oral first-line agents *(27,28)* but synergy data with second-line drugs is absent. Most experts consider clarithromycin a very weak anti-TB drug and consider it to have no role in MDR-TB treatment.

BOX 5.1 EXAMPLES OF STANDARD DRUG CODE USED TO DESCRIBE DRUG REGIMENS

$8Km^{6}$-Lfx^{7}-Eto^{7}-Cs^{7}-Z^{7}/$12Lfx^{7}$-Eto^{7}-Cs^{7}-Z^{7}

The initial phase consists of five drugs and lasts for eight months in most patients (see Section 5.9). Kanamycin is given six days a week and all other drugs are given seven days a week. In this example, the phase without the injectable continues all the oral agents for a minimum of 12 months, for a total minimum treatment of at least 20 months (see Section 5.10).

Sometimes only the initial treatment is written with the assumption that the injectable will be stopped according to the programme protocol. This type of notation is used without a coefficient, i.e. **Z-Km-Lfx-Eto-Cs**.

5.5 Standard code for TB treatment regimens

There is a standard code for writing TB treatment regimens. Each anti-TB drug has an abbreviation (shown in Table 5.1 and in the abbreviations list provided at the front of this book). A drug-resistant TB regimen consists of two phases: the first phase is the period in which the injectable agent is used, and the second is after it has been stopped. These two phases are generally separated by a backslash (/). The number before each phase stands for phase duration in months, and this number is the minimum amount of time that the stage should last. The number in subscript (e.g. $_3$) after a letter is the number of drug doses per week. If there is no number in subscript, treatment is daily (injectables are generally given for 5–6 days per week). The drugs in the higher groups are written first followed by others in descending group order. Examples are given in Box 5.1.

5.6 Role of drug susceptibility testing

See Chapter 3 for a full discussion on the use of DST in programmatic management of drug-resistant TB. Countries have varying access to reliable mycobacterial laboratories, and many do not have regular local access to DST. The inability to do routine DST in all patients should not be a barrier for patients that need MDR regimens. Fully standardized regimens using second-line anti-TB drugs have been shown to be feasible and cost-effective in drug-resistant TB treatment *(29–31)*.

The reliability and clinical value of DST for some first-line and most second-line anti-TB drugs is not fully determined (see Chapter 3). DST does not predict with 100% certainty the effectiveness or ineffectiveness of a drug *(32)*. DST for ethambutol, streptomycin, pyrazinamide, Group 4 and 5 drugs presents problems with accuracy and reproducibility in most settings. Thus, current WHO guidelines caution against basing individual regimens on DST results to these drugs. DST to isoniazid, rifampicin, the fluoroquinolones, and the second-line injectable agents are considered accurate and reproducible; when DST results are from a quality-assured laboratory, individual regimens can be based on the DST results for these drugs.

In countries where reliable DST is not available, the Xpert MTB/RIF assay can be quickly introduced and used as initial diagnostic tool for MDR-TB (see Chapter 4 for more

information on the use of Xpert as a test for MDR-TB). While strategies can be designed with Xpert MTB/RIF as the only DST mechanism or even just based on TB treatment history to identify MDR-TB, every effort should be made to improve laboratory capacity of a TB programme to have access to conventional phenotypic DST and/or a secondary molecular DST method (see Chapter 3).

5.7 Designing and administrating an MDR-TB regimen

This section describes the methods for designing and administrating an MDR regimen. It applies to standardized and individualized regimens. WHO interim policy on the use of delamanid was released in 2014, and should be taken into account when designing a MDR-TB treatment regimen.

5.7.1 General principles

The following are the basic principles involved in the treatment of MDR-TB (recommendations from the 2011 update of *Guidelines for the programmatic management of drug-resistant tuberculosis* have been incorporated and indicated where applicable) *(1)*.

- Early MDR-TB detection and the prompt initiation of an effective treatment are important factors in obtaining successful outcomes.
- **The intensive phase of MDR-TB treatment should consist of at least four second-line anti-TB drugs that are likely to be effective (including an injectable anti-TB drug), as well as pyrazinamide (conditional recommendation, very low quality evidence)** *(1)*. Where there is unclear evidence about the effectiveness of a certain drug, this drug can still be part of the regimen, however, it should not be depended upon for success.
- **MDR regimens should include at least pyrazinamide, a fluoroquinolone, an injectable anti-TB drug, ethionamide (or prothionamide) and either cycloserine or PAS (para-aminosalycylic acid) if cycloserine cannot be used (conditional recommendation, very low quality evidence)** *(1)***.**
- The drugs in the regimen should be judged to be "likely to be effective". An anti-TB drug is considered as such when:
  - The drug has not been used in a regimen that failed to cure the individual patent.
  - DST performed on the patient's strain indicates that it is susceptible to the drug (DST for isoniazid, rifampicin, Groups 2 and 3 drugs is considered reliable; DST for all other drugs is considered not reliable enough for individual patient management).
  - No known resistance to drugs with high cross-resistance (see Chapter 3, Table 3.2).
  - No known close contacts with resistance to the drug.
  - Drug resistance surveys demonstrate that resistance to the drug is rare in patients with similar TB history. This final criterion is relevant in the absence of DST or for drugs in which individual DST is not reliable. Note: It is not always possible that information of all five criteria can be ascertained. Therefore, clinical judgment is often necessary on whether to count a drug as "likely to be effective".
- There are conditions when more than five drugs are used. These conditions would be applicable when the effectiveness for a drug(s) is unlikely or questionable. One such relatively common condition is the treatment of XDR-TB (see Section 5.15).

- Drugs that the patient is known to have a strong contraindication of usage due to – drug–drug interactions, overlying toxicities, co-morbidities, history of severe allergy or other adverse reactions, and/or pregnancy – should not be used.
- **A fluoroquinolone should be used (strong recommendation, very low quality evidence)** *(1)*.
- **A later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (conditional recommendation, very low quality evidence)** *(1)*.
- **In the treatment of patients with MDR-TB, ethionamide (or prothionamide) should be used (strong recommendation, very low quality evidence)** *(1)*. This recommendation assumes the recommended drugs meet the criteria of "likely to be effective" and there are no contraindications to its use (such as a severe adverse effects).
- The intensive phase (i.e. the initial part of treatment during which a Group 2 injectable agent is used) lasts at least eight months in total, but the duration can be modified according to the patient's response to treatment *(1)*. The optimal duration of intensive phase following culture conversion, which is associated with treatment success, could not be inferred directly from the analysis used to revise the WHO programmatic management of drug-resistant TB guidelines in 2011. Some clinical experts may prefer that the intensive phase is continued for at least four months past culture conversion (see Section 5.9 on length of intensive phase).
- The total length of treatment is expected to be at least 20 months in most patients not previously treated for MDR-TB *(1)*. Some clinical experts may prefer that total treatment be for at least 12 months past the point at which culture converts to negative and, some others may prefer not to give less than 20 months in total (see Section 5.10 on length of treatment).
- Each dose is given under a patient-centred directly observed therapy throughout the treatment. A treatment card is marked for each observed dose (see Part 4 – Forms for drug-resistant TB programmes). DOT can be performed either at facility-based or community-based levels, keeping in mind that social support is an *essential* component of care and treatment delivery (see Chapters 12 and 18).
- Any adverse effects of drugs should be managed immediately and adequately to relieve suffering, minimize the risk of treatment interruptions, and prevent morbidity and mortality due to serious adverse effects (see Chapter 11).
- Antiretroviral therapy (ART) is recommended for all patients with HIV and drug-resistant TB, irrespective of CD4 cell-count, as early as possible (within the first eight weeks) following initiation of the anti-TB treatment (strong recommendation) *(1)*.
- The drug dosage is usually determined by age and weight. A suggested weight-based dosing scheme is shown in Annex 2. Dosing for paediatric cases is described in Chapter 7 and Annex 3.
- Pyrazinamide, ethambutol and fluoroquinolones should be given once a day. Depending on patient tolerance, once-a-day dosing is also used for oral second-line anti-TB drugs from Group 4, however, ethionamide/prothionamide, cycloserine and PAS have traditionally been given in split doses during the day to reduce adverse effects.
- All anti-TB drugs can be started at full dose. However, if tolerance is an issue, cycloserine, ethionamide and PAS dosing can be increased gradually over a two-week period *(11)*.
- Injectable drugs can be given five to seven days a week depending on the availability of a skilled medical person to give the intramuscular injections. Injectable anti-TB drugs should be given once daily, i.e. do not split the dose over the day. If adverse effects are problematic in

a patient, the injectable agent may be given three times a week, preferably only after culture conversion *(11)*.

- When possible, oral drugs are to be given seven days a week under directly observation. Some programmes suggest giving all drugs six days a week, but it is not known if this is equal to seven days a week. Oral drugs should not be given five days a week (only the injectable agent is allowed to be on a five days a week schedule, see above).
- Pyrazinamide can be used for the entire treatment. Many drug-resistant TB patients have chronically inflammed lungs, which theoretically produce the acidic environment in which pyrazinamide is more effective. Alternatively, in patients doing well, pyrazinamide can be stopped with the injectable drug if the patient can continue with at least three likely effective drugs.
- In MDR treatment strategies that initially enrol patients based on their strain being resistant to rifampicin alone, isoniazid may be included in the MDR regimen until DST to isoniazid can be done to determine if the isoniazid should be continued.
- **Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization (conditional recommendation, very low quality evidence)** *(1,33)*.

5.7.2 Adjusting an empiric standardized regimen or designing an individualized regimen

Empiric standardized regimens often need to be adjusted based on patient clinical history, once additional history or when DST results becomes available. Individual regimens are designed based on DST of the infecting strain, patient's history of TB treatment and contact history. Figure 5.1 describes the steps to build a regimen for drug-resistant TB treatment.

Figure 5.1 Building an MDR-TB Regimen *(34)*

STEP 1	**Choose an injectable (Group 2)**	**Kanamycin** **Amikacin** **Capreomycin**
	Choose a drug based on DST and treatment history. Streptomycin is generally not used because of high rates of resistance in patients with MDR-TB.	
STEP 2	**Choose a higher generation fluoroquinolone (Group 3)**	**Levofloxacin** **Moxifloxacin**
	Use a later generation fluoroquinolone. If levofloxacin (or ofloxacin) resistance is documented, use moxifloxacin. Avoid moxifloxacin if possible when using bedaquiline or delamanid (see Annexes 4.1–4.2).	
STEP 3	**Add Group 4 drugs**	**Cycloserine/terizidone** **Para-aminosalicylic acid (PAS)** **Ethionamide/prothionamide**
	Add two or more Group 4 drugs until there are at least four second-line anti-TB drugs likely to be effective. Ethionamide/prothionamide is considered the most effective Group 4 drug. Consider treatment history, side-effect profile, and cost. DST is not considered reliable for the drugs in this group.	

STEP 4	**Add Group 1 drugs**	**Pyrazinamide** **Ethambutol**
	Pyrazinamide is routinely added in most regimens; ethambutol can be added if the criteria for an effective drug are met (see Section 5.7.1 for definition of "effective drug"). If isoniazid is unknown or pending it can be added to the regimen until DST results become available, see Section 5.8.	
STEP 5	**Add Group 5 drugs**	**Bedaquiline** **Delamanid** **Linezolid** **Clofazimine** **Amoxicillin/clavulanate** **Imipenem/cilastatin plus clavulanate** **Meropenem plus clavulanate** **High-dose isoniazid** **Clarithromycin** **Thioacetazone**
	Consider adding Group 5 drugs if four second-line anti-TB drugs are not likely to be effective from Groups 2–4. If drugs are needed from this group, it is recommended to add two or more. DST is not standardized for the drugs in this group. The drug–drug interactions between bedaquiline and delamanid have not been established and a recommendation about its combined use is not made in the WHO interim policy on these two drugs.	

5.8 Designing a treatment strategy for the drug-resistant TB component of the TB programme

Treatment strategies for drug-resistant TB may vary depending on access to DST and drugs, rates of drug-resistant TB, HIV prevalence, technical capacity and financial resources. **TB programmes may need to adjust the strategy to meet special circumstances and the local context.**

Representative DST survey data for different types of patients – new, relapse, retreatment after loss to follow-up, failure of initial or retreatment with first-line anti-TB treatment, and failure of treatment with second-line anti-TB drugs – are critical when making choices in treatment strategies.

For a standardized regimen that will treat the vast majority of patients with four effective second-line anti-TB drugs plus pyrazinamide, it is may be necessary to use more than four second-line drugs plus pyrazinamide to cover all possible resistance patterns.

When using an empiric standardized regimen, TB programmes are strongly encouraged to also order drugs from groups and classes that are not routinely included in the standardized regimen. For example, a programme that uses an empiric standardized regimen that does not include PAS will still need PAS in the following situations: (i) patients intolerant to one of the core drugs; (ii) pregnant patients with drug-resistant TB who cannot take all the drugs in the standard regimen; (iii) as part of a regimen in whom the standardized MDR treatment

regimen has failed or in regimens for XDR-TB. All programmes are encouraged to have regimens designed to treat XDR-TB for when the standardized MDR regimen fails.

In MDR treatment strategies that initially enrol patients based on their strain being resistant to rifampicin alone, isoniazid may be included in the standard regimen until DST to isoniazid can be done to determine if it should be continued. Even when mono- or poly-rifampicin resistance is relatively common, isoniazid can be added to the regimen. However, in situations where mono- or poly-rifampicin resistance is extremely rare (only 1% or 2% of all rifampicin resistance), it is reasonable to leave isoniazid out of an empiric standardized MDR treatment regimen; it can be added later if the patient's strain is determined to be susceptible.

BOX 5.2 EXAMPLES OF STANDARDIZED AND INDIVIDUALIZED REGIMEN DESIGN

EXAMPLE 1: A standardized MDR regimen based on drug resistance survey data where resistance to second-line anti-TB drugs is low.
Survey data from 200 consecutively enrolled **relapse** patients from a resource-constrained area show that 15% have MDR-TB and 1.5% have mono- or poly-rifampicin resistance (this translate roughly to 91% of the rifampicin resistance as MDR-TB and 9% as mono- or poly-rifampicin resistance). Of these MDR-TB cases, resistance to other drugs is E = 30%, S = 60%, Z = 20%, Ofx = 3%, Km = 5%, Cm = 3%, XDR-TB = 0%. There is virtually no history of use of any of the second-line drugs in the area. What re-treatment strategy is recommended in this group of relapse patients?

Answer: Given the above circumstances, one strategy is to test all relapse patients with a rapid DST such as Xpert MTB/RIF. If rifampicin resistance is found it is likely there will also be isoniazid resistance. The use of Xpert MTB/RIF as a diagnostic tool in a population with an MDR-TB prevalence of 15% (and rifampicin resistance prevalence of 15 + 1.5 = 16.5%) will result in a high positive predictive value of rifampicin resistance. Therefore, we can be confident that most Xpert RIF-positive results from this group of relapse patients are true positives (See Chapter 4 and Table 4.1 for further discussions on confirmation of DST).

Information from drug resistance surveys is important to determine if isoniazid should be added routinely to a standardized MDR regimen while awaiting DST results to isoniazid. If a line probe assay rapid test for isoniazid can be done then isoniazid can be included for those testing susceptible (high-dose isoniazid can be considered for those testing positive for inhA gene on line probe assay rapid test). If a longer DST test for isoniazid is being done, then isoniazid can be included in the regimen until results are known. An example of an empiric standardized regimen for those with RR-TB or MDR-TB could be:

8 Am-Lfx-Pto-Cs-Z-(+H)/12 Lfx-Pto-Cs-Z-(±H).

- Other options for drugs in this regimen include Km or Cm as the injectable drug, ethionamide instead of prothionamide, other fluoroquinolones (later-generation ones are much preferred), and PAS can replace cycloserine if the latter cannot be used.

- Isoniazid is given in normal doses until DST results become available; isoniazid can be continued if susceptible, stopped if resistant or adjusted to high-dose isoniazid if low level resistance is present (or InhA gene is present).
- Pyrazinamide can be stopped in the continuation phase for those patients with minimal lung damage and who are doing well.

DST to second-line drugs should be done at the start of treatment. If resources for DST to second-line drugs are constrained, it can be done in those patients that do not respond to the standard regimen. For example, those still smear- or culture-positive at month three.

EXAMPLE 2: A standardized MDR regimen based on drug resistance survey data where resistance to second-line anti-TB drugs is high. Survey data from 300 consecutively enrolled patients with treatment failure **of a new regimen** from a resource-constrained area show that 40% have MDR-TB and 0.3% have mono- or poly-rifampicin resistance (this translates roughly to 99% of the rifampicin resistance as MDR-TB and less than 1% as mono- or poly-rifampicin resistance). Of these MDR-TB cases, resistance to other drugs is E = 60%, S = 90%, Z = 40%, Ofx = 24%, Km = 29%, Cm = 3%, XDR-TB = 16%. There is considerable second-line drug use in the private sector in the area. What re-treatment strategy is recommended in this group of relapse patients?

Answer: Given the circumstances, one strategy is to test all relapse patients with a rapid DST such as Xpert MTB/RIF. If rifampicin resistance is found it is highly likely there will also be isoniazid resistance. The use of Xpert MTB/RIF as a diagnostic tool in a population with an MDR-TB prevalence of 40% will result in a very high positive predictive value of rifampicin resistance. Therefore, we can be confident that most Xpert RIF-positive results from this group of relapse patients are true positives (See Chapter 4 and Table 4.1 for further discussions on confirmation of DST).

The information from drug-resistant surveys also reveals that mono- and poly-rifampicin resistance is quite rare. An example of an empiric standardized regimen for those with RR-TB or MDR-TB could be:

8 Cm-Lfx-Eto-Cs-PAS-Z/12 Lfx-Eto-Cs-PAS-Z.

Other options for drugs in this regimen include prothionamide instead of ethionamide; later-generation fluoroquinolone must be used in this regimen with moxifloxacin being an option. There is little value of routinely adding isoniazid in the empiric regimen, but it can be added if further DST reveals susceptibility.

DST for second-line drugs for all MDR-TB cases at the start of treatment is instrumental to the programmatic design of an effective regimen under these circumstances. If the patient does have resistance to second-line drugs the empiric standard regime will need to be adjusted, see Section 5.15 on XDR-TB below and the Annexes 4.1 and 4.2 for options to incorporate bedaquiline or delamanid into regimens with second-line drug or in patients at high risk for treatment failure or death.

EXAMPLE 3. A patient in whom two courses of first-line anti-TB drugs have failed (2HREZ/4HR followed by 2SHREZ/HREZ/5HRE) with known DST pattern. DST results reveal that the infecting strain is resistant to H-R-S and susceptible to all

other medications including E-Km-Cm-Ofx; resistance to Z is unknown. The patient has received HRE for three months since the date of the DST. What individualized regimen is recommended?

Answer: This patient received two courses of treatment containing E and Z, and was on functional monotherapy with E for at least three months. The utility of ethambutol must be questioned despite the DST results. Pyrazinamide should be included in the regimen since it has been shown to increase the chance of cure when added in this circumstance (DST for Z unknown). Therefore, Z should be added to the regimen and E in this circumstance is generally not added. The injectable of choice may depend on the prevalence of resistance in the community, but since this patient never received Km, Km is low in cost, and if the DST is reported to be susceptible it may be the first choice in this case: **Z-Km-Lfx-Eto-Cs**

Note: Other options for drugs in this regimen include amikacin or capreomycin for the injectable drug, prothionamide instead of ethionamide, moxfloxacin instead of levofloxacin, and PAS can replace cycloserine if the latter cannot be used.

Box 5.2 provides three examples to design an MDR treatment regimen. The first example is designing a standardized regimen based on drug resistance survey data and the second example illustrates designing a regimen based on individual DST. Regimen design for XDR-TB is described in Section 15.5.

Some programmes or clinicians may choose to use a shorter (e.g. 9–12 months) MDR-TB treatment regimen consisting of combinations of later-generation fluoroquinolones (moxifloxacin or gatifloxacin), clofazimine, ethambutol and pyrazinamide throughout the treatment period supplemented by prothionamide, kanamycin, and high-dose isoniazid during an intensive phase. The evidence for these shorter regimens comes from limited observational studies. By May 2014, only one study of a patient series in Bangladesh using a short regimen had as yet been published in a peer-reviewed journal *(17)*. An ongoing randomized clinical trial is evaluating the efficacy and safety of a shorter regimen to treat MDR-TB treatment and results should be available around 2017 *(52)*. Those who choose to use shorter regimens should be aware that these regimens have not been evaluated in the treatment of XDR-TB, and are likely to acquire additional resistance in patients already harbouring bacilli resistant to second-line drugs. Hence such regimens should not be considered for treatment of XDR-TB, among patients with demonstrated resistance to a second–line injectable or any fluoroquinolone, or for patients who have been previously exposed for more than one month to second-line anti-TB drugs. The combined off-label use of clofazimine and other drugs that prolong the QTc interval on the ECG (i.e. fluoroquinolones) in these regimens require active pharmacovigilance (see Chapter 11) to enable proper surveillance management of safety issues. The longer treatment regimens for MDR-TB represent the standard of care that has been used more widely and for much longer *(53)*; they also have shown to bear good outcomes in a number of countries and the adverse drug reactions associated with them have been well documented *(54)*. It is therefore imperative that clinicians and/or NTPs pursue an informed consent process with patients before the start of treatment, under the oversight of a national or local ethics committee. Some

programmes may choose to enrol cohorts of patients for treatment with shorter regimens within the context of observational studies, aimed at producing evidence on its safety and effectiveness to inform local and global policy. Adherence to the international standards of good clinical practice should be applied by the corresponding programme managers of those observational studies, including appropriate independent monitoring *(55)*.

5.9 Duration of the intensive phase (length of use of injectable drugs)

The time the MDR-TB patient is on injectable anti-TB drugs is referred to as the intensive phase of treatment.

In the treatment of patients with MDR-TB, an intensive phase of eight months is suggested for most patients, and the duration may be modified according to the patient's response to therapy (conditional recommendation, very low quality evidence) *(1)*.

The main indication of response to therapy is smear- and culture-conversion (defined in Chapter 2), however, the overall clinical picture (weight gain, resolution or improvement of respiratory symptoms and/or lesions in pulmonary images) can also be taken into consideration in deciding whether to continue an injectable agent for longer than eight months. In a meta-analysis conducted in the preparation of the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis* ***(1)***, there was no demonstrated benefit of injectable phases beyond eight months and, in general, failure of treatment should be started to be considered for those who have not culture converted by month eight.

In respect to smear- and culture-conversion, expert opinion is that the intensive phase should **also** continue for at least four months past conversion; but little evidence exists and the optimal time past conversion has not been determined. The optimal duration of the injectable phase in patients with minimal disease has also not been determined; programmes may decide on a case-by-case basis that such patients could receive less than an 8-month intensive phase, provided that they have converted for at least four months.

Intermittent therapy with the injectable agent (three times a week) can also be considered in patients who have been on the injectable for a prolonged period of time and when toxicity becomes a greater risk to the patient *(11)*. This is based on expert opinion, as no direct comparisons of three times a week versus daily doses exist.

If the patient was on an empiric regimen of more than four second-line anti-TB drugs, some of the oral second-line anti-TB drugs, in addition to the injectable agent, can be considered for suspension at the end of the intensive phase. This is usually done when DST results show susceptibility to at least four second-line agents, the drugs are still considered effective, and the patient has had a good response to therapy.

Usually, pyrazinamide is continued for the entire treatment, especially if there is extensive parenchymal lung damage. However, there is no data on the optimal length of time to use pyrazinamide in MDR-TB treatment. If the patient has minimal disease, some clinicians stop

pyrazinamide with the injectable agent at the end of the intensive phase. In all situations, the patient should at the very least continue with three of the most potent second-line anti-TB drugs that are determined to be effective against the patient's infecting strain of *M. tuberculosis*. For the length of treatment with bedaquiline or delmanid see Annexes 4.1 and 4.2 respectively. Both of these anti-TB drugs are used for part of the intensive phase (usually 6 months) and are not presently recommended for the whole MDR-TB treatment duration.

5.10 Total duration of treatment

In the treatment of patients newly diagnosed with MDR-TB (i.e. not previously treated for MDR-TB), a total treatment duration of 20 months is suggested for most patients, and the duration may be modified according to the patient's response to therapy (conditional recommendation, very low quality evidence) *(1)*.

The main method used to assess response to therapy is through smear- and culture-conversion (defined in Chapter 2); however, clinical symptoms and radiographs can also be taken into consideration when deciding if treatment should be longer than 20 months. Whether the total treatment duration should be based on time past conversion has not been determined. Some clinicians and programmes may prefer to treat at least twelve months past conversion (but not less than 20 months total).

The meta-analysis conducted in preparation of the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis* ***(1)*** indicated that in patients previously-treated with MDR regimen a total duration of treatment of more than 24 months was more successful, although the number of patients observed was relatively small. Therefore, patients previously treated for MDR-TB (and often XDR-TB patients) generally receive at least 24 months of therapy in most programmes.

5.11 Extrapulmonary and central nervous system drug-resistant TB

Extrapulmonary drug-resistant TB is treated with the same strategy and duration as pulmonary drug-resistant TB; the one exception is central nervous system involvement. If the patient has symptoms suggestive of central nervous system involvement and is infected with drug-resistant TB, then the regimen should use drugs, which have adequate penetration into the central nervous system. Isoniazid, pyrazinamide, prothionamide/ethionamide and cycloserine, all have good penetration into the cerebrospinal fluid, whereas kanamycin, amikacin and streptomycin do so only in the presence of meningeal inflammation. Additionally, the penetration of capreomycin is less studied and not well determined. PAS and ethambutol have poor or no penetration. The fluoroquinolones have variable cerebrospinal fluid penetration, with better penetration of moxifloxacin based on animal studies. There is no data on central nervous system penetration of clofazimine or clarithromycin. Linezolid is believed to penetrate the central nervous system, and has been used in meningitis treatment *(35)*. Imipenem has good central nervous system penetration, but children with meningitis treated with imipenem, had high rates of seizures (meropenem is preferred for meningitis cases and children) *(11,36,37)*. No data are available regarding CNS penetration of bedaquiline or delamanid.

5.12 Surgery in treatment of drug-resistant TB

The most common surgical procedure in patients with pulmonary drug-resistant TB is resection surgery (taking out part or all of a lung). Large case series analysis has proven resection surgery to be effective and safe under appropriate surgical conditions *(38)*. It is considered an adjunct to chemotherapy and appears to be beneficial for patients when skilled thoracic surgeons and excellent postoperative care are available *(39)*. It is not indicated in patients with extensive bilateral disease. The case series that showed surgery to be effective may have a selection bias, as very sick patients with co-morbidities, older patients, and those with extensive disease are often excluded from surgery.

Resection surgery should be timed such that the patient has the best possible chance of cure with the least morbidity. Thus, the timing of surgery may be earlier in the course of the disease when the patient's risk of morbidity and mortality are lower, for example, when the disease is still localized to one lung or one lung lobe. In other words, surgery should not be considered a last resort. Generally, at least two months of therapy should be given prior to resection surgery to decrease the bacterial infection in the surrounding lung tissue. Even with successful resection, the intensive phase and total treatment duration should be guided by the recommendations in Sections 5.9 and 5.10.

Specialized surgical facilities should include stringent infection control measures, given that infectious substances and aerosols are generated in large quantities during surgery, mechanical ventilation and post-operative pulmonary hygiene manoeuvres.

Many programmes will have limited access to surgical interventions. General indications for resection surgery for programmes with limited access to surgery include patients that remain smear-positive, with resistance to a large number of drugs; and localized pulmonary disease. Computerized tomography, pulmonary function testing and quantitative lung perfusion/ventilation is recommended as part of the preoperative work-up. In programmes with sub-optimal surgical facilities with no trained thoracic surgeons, resection surgery should not be performed as the result may increase morbidity or mortality.

5.13 Adjuvant therapies in drug-resistant TB treatment

The role of adjuvant therapies has not been well established. Nonetheless, some adjunctive modalities have proven beneficial in specific indications (i.e. the use of corticosteroids in certain forms of TB such as central nervous system and pericardial involvement) while others show potential to improve outcomes (i.e. immunomodulators) *(40)*.

5.13.1 Corticosteroids

In drug-resistant TB patients, the adjuvant use of corticosteroids has been shown not to increase mortality when the patient is on an effective regimen. Corticosteroids can be beneficial in conditions like severe central nervous system or pericardial involvement. Expert opinion is that they may also help in respiratory insufficiency and miliary TB. Prednisone is commonly used with a tapering of dosage over several weeks *(21)*.

Corticosteroids may also alleviate symptoms in patients with an exacerbation of obstructive pulmonary disease. When a more immediate response is needed, injectable corticosteroids are often initially used. Corticosteroids can weaken the body's response to fight TB and therefore should only be used if clearly indicated and if the patient is on an adequate effective regimen. If corticosteroids are used in an inadequate regimen, this could accelerate the deterioration of the patient.

5.13.2 Adjunctive therapy using immunotherapeutic interventions

Results from the use of immunotherapeutic interventions have thus far been only moderately encouraging. Evidence reviewed by an expert group in 2007 concluded that immunomodulators have the potential to improve outcomes of all TB including M/XDR-TB *(40)*. Further evaluation of the efficacy and safety of such therapy is needed before any recommendations on specific therapy can be made.

5.14 Nutritional support

Drug-resistant TB treatment (as with all TB treatment) and care should contain integrated nutritional assessment counselling and support for the duration of the illness.

In addition to causing malnutrition, as in other forms of TB, drug-resistant TB can be exacerbated by poor nutritional status. Without nutritional support, patients, especially those already suffering from borderline hunger, can become enmeshed in a vicious cycle of malnutrition and disease. The second-line anti-TB medications can also further decrease appetite, making adequate nutrition a greater challenge. Providing free food probably does improve weight gain during treatment, and is thought to improve quality of life but further research is necessary *(41)*. Food support may improve treatment adherence in settings were food insecurity is an important access barrier.

Vitamin B6 (pyridoxine) should be given to all MDR-TB patients receiving cycloserine or terizidone, and a high dosage of isoniazid or linezolid to prevent neurological side-effects (see Chapter 11 for dosing and more information). Vitamin (especially vitamin A) and mineral supplements can be given in areas where a high proportion of the patients have these deficiencies. If multivitamins and minerals (zinc, iron, calcium, etc.) are given they should be dosed three to four hours apart from the fluoroquinolones, as these can interfere with the absorption of these drugs. Of note, no studies have assessed whether vitamins improve TB cure. Vitamins probably do not improve weight gain, and no studies have assessed their effect on quality of life *(41)*.

5.15 Treatment of XDR-TB

XDR-TB was first defined in 2006 and is estimated to occur in about 9.0% of MDR-TB patients *(42)*. While it occurs all over the world, it has been reported as a significant problem in a number of countries *(39,42)*. Likelihood of cure has proven to be much lower than in other MDR-TB cases and deaths are higher, especially in PLHIV *(39,44–48)*. There is very limited data on the different clinical approaches to XDR-TB and a recent review of treatment outcomes of XDR-TB patients could not find any associations between any specific drug or regimen and success; however, the analysis did indicate that success in XDR-TB patients

was highest if at least six drugs were used in the intensive phase and four in the continuation phase *(48)*. A different meta-analysis provides empiric evidence that the use of later-generation fluoroquinolones significantly improved treatment outcomes in patients with XDR-TB, even though DST demonstrated resistance to a representative fluoroquinolone *(47)*.

While data on efficacy and safety is limited, the incorporation of bedaquiline or delamanid into regimens designed to treat XDR-TB may be considered *(49,50)* (See Annexes 4.1 and 4.2).

BOX 5.3 TREATMENT MANAGEMENT FOR PATIENTS WITH DOCUMENTED, OR ALMOST CERTAIN, XDR-TB

- Use pyrazinamide and any other Group 1 agent that may be effective.
- Use an injectable agent to which the strain is susceptible and consider an extended duration of use (12 months or possibly the whole treatment). If resistant to all injectable agents consider designing the regimen with an injectable agent that the patient has never used before[a] or consider designing the regimen without an injectable agent. If toxicity is a limiting factor for the use of the injectable agent, and one of the injectable agents is considered effective, consider using inhaled version via a nebulizer.[b]
- Use a higher-generation fluoroquinolone such as moxifloxacin or gatifloxacin.
- Use all Group 4 agents that have not been used extensively in a previous regimen or any that are likely to be effective.
- Add two or more Group 5 drugs (consider adding bedaquiline or delamanid (see Annexes 4.1 and 4.2).
- Consider adding a new investigational drug eligible for use under the compassionate use scheme if policy of the WHO endorses[c] its use for XDR-TB (see Chapter 22).
- Consider high-dose isoniazid treatment if low-level resistance or absence of the katG gene is documented.
- Consider adjuvant surgery if there is localized disease.
- Ensure rigorous respiratory infection control measures at the site where the patient is being treated (Chapter 14).
- Consider the option of treatment in a hospital if the clinical condition of the patient is poor or major comorbidities coexist, or a shelter if the social condition of the patient prevents proper home care.
- Manage HIV co-infection as per Chapter 8.
- Provide comprehensive monitoring (see Chapter 9) and full social support to enable adherence to treatment (see Chapter 10).
- Ensure that all patients have full access to palliative and end-of-life care services, with a patient-centred approach to relief the suffering of the disease and its treatment (see Chapter 13).

[a] This advice is made because while the accuracy and reproducibility of DST to injectables are good, there is little data on clinical efficacy of injectable resistant in DST. Options with XDR-TB are very limited and some strains may be affected *in vivo* by an injectable agent even though they are testing resistant *in vitro*.

[b] No experience of the use of nebulization of injectable agents for TB has been published. Kanamycin and amikacin have been used via nebulization for cystic fibrosis. The effectiveness and safety of delivering injectable drugs via nebulization in TB is unknown. Do not count nebulized aminoglycosides as one of the four effective second-line anti-TB drugs needed to form an effective regimen. Renal toxicity and ototoxicity can still occur with nebulization.

[c] Check the WHO website for periodic updates on the use of new investigational drugs and also see Chapter 22.

New anti-TB drugs are currently being developed and programme managers should keep abreast of WHO recommendations as they are released and updated though the website of the Task Force for New Drug Policy Development *(51)*. For more information on compassionate use and early access programmes see Chapter 22.

Box 5.3 summarizes the latest expert consensus on managing XDR-TB and Box 5.4 provides an example of designing a regimen for the treatment of XDR-TB.

BOX 5.4 EXAMPLE OF AN XDR-TB REGIMEN DESIGN

EXAMPLE 1. A patient failed the standardized regimen of Z-Km-Lfx-Eto-Cs and remained sputum smear-positive after eight months of treatment. The DST from a specimen taken four months ago revealed resistance to HRZE-S-Km-Cm-Lfx and susceptibility to Eto. What treatment regimen is recommended?

Answer: The patient may now have developed resistance to Eto as the patient was on only one or two effective drugs since the specimen collection and has remained smear-positive. Cs, while not tested for DST in this example, is also likely not effective with the strain being resistant. Furthermore, the DST is not reproducible or reliable enough for Eto, E or Z and we should depend on history more than DST – all of which are likely compromised. The later-generation fluoroquinolone Mfx may have some effect, even though Lfx is testing resistant. Options are limited and there is no expert consensus on a specific regimen that would be best for this patient. See Annexes 4.1 and 4.2 for more information on the use of Bdq or Dlm in XDR-TB.

The following regimens would be considered acceptable options to treat this case of XDR-TB (these are based on Figure 5.1 and Box 5.3):

- Z-Mpm (plus Clv)-Mfx-PAS-Lzd-Cfz
- Z-Mpm (plus Clv)-Bdq-PAS-Lzd-Cfz
- Z-Mpm (plus Clv)-Dlm-PAS-Lzd-Cfz
- Z-Mfx-PAS-Amx (plus Clv)-Cfz-Lzd

Notes:

- Other possibilities exist apart from the above four regimens.
- The injectable drugs in the regimen are generally used for eight months but in cases where there is confidence in very few drugs and high confidence in the injectable agent, it can be used for a longer period.

For dosing of drugs see Part 3 – Individual Drug Sheets.

- High-dose isoniazid can be added to any regimen if low-level resistance or absence of the katG gene is documented.
- If Bdq or Dlm is added to the regimen, currently its maximum recommended duration of use is six months (see Annexes 4.1 and 4.2).
- Adding Clv to a regimen containing a carbapenem (Mpm or Ipm) may improve the effectiveness of the carbapenem *(56)*. The Clv is often given as 125 mg orally 30 minutes prior to the IV infusion. If Clv is not available without the combination of Amx added to it, it can be given with the Amx component. It is not known which carbapenem (Mpm or Imp/Cls) is more effective against tuberculosis. Mpm has advantages in children.
- If a carbapenem is not an available option, Amx (plus Clv) can be substituted in the any of the first three regimens but many experts consider the combination of a carbapenem (plus Clv) superior to Amx (plus Clv). The combination of carbapenems and clavulanate is bactericidal in vitro and has demonstrated an improved survival of mice infected with TB (56). There is very limited data on the effectiveness of carbapenems (plus Clv) in humans.

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CHAPTER 6

Mono- and poly-resistant strains (drug-resistant TB other than MDR-TB)

6.1 Introduction

Mono- and poly-resistance are defined in Chapter 2. For the purpose of discussion in this chapter, mono-resistance cases refer to resistance to a single first-line drug, and poly-resistance cases refer to resistance to two or more first-line drugs but not to both isoniazid and rifampicin i.e. not MDR–TB.

Advisory note: The guidance in this chapter is based on expert opinion and has NOT undergone the process for evidence gathering, assessment and formulation as outlined in the WHO Handbook for Guideline Development *(1)*. (A full evaluation of the evidence of the optimal method to treat mono- and poly-resistance involving isoniazid is planned by WHO in 2015).

TB control programmes generally focus on MDR-TB because these highly resistant strains are the most difficult to treat, and cause much morbidity and mortality. Yet drug resistance surveys have shown that mono- and poly-resistant TB are actually more common than MDR-TB (global prevalence of MDR-TB in new cases is around 3.5% while the prevalence of mono- and poly-resistant strains is almost 17% *(2)*). Many of these cases contribute towards amplification of resistance and, eventually, lead to MDR if they are not properly managed. Mono-resistant and poly-resistant TB often remain undiagnosed in resource-limited settings because DST is not available outside of designated groups of patients who are considered to be at high risk for MDR-TB. This means that undiagnosed mono- and poly-resistant TB are likely often to be treated with standardized first-line drug regimens. Some of these patients may experience

transient clinical and bacteriological improvement but are at risk for failure or relapse, often with amplified resistance patterns. Correct treatment of mono- and poly-resistant TB can therefore prevent the development of MDR-TB.

Through evidence that relied on simulations from modelling work, performing drug susceptibility testing (DST) in all patients before treatment using a rapid test that detects resistance to isoniazid and rifampicin was the most cost-effective strategy for averting deaths and preventing acquired MDR-TB *(3)*. **Rapid DST of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis of TB, subject to available resources (conditional recommendation/very low quality evidence)** *(4)***.** Performing rapid DST to isoniazid and rifampicin at the start of treatment would help identify many more cases of mono- and poly-resistant TB. Clinicians should therefore expect to see more cases of mono- and poly-resistant TB in the future as rapid DST becomes more commonly used.

The WHO standardized six-month regimen for new patients (2HREZ/4HR) or the eight-month regimen for retreatment patients (2SHREZ/1HREZ/5HRE)[6] for mono- or poly-resistance involving isoniazid or rifampicin does not give the required results for a significant number of cases. The WHO eight-month retreatment regimen, in particular, was thought previously to be adequate to treat lesser forms of resistance such as isoniazid mono- or poly-resistance, which are common in retreatment cases. While the sample sizes have been small, the few cohort studies of the outcomes of this regimen in the treatment of mono- or poly-resistant TB have shown poor results (failure rates were 18%–44% in those with isoniazid resistance) *(5)*. Furthermore, treatment of mono- and poly-resistance with WHO standardized first-line anti-TB drug regimens has been shown to increase the risk of treatment failure and even worse, amplification (acquisition of additional resistance) to multidrug resistance *(6–9)*. Very few randomized clinical trials have been performed to determine the best treatment for mono- or poly-resistant TB *(5)*. In the absence of such evidence, the following practices are based on limited data from observational cohort studies and the recommendations of expert panels. They also take into account that access to DST is evolving rapidly throughout the world.

6.2 Treatment of patients with mono- and poly-resistant TB

Resistance testing to both isoniazid and rifampicin using LPA gives results within a day or two. If conventional DST is used, however, the diagnosis may not be known for weeks or months. Because Xpert MTB/RIF only tests for rifampicin resistance, it cannot by itself distinguish between mono-resistant TB, poly-resistant TB and MDR-TB. (Rifampicin resistance when identified will be treated similar to MDR-TB, see below).

When the DST results are received, patients should undergo a careful evaluation to determine if the results are likely to accurately reflect the bacterial population at the time the test result was reported since it reflects the bacterial population at the time the sputum was collected (in other words, one should determine if the possibility of resistance amplification has taken place since the collection of the specimen for DST). For rapid DST, where the results return in just

[6] H=isoniazid; S=streptomycin; R=rifampicin; Z=pyrazinamide; E=ethambutol

a few days, there is unlikely to be amplification. However, results from conventional DST are available often several months after sputum collection and amplification may have taken place in the intervening period.

Further resistance should be suspected if the patient was on the functional equivalent of only one or two drugs for a significant period of time (usually considered as one month or more, but even time periods of less than one month on inadequate therapy can lead to resistance). See Box 6.1 for an example of how to accurately interpret a DST result of mono- or poly-resistance.

BOX 6.1 EXAMPLE OF EVALUATION OF DST IN A PATIENT WITH MONO- OR POLY-RESISTANCE

A patient's sputum is collected for DST at the start of treatment. Four months later the results are returned to the treating physician as susceptible to rifampicin and ethambutol but resistant to isoniazid. As the results did not come back until after fours months of treatment, consideration must be made of whether amplification of resistance has occurred.

If the patient entered the continuation phase with a fixed dose combination isoniazid–rifampicin tablet at month two of treatment, then *the patient was functionally receiving only rifampicin in the continuation phase for two months*. Resistance to rifampicin may have developed during the continuation phase in this patient. Thus, it is crucial to consider which functional drugs the patient received between the time of DST sputum sample collection and the time of the new regimen design (i.e. consider whether resistance has developed to any of the functional drugs).

If Xpert MTB/RIF is available, the rapid test should be performed to see if resistance to rifampicin has developed BEFORE changing to a mono- or poly-resistance regimen. If rifampicin resistance has developed, the regimen should be changed to an MDR-TB regimen.

The regimens in Table 6.1 are based on the assumption that the pattern of drug resistance has not changed during the interval between sputum collection and initiating a re-design of the anti-TB drug regimen. *Table 6.1 should therefore* ***not*** *be referred to if further resistance to any of the anti-TB drugs is suspected,* rather a regimen covering any possible amplification of resistance should be used until repeat DST can be performed and the results become available.

Finally, the reader is reminded that the DST result should be interpreted as only giving an indication that a drug is likely to be effective or not. A patient clinically doing poorly and failing a first-line treatment regimen could be resistant to all the drugs being given even though the DST reports susceptibility to some. In cases where the clinical history suggests the DST could be wrongly reporting susceptibility, it should err on the side of caution and not depend on the drug in question. In cases where DST is pan-susceptible and the patient is clinically and bacteriologically failing a TB regimen, adherence should be reviewed.

6.2.1 Patients with isoniazid mono-resistance

Patients diagnosed with isoniazid mono-resistance (or resistance to isoniazid and streptomycin only) are often treated with six to nine months of rifampicin, ethambutol and pyrazinamide *(5,10)*. However, because DST to ethambutol and pyrazinamide are not considered reliable enough to base individual patient treatment decisions, it is often unknown if the patient truly has mono-resistance to isoniazid and not a poly-resistant strain. (While DST to ethambutol and pyrazinamide are not reliable for routine regimen design, a DST from a reliable laboratory showing resistance to ethambutol or pyrazinamide should be taken as resistant and the drugs should not be relied upon in a regimen designed to treat mono- or poly-resistant TB.) The rifampicin–ethambutol–pyrazinamide regimen for the treatment of mono-isoniazid resistance treatment should be done with caution and with monitoring for possible rifampicin amplification. For example, patients not responding clinically and remaining smear- or culture-positive at two to three months could be tested with Xpert MTB/RIF to determine rifampicin resistance and the regimen adapted to an MDR-TB regimen if rifampicin resistance is detected.

In addition, if the certainty of the efficacy of ethambutol or pyrazinamide is in question based on clinical history, the regimen for isoniazid poly-resistance with resistance pattern H, E, Z, (± S) could be used (see Table 6.1).

Finally, some experts treat mono-resistant isoniazid strains with rifampicin–ethambutol–pyrazinamide plus a fluoroquinolone. Monitoring for rifampicin resistance should still be done as per Table 6.1.

6.2.2 Patients with isoniazid poly-resistance

While there have been few studies of the treatment of isoniazid mono-resistance, there have been even fewer of the treatment of isoniazid poly-resistance *(5)*. Treatment of poly-resistant strains is particularly dangerous because of the higher risk of amplification to multidrug resistance if treatment fails. If rifampicin resistance develops, start an MDR-TB regimen.

6.2.3 New patients with rifampicin mono- and poly-resistance

The frequency of rifampicin mono- and poly-resistance can vary between different settings, but is often low. All TB patients infected with strains resistant to rifampicin should be treated using a full MDR-TB regimen, with isoniazid being added to/included in the regimen until DST results to isoniazid are available and appropriate adjustments to the regimen can be made. If DST of isoniazid shows susceptibility, isoniazid can be continued in the MDR-TB regimen. If isoniazid susceptibility is not known for a case of RR-TB, as in patients diagnosed using Xpert MTB/RIF alone, it is recommended to test for isoniazid using molecular testing such as line probe assays or conventional phenotypic methods. If isoniazid susceptibility cannot be ascertained, the addition of isoniazid to the regimen may be considered (see Chapter 5 for more information).

TABLE 6.1 **Treatment regimens for the management of mono- and poly-resistant TB**

PATTERN OF DRUG RESISTANCE	SUGGESTED REGIMEN	MINIMUM DURATION OF TREATMENT (MONTHS)	COMMENTS[a]
H (± S)	R, Z and E (± FQ)	6–9	Use Xpert MTB/RIF at month 0, 2, and 3 and if rifampicin resistance is found switch to full MDR-TB treatment. Some experts add a FQ to the regimen.
H and E (± S)	R, Z, and FQ	9–12	Use Xpert MTB/RIF at month 0, 2, and 3 and if rifampicin resistance is found switch to full MDR-TB treatment and check DST to first- and second-line anti-TB drugs. Some experts recommend using a second-line injectable agent for the first three months *(11)*.
H, E, Z, (± S)	R, FQ, plus ethionamide, plus a second-line injectable agent for the first 2–3 months. (± Z)	18	A longer course (6 months) of the second-line injectable may strengthen the regimen for patients with extensive disease. Z should be added if resistance is uncertain. Use Xpert MTB/RIF at month 0, 2 and 3 and if rifampicin resistance is found switch to full MDR-TB treatment and check DST to second-line anti-TB drugs. If culture positive after month 2, repeat DST to first- and second-line anti-TB drugs.
R mono- or poly-drug resistance	Full MDR-TB regimen plus H	20	See Chapter 5 for MDR-TB regimen design and Chapter 9, 10, and 11 for initiation of treatment and monitoring. See Chapter 5, Section 5.8 for indications of adding H to regimens when DST to R is resistant and H is unknown.

[a] The use of Xpert MTB/RIF at month 0, 2 and 3 is not intended for monitoring response to therapy as the test may be positive for *M. tuberculosis* for patients with a positive response and even after cure. Rather, it is intended only to detect rifampicin resistance amplification during therapy.

H=isoniazid; S=streptomycin; R=rifampicin; Z=pyrazinamide; E=ethambutol; FQ=fluoroquinolone.

6.3 Registration and reporting of patients with mono- and poly-resistant TB

Patients who receive mono- and poly-drug-resistant regimens, should be registered in the Second-line TB treatment register (see Chapter 2, Section 2.3), but clearly designated as not having MDR-TB. The only exception would be patients who receive mono- or poly-drug-resistant regimens using only first-line anti-TB drugs – such cases can be recorded in the Basic Management Unit (BMU) TB register and noted as a modified first-line regimen for mono- or poly-resistance.

In sites testing with Xpert MTB/RIF alone, the indicators should be modified in the Second-line TB treatment register to include RR-TB cases started on a full MDR-TB treatment regimen. Likewise, reporting of detection, enrolment, interim results and final outcomes should include both RR-TB and MDR-TB cases together given that both of these types of patients receive a full MDR-TB regimen (see Chapter 2).

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CHAPTER 7

Treatment of drug-resistant TB in special conditions and situations

7.1 Introduction

This chapter outlines the management of drug-resistant TB in selected special conditions and situations. HIV infection is addressed separately in Chapter 8.

7.2 Pregnancy

All female patients of childbearing age should be tested for pregnancy upon initial evaluation. Pregnancy is not a contraindication for treatment of active drug-resistant TB, but poses great risk to the lives of both the mother and fetus *(1,2)*. Pregnant patients should be carefully evaluated, taking into consideration the gestational age and severity of drug-resistant TB. The risks and benefits of treatment should be carefully considered, with the primary goal of smear conversion to protect the health of the mother and child, both before and after birth. The following are some general principles to consider when treating pregnant women.

- **Benefits and risks of treatment.** Most pregnant patients should be started on treatment as soon as the diagnosis is made. However, since the majority of teratogenic effects occur in the

first trimester, treatment may be delayed until the second trimester when the patient is very stable with minimum disease. Delaying treatment carries a risk as TB can advance quickly in a pregnant patient. A decision to start treatment in the first trimester or to postpone until after the first trimester should be agreed to by at least the patient and the doctor, after analysis of the risks and benefits. Other family members, especially the father-to-be, may need to be consulted depending on the relevant family, religious, cultural and social dynamics. The decision is based primarily on clinical judgment established on the basis of signs/symptoms and severity/aggressiveness of the disease.

- **Treat with three or four second-line anti-TB drugs plus pyrazinamide.** Treat with three or four oral second-line anti-TB drugs which are likely to be highly effective (see Chapter 5) against the infecting strain plus pyrazinamide. The regimen should be reinforced with an injectable agent and other drugs as needed immediately postpartum *(3)*.
- **Avoid injectable agents.** Aminoglycosides can be particularly toxic to the developing fetal ear. Because there is little experience or evidence of the use of capreomycin in pregnancy, the risks/benefits of its use should be discussed with the mother. Capreomycin may also carry a risk of ototoxicity but is the injectable drug of choice if an injectable agent cannot be avoided because of an immediate life-threatening situation resulting from multidrug-resistant TB (MDR-TB). The option of using capreomycin thrice weekly from the start can be considered to decrease drug exposure to the fetus.
- **Avoid ethionamide**. Ethionamide can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies.
- **Consider termination of pregnancy if the mother's life is compromised.** When the condition of the mother is so poor that a pregnancy would carry a significant risk to her life, a medical abortion may be indicated. The decision is based primarily on clinical judgment of the severity of the disease, the effective treatment and care options available, and assessment of the risk/benefits with the mother. Whenever this decision is made, the TB programme, in coordination with other relevant health care providers, must facilitate access to safe abortion care in the context of the existing country legislation for abortion (For further information see *Safe abortion: technical and policy guidance for health systems*. 2nd edition. Geneva: World Health Organization; 2012).

Despite limited data on safety and long-term use of fluoroquinolones (cycloserine, para-aminosalicylic acid (PAS) and amoxicillin/clavulanate) in pregnancy, they are considered the drug of choice for MDR-TB treatment during pregnancy.

If the injectable agents, ethionamide/prothionamide, or other drugs were withheld because of the pregnancy, they can be added back postpartum to make a more complete regimen. There may not be a clear transition between the intensive phase and continuation phase, and the injectable agent can be given for three to six months postpartum even in the middle of treatment. Alternatively, if the patient is doing well and past the normal eight-month period for the injectable agent, it need not be added. Any addition of drugs should be mindful of the principle of never adding a single drug to a failing regimen.

The total treatment duration is the same as for MDR-TB treatment (see Chapter 5).

National TB control programmes should provide clear instructions on the management of MDR-TB in pregnancy and standardized regimens need adjustments in almost all cases.

The child should receive Bacillus Calmette–Guérin (BCG) vaccination at birth as per WHO policy.

7.3 Breastfeeding

In lactating mothers on treatment, most anti-TB drugs will be found in the breast milk in concentrations that would equal only a small fraction of the therapeutic dose used in an infant. However, any effects on infants of such exposure during the full course of drug-resistant TB treatment have not been established. Therefore, it is preferable to provide infant formula options as an alternative to breastfeeding. The infant formula should be available free of charge for the patient, especially in resource-poor settings, and the drug-resistant TB control programme must budget in advance for the estimated number of patients who may need this support. Clinicians and parents may agree to breastfeeding when the formula is not a feasible option. A woman who is breastfeeding and has active drug-resistant TB should receive a full course of anti-TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to the baby.

The mother and her baby should not be completely separated. However, if the mother is sputum smear positive, the care of the infant should be left to family members until she becomes sputum smear negative, if this is feasible. When the mother and infant are together, this common time should be spent in well-ventilated areas or outdoors. The mother should use a surgical mask (see Chapter 13) until she becomes sputum smear negative.

7.4 Contraception

Birth control is strongly recommended for all non-pregnant sexually active women receiving therapy for drug-resistant TB because of the potential consequences for both the mother and fetus resulting from drug-resistant TB treatment during pregnancy.

There is no contraindication to the use of oral contraceptives with non-rifamycin containing regimens. Patients who vomit directly after taking an oral contraceptive can be at risk of decreased absorption of the drug and therefore of decreased efficacy. These patients should be advised to take their contraceptives apart from times when they may experience vomiting caused by the anti-TB treatment medications. Patients who vomit at any time directly after, or within the first two hours after taking the contraceptive tablet, should use a barrier method of contraception until a full month of the contraceptive tablets being tolerated.

For patients with mono- and poly-resistant TB but who are susceptible to rifampicin, the use of rifampicin interacts with the contraceptive drugs resulting in decreased efficacy of protection against pregnancy. A woman on oral contraception while receiving rifampicin treatment may choose between two options following consultation with a physician: (i) the use of an oral contraceptive pill containing a higher dose of estrogen (50 μg); or (ii) the use of another form of contraception.

Condoms are a reasonable solution for patients who do not want to take additional pills and/or when protection against sexually transmitted diseases is also needed. Patients should be aware that condom use is not as effective as contraceptive pills, especially when not used correctly. Medroxyprogesterone intramuscular injections and other methods of contraception can also be considered (For further information on contraception see *Medical eligibility criteria for contraceptive use*. 4th edition. Geneva: World Health Organization; 2010).

7.5 Children

Children with drug-resistant TB generally have initial resistance transmitted from a primary case with drug-resistant TB. Evaluation of children who are contacts of drug-resistant TB patients is discussed in Chapter 13. When DST is available it should be used to guide therapy. Detection of drug-resistant TB in children is discussed in Chapter 4, Section 4.8.

The treatment of culture negative children with clinical evidence of active TB disease and a contact with a documented case of drug-resistant TB should be guided by the results of DST and the history of the contact's exposure to anti-TB drugs (also see Chapter 13) *(4)*.

There is limited reported experience on the use of second-line drugs for extended periods in children *(5)*. The risks and benefits of each drug should be carefully considered while designing a regimen. Frank discussions with family members is critical, especially at the outset of therapy. Drug-resistant TB is life-threatening, and no anti-TB drugs are contraindicated in children (although new anti-TB drugs that have recently been introduced into the market have no safety data on children and should be considered for use in any extreme life threatening cases, with risk/benefits fully disclosed, and intense safety monitoring). Children who have received treatment for drug-resistant TB have generally tolerated the second-line drugs well *(4–6)*.

Although fluoroquinolones have been shown to retard cartilage development in beagle puppies *(7),* similar effects in humans have not been demonstrated *(8,9)*. The benefit of fluoroquinolones in treating drug-resistant TB in children have shown to outweigh any risk. Additionally, ethionamide, para-aminosalicylic acid (PAS) and cycloserine have been used effectively in children and are well tolerated.

In general, anti-TB drugs should be dosed according to body weight (See Annex 3 for weight-based dosing). Monthly monitoring of body weight is therefore especially important in paediatric cases, with adjustment of doses as children gain weight.

Expert opinion is that all drugs, including fluoroquinolones, should be dosed at the higher end of the recommended ranges whenever possible, except ethambutol. Ethambutol should be dosed at 15 mg/kg, and not at 25 mg/kg as sometimes used in adults with drug-resistant TB, as it is more difficult to monitor optic neuritis in children.

Dosing of anti-TB drugs in children is weight-based and presented in Annex 3.

In children, microbiological monitoring of the response to treatment is often difficult (for the same reasons it is difficult to obtain a microbiological diagnosis). This makes it difficult to diagnose treatment failure in children. Persistent abnormalities on chest radiographs do not necessarily signify a lack of improvement. In children, weight loss or, more commonly, failure

to gain weight adequately in the presence of proper nutritional intake, is of particular concern and often one of the first (or only) signs of treatment failure. This is another key reason to monitor weight carefully in children.

Early diagnosis, strong social support, parental and family counselling and a close relationship with the health care providers may help to improve outcomes in children.

More information on the management of MDR-TB in children can be found in other sources *(5,10)*.

BOX 7.1 EXAMPLE OF REGIMEN DESIGN FOR PAEDIATRIC CASES

A mother on treatment for MDR-TB for nine months has been smear-negative and culture-negative for six months. She brings her child to the health centre for evaluation. The child is 11 months old and weighs 8.1 kg. The child received BCG vaccination at birth and now presents with four months of failure to thrive, poor appetite and intermittent low-grade fever for three months. Tuberculin skin testing is 16 mm, and chest radiography reveals hilar adenopathy but with no infiltrates. There are no other known TB contacts. TB was first diagnosed in the mother shortly after giving birth to the child. The mother had both Category I and II treatment failure. Her resistance pattern from the start of treatment for drug-resistant TB was:

- resistance to H, R, E, S;
- susceptible to Amk-Cm-Ofx; and
- DST to PAS, Eto and Cs were not done because the tests to these drugs are not reproducible. DST to Z is not known in this case.

The mother is receiving **Kmk-Lfx-Pto-Cs-Z** and is doing very well clinically. What advice and regimen is recommended for the child?

Answer: It should be well explained to the mother that the child very likely has TB, most probably MDR-TB. Links with an accredited TB laboratory should be established to obtain DST. While awaiting DST results, or if the diagnostic procedure is not available, the child should be started on an empiric regimen based on the DST pattern of the mother and on the mother's regimen since she is responding well to therapy.

The dose should be calculated using the chart in Annex 3 and using the weight band that falls within the 8 kg range:

- **Kanamycin:** Calculating on the basis of 15–30 mg/kg, the dose should be between 122–243 mg.
  - Lower end of dosing: 15 mg/kg x 8.1 kg = 122 mg
  - Higher end of dosing: 30 mg/kg x 8.1 kg = 243 mg
  - Choose a convenient dosing between the two numbers of the low and high dose based on 15–30 mg/kg and toward the higher number.

    In this case, 200 mg can be considered an appropriate dose.

Calculate the number of ml to draw up in the syringe based on the mg/ml concentration of the preparation. Mix 1 gram in 5 ml sterile water, which gives a 200 mg/ml solution. Give 1.0 ml of the prepared solution daily (200 mg).

- **Levofloxacin:** Levofloxacin is not recommended for children under 10 kg, however it is among the most important drugs in the treatment of MDR-TB. The risks and benefits should be discussed with the mother and if the mother agrees give ¼ of a 250 mg tablet twice a day. (This is based on the dosing of 15–20 mg/kg per day split into two doses for children under five years of age.)
- **Prothionamide:** Give ½ of a 250 mg tablet daily. If tolerance is an issue (nausea and vomiting), give ¼ tablet in the morning and ¼ tablet in the evening.
- **Cycloserine:** Give ½ of a 250 mg capsule daily (125 mg daily). Dissolve a full capsule in 10 ml of water and give 5 ml once daily. If tolerance is an issue, give 2.5 ml in the morning and 2.5 ml in the evening.
- **Pyrazinamide:** Give ½ of a 500 mg tablet = 250 mg – or – ¾ of a 400 mg tablet = 300 mg.

Tablets can be given with food or with something sweet to mask the taste.

As the child gains weight the doses will have to be adjusted (check weight at least every month and more often in children gaining weight rapidly).

7.6 Diabetes mellitus

Diabetic patients with MDR-TB are at risk for poor treatment outcomes *(11)*. In addition, the presence of diabetes mellitus may potentiate the adverse effects of anti-TB drugs, especially renal dysfunction and peripheral neuropathy. Diabetes must be managed closely throughout the treatment of drug-resistant TB. The health care provider should be in close communication with the physician who manages the patient's diabetes. Oral hypoglycaemic agents are not contraindicated during the treatment of drug-resistant TB but may require the patient to increase the dosage as the use of ethionamide or prothionamide may make it more difficult to control insulin levels. However, none of the anti-TB drugs are contraindicated. Creatinine and potassium levels should be monitored more frequently, often weekly for the first month and then at least monthly thereafter in view of the renal effects of aminoglycosides.

7.7 Renal insufficiency

Renal insufficiency caused by longstanding TB infection itself or previous use of aminoglycosides is not uncommon. Great care should be taken in the administration of second-line drugs in patients with renal insufficiency, and the dose and/or the interval between dosing should be adjusted according to Table 7.1. The dosing is based on the patient's **creatinine clearance,** which is an estimate of the glomerular filtration rate or renal function.

TABLE 7.1 **Adjustment of anti-TB drugs in renal insufficiency**[a]

DRUG	RECOMMENDED DOSE AND FREQUENCY FOR PATIENTS WITH CREATININE CLEARANCE <30 ML/MIN OR FOR PATIENTS RECEIVING HAEMODIALYSIS (UNLESS OTHERWISE INDICATED DOSE AFTER DIALYSIS)
Isoniazid	No adjustment necessary
Rifampicin	No adjustment necessary
Pyrazinamide	25–35 mg/kg per dose three times per week (not daily)
Ethambutol	15–25 mg/kg per dose three times per week (not daily)
Rifabutin	Normal dose can be used, if possible monitor drug concentrations to avoid toxicity.
Rifapentine	No adjustment necessary
Streptomycin	12–15 mg/kg per dose two or three times per week (not daily)[b]
Capreomycin	12–15 mg/kg per dose two or three times per week (not daily)[b]
Kanamycin	12–15 mg/kg per dose two or three times per week (not daily)[b]
Amikacin	12–15 mg/kg per dose two or three times per week (not daily)[b]
Ofloxacin	600–800 mg per dose three times per week (not daily)
Levofloxacin	750–1000 mg per dose three times per week (not daily)
Moxifloxacin	No adjustment necessary
Gatifloxacin	400 mg three times a week
Cycloserine	250 mg once daily, or 500 mg/dose three times per week[c]
Terizidone	Recommendations not available
Prothionamide	No adjustment necessary
Ethionamide	No adjustment necessary
Para-aminosalicylic acid[e]	4 g/dose, twice daily maximum dose[d]
Bedaquiline	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution).
Delamanid	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution).
Linezolid	No adjustment necessary
Clofazimine	No adjustment necessary
Amoxicillin/clavulanate	For creatinine clearance 10–30 ml/min dose 1000 mg as amoxicillin component twice daily; for creatinine clearance <10 ml/min dose 1000 mg as amoxicillin component once daily
Imipenem/cilastin	For creatinine clearance 20–40 ml/min dose 500 mg every 8 hours; for creatinine clearance <20 ml/min dose 500 mg every 12 hours
Meropenem	For creatinine clearance 20–40 ml/min dose 750 mg every 12 hours; for creatinine clearance <20 ml/min dose 500 mg every 12 hours

High dose isoniazid	Recommendations not available
Clarithromycin	500 mg daily

[a] Adapted from Tuberculosis drug information guide. 2nd edition, 2012 *(13)*.

[b] Caution should be used with injectable agents in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity. If on dialysis, dose after dialysis.

[c] The appropriateness of 250 mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity (if possible measure serum concentrations and adjust accordingly).

[d] Sodium salt formulations of PAS may result in an excessive sodium load and should be avoided in patients with renal insufficiency. Formulations of PAS that do not use the sodium salt can be used without the hazard of sodium retention and are the preferred formulation in patients with renal insufficiency.

An example of how to estimate a patient's creatinine clearance is provided in Box 7.2.

BOX 7.2 CALCULATING CREATININE CLEARANCE

$$\textbf{Estimated glomerular filtration rate} = \frac{\textbf{weight (kg) x (140 – age) x (constant)}}{\textbf{serum creatinine (µmol/L)}}$$

The creatinine is measured in the serum.

The constant in the formula is = 1.23 for men and 1.04 for women

If creatinine is reported in conventional units (mg/dl) from the laboratory, it can be converted it to a SI Unit (µmol/l) by multiplying by 88.4.

(For example, a creatinine = 1.2 mg/dl is equivalent to (88.4 x 1.2) = 106.1 µmol/l.)

Normal values for creatinine clearance are:

Men: 97 to 137 ml/min

Women: 88 to 128 ml/min

Example: If a female patient (age = 46 years, weight = 50 kg) has serum creatinine = 212 µmol/l, what is the creatinine clearance?

Calculation of creatinine clearance:

Weight (kg) x (140 – age) x (constant) / serum creatinine =

50 x (140 – 46) x (1.04 for women)/ 212 =

23.0 ml/min

The creatinine clearance is below 30; every drug in the regimen should be examined and adjusted if necessary according to Table 7.1.

Note: Creatinine clearance can also be calculated with a 24 hour urine and serum creatinine, but that is usually more cumbersome.

7.8 Liver disorders

All first-line drugs – isoniazid, rifampicin and pyrazinamide – are associated with hepatotoxicity. Of the three, rifampicin is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice. Pyrazinamide is the most hepatotoxic of the three first-line drugs. Among the second-line drugs, ethionamide, prothionamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with fluoroquinolones.

Patients with history of liver disease can receive the usual anti-TB drug regimens provided there is no clinical evidence of severe chronic liver disease, hepatitis virus carriage, recent history of acute hepatitis or excessive alcohol consumption. However, hepatotoxic reactions to anti-TB drugs may be more common in these patients and should be anticipated.

In general, patients with chronic liver disease should not receive pyrazinamide. All other drugs can be used, but close monitoring of liver enzymes is advised. If significant aggravation of liver inflammation occurs, the drugs responsible may have to be stopped.

Uncommonly, a patient with TB may have concurrent acute hepatitis that is unrelated to TB or anti-TB treatment; and here clinical judgment becomes necessary. In some cases, it is possible to defer anti-TB treatment until the acute hepatitis has been resolved. In other cases when it is necessary to treat drug-resistant TB during acute hepatitis, the combination of four non-hepatotoxic drugs is the safest option. Viral hepatitis should be treated if medically indicated and treatment can occur during drug-resistant TB treatment.

7.9 Seizure disorders

Some patients requiring treatment for drug-resistant TB will have a previous or current medical history of a seizure disorder. The first step in evaluating such patients is to determine whether the seizure disorder is under control and whether the patient is taking antiseizure medication. If the seizures are not under control, initiation or adjustment of antiseizure medication will be needed before the start of drug-resistant TB therapy. In addition, any other underlying conditions or causes of seizures should be corrected.

Cycloserine should be avoided in patients with active seizure disorders that are not well controlled with medication. However, in cases where cycloserine is a crucial component of the treatment regimen, it can be given and the antiseizure medication adjusted as needed to control the seizure disorder. The risks and benefits of using cycloserine should be discussed with the patient and the decision on whether to use cycloserine should be made together with the patient.

High dose isoniazid also carries a high risk of seizure and should be avoided in patients with active seizure disorders.

The prophylactic use of oral pyridoxine (vitamin B6) can be used in patients with seizure disorders to protect against the neurological adverse effects of isoniazid or cycloserine. The suggested prophylactic dose for at-risk patients on isoniazid is 10 to 25 mg/day and for patients on cycloserine is 25 mg of pyridoxine for every 250 mg of cycloserine daily. The

optimal prophylactic dose of pyridoxine for children has not been established, nonetheless 1–2 mg/kg/day has been recommended in some reports *(14)* with a usual range of 10–50 mg/day for paediatric patients at risk for neurological sequella.

In mono- and poly-resistant cases, the use of isoniazid and rifampicin may interfere with many of the antiseizure medications. Drug interactions should be checked before their use.

Seizures that present for the first time during anti-TB therapy are likely to be the result of an adverse effect of one of the anti-TB drugs. More information on the specific strategies and protocols to address a seizure when it is an adverse effect is provided in Chapter 9.

7.10 Psychiatric disorders

It is advisable for psychiatric patients to be evaluated by a health care worker with psychiatric training before the start of treatment for drug-resistant TB. The initial evaluation documents and any existing psychiatric condition establish a baseline for comparison if new psychiatric symptoms develop while the patient is on treatment. Any psychiatric illness identified at the start of or during treatment should be fully addressed. There is a high baseline incidence of depression and anxiety in patients with drug-resistant TB, often connected with the chronicity and socioeconomic stress factors related to the disease *(13)*.

Treatment with psychiatric medication, individual counselling and/or group therapy may be necessary to manage the patient suffering from a psychiatric condition or an adverse psychiatric effect caused by medication. Group therapy has been very successful in providing a supportive environment for drug-resistant TB patients and may be helpful for patients with or without psychiatric conditions *(15,16)*. (Adequate measures to prevent infection risk should be in place for the group therapy; see Chapter 14).

The use of cycloserine is not absolutely contraindicated for the psychiatric patient. Adverse effects from cycloserine may be more prevalent in the psychiatric patient, but the benefits of using this drug may outweigh the potentially higher risk of adverse effects. Close monitoring is recommended if cycloserine is used in patients with psychiatric disorders.

All health care workers treating drug-resistant TB should work closely with a mental health specialist and have an organized system for psychiatric emergencies. Psychiatric emergencies include psychosis, suicidal ideation and any situation involving the patient being a danger to oneself or others. (Additional information on psychiatric adverse effects is provided in Chapter 11, Table 11.3).

7.11 Substance dependence

Patients with substance dependence disorders should be offered treatment for their addiction, although active consumption is not a contraindication for anti-TB treatment. Complete abstinence from alcohol or other substances should be strongly encouraged but should not be pursued at the expense of compromising adherence to drug-resistant TB treatment. If the treatment is repeatedly interrupted because of the patient's dependence, therapy should be suspended until measures to ensure adherence have been established. Patient-centred directly

observed therapy gives the patient contact with and support from health care providers, which often allows complete treatment even in patients with substance dependence.

Cycloserine will have a higher incidence of adverse effects (as in the psychiatric patient) in patients dependent on alcohol or other substances, including a higher incidence of seizures; the drug is contraindicated in severe central nervous system disease *(12)*. However, if central nervous system disease is not severe and cycloserine is considered important to the regimen, it can be used in these patients under close observation for adverse effects and prompt treatment if any develop.

7.12 HIV-infected patients

Given the important interactions between HIV infection and drug-susceptible and drug-resistant TB, a full chapter (Chapter 8) is devoted to this subject.

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CHAPTER 8

Drug-resistant TB and HIV

8.1 General considerations

The link between multidrug-resistant TB (MDR-TB) and HIV has been important since the earliest reports of the spread of MDR-TB among immunocompromised patients *(1)*. HIV is a powerful risk factor for all forms of TB, drug-susceptible and drug-resistant *(2)*.

While epidemiological studies have been equivocal about the statistical significance of the association between HIV-positivity and MDR-TB *(3)*, it is clear that HIV-positive patients are vulnerable to drug-resistant TB. This was best illustrated by the rapid and deadly spread of extensively drug-resistant TB (XDR-TB) among HIV-positive patients in South Africa and elsewhere *(4,5)*.

Drug-resistant TB is often associated with higher mortality rates in people living with HIV (PLHIV), meaning that better integration of HIV and drug-resistant TB services is necessary, both in high HIV prevalence settings, but also in any setting where HIV co-infection is common among TB patients. Early diagnosis of drug-resistant TB and HIV, prompt initiation of appropriate second line anti-TB drugs and antiretroviral treatment (ART), sound patient support, and strong infection control measures are all essential components in the management of drug-resistant TB in PLHIV.

8.2 Drug-resistant TB and HIV collaborative activities

The list below is based on the WHO policy on TB/HIV collaborative activities *(6)* and has been adapted to be specifically applicable to drug-resistant TB.

- **Perform provider-initiated HIV testing and counselling in all patients with presumed or diagnosed drug-resistant TB**. WHO recommends HIV testing for all patients presumed to have TB or diagnosed with TB (both drug-susceptible and drug resistance) as it enhances earlier HIV diagnosis and paves the way for quality care *(7)*. Provider-initiated testing can be done at the same time the sputum is sent for smear microscopy, culture or drug susceptibility testing (DST). This is more efficient and more likely to be successful than referring patients elsewhere for HIV testing and counselling *(8)*.
- **Include HIV testing in anti-TB drug resistance surveillance:** Incorporating HIV testing with anti-TB drug resistance surveillance offers an opportunity to expand HIV testing and improve knowledge among national TB control programmes on the relationship between HIV and drug-resistant TB at the population level *(9)*. It also provides critically important individual benefits to PLHIV, including better access to testing, early case detection and rapid initiation of treatment for drug-resistant TB. Unlinked anonymous testing for HIV is not recommended because the results cannot be traced back to individuals who need HIV care and treatment.
- **Use Xpert MTB/RIF molecular assay in HIV-positive TB suspects (see Chapter 4).** This rapid DST method has significant advantages in HIV-positive patients. It detects TB cases twice as effectively as smear microscopy without significant difference in performance by HIV status. It also simultaneously detects mutations associated with rifampicin resistance, thus shortening the time to diagnosis of MDR-TB. WHO recommends Xpert MTB/RIF as the initial diagnostic test in settings with high prevalence of HIV-associated TB and/or MDR-TB *(10)*. The WHO TB diagnostic algorithms for PLHIV are also modified with the inclusion of this molecular assay for implementation and evaluation in HIV prevalent settings *(11)*.
- **Use mycobacterial cultures in HIV-positive TB suspects**. TB in HIV-infected patients is more likely to be smear-negative or extrapulmonary. This means that a heavy reliance on smear microscopy has significant limitations and is insufficient to reliably diagnose a significant proportion of HIV co-infected patients. When Xpert MTB/RIF is negative but TB is still suspected (or if Xpert MTB/RIF is not available), mycobacterial cultures of the sputum or other fluids and tissues are recommended to help in the diagnosis of sputum smear-negative and extrapulmonary TB in PLHIV *(12)*. Mycobacterial cultures are also important for use of phenotypic DST in cases where confirmation of rifampicin resistance is needed (see Chapter 4).
- **Perform DST at the start of TB therapy.** Unrecognized drug-resistant TB carries a high risk of mortality in PLHIV *(13)*. Prompt initiation of appropriate anti-TB treatment can reduce mortality among HIV-infected patients infected with drug-resistant TB *(14,15)*. Because unrecognized MDR- and XDR-TB are associated with such high mortality in HIV-infected patients, many international protocols dictate the performance of DST or rapid DST for all TB/HIV co-infected patients. While this may be difficult in many resource-limited settings, universal access to DST is the long-term goal for all settings. At present, Xpert MTB/RIF is the initial test of choice (see Chapter 4).

- **Consider empirical treatment with second-line anti-TB drugs.** Patients at high-risk for MDR-TB should be started on an empiric MDR regimen, even before laboratory confirmation of MDR-TB (Chapter 5). This strategy can be applied to all patients regardless of HIV status, but is especially important in HIV-positive patients.
- **Initiate ART promptly in drug-resistant TB/HIV patients.** ART should be started promptly in all HIV-infected patients with MDR-TB regardless of CD4 cell count. Second-line anti-TB drugs should be initiated first, followed by ART as soon as second-line anti-TB drugs are tolerated. Generally this should be within the first two weeks of initiating MDR-TB treatment.
- **Provide co-trimoxazole preventive therapy for patients with active TB and HIV.** Provide co-trimoxazole to all patients with HIV according to WHO recommendations. Co-trimoxazole is not known to interact significantly with any of the second-line anti-TB drugs. There are, however, overlapping toxicities between ART, second-line anti-TB drugs, and co-trimoxazole, so co-infected drug-resistant TB patients should be monitored closely (see Table 8.1).
- **Implement sound patient follow up and monitoring system.** Care providers should be familiar with the clinical aspects of the treatment of both drug-resistant TB and HIV. There should be close monitoring of potential adverse effects including psychiatric assessments and nutritional status (see Chapter 11 for monitoring for adverse effects in HIV and Table 8.1 for overlapping toxicities of ART with second-line anti-TB drugs). There should also be periodic assessments of therapeutic response to both infections (see Chapter 11 for monitoring the response the MDR-TB treatment and for response to ART see the latest WHO recommendations and guidelines).
- **Implement additional nutritional and socioeconomic support.** Patients with drug-resistant TB and HIV may suffer from severe wasting, diarrheal diseases and malabsorption syndromes. A comprehensive package of prevention, diagnosis, treatment and care interventions (continuum of care) should be provided to all PLHIV. Additionally, treatment with second-line anti-TB drugs may result in adverse effects that affect treatment adherence and require more frequent visits to health facilities. Wherever possible, patients with drug-resistant TB living with HIV should be offered socioeconomic and nutritional support.
- **Provide integrated TB and HIV services.** Co-treatment of drug-resistant TB and HIV is particularly difficult due to the long duration, heavy pill burden and numerous side-effects. These patients should receive treatment for TB and HIV – and any other comorbidities – at the same place and time as possible. This improves adherence and quality of care, because a single care team understands and manages all of the needs of the patient (see below).
- **Ensure effective TB infection control.** Strict application of TB infection control measures is mandatory. Implementation of the WHO policy recommendations *(16,17)* can greatly decrease the risk of drug-resistant TB transmission and protect HIV-infected patients. Also see Chapter 14 on drug-resistant TB and infection control.
- **Involve key stakeholders in drug-resistant TB and HIV activities.** Effective coordinating bodies that operate at all levels and which include the participation of all stakeholders – from HIV programmes and TB control programmes, civil society organizations, patients and communities – are feasible and ensure broad commitment and ownership. These key stakeholders should be involved in the planning and monitoring of drug-resistant TB and HIV activities and programmes *(6)*.

8.3 Clinical features and diagnosis of drug-resistant TB in HIV-infected patients

The diagnosis of TB (including MDR-TB and XDR-TB) in PLHIV is more difficult and may be confused with other pulmonary or systemic infections. The presentation is more likely to be extrapulmonary or sputum smear-negative than in HIV-uninfected TB patients, especially as immunosuppression advances *(18)*. This can result in misdiagnosis or delays in diagnosis, and in turn, higher morbidity and mortality. WHO recommends algorithms with the aim of improving and expediting the diagnosis of smear-negative pulmonary and extrapulmonary TB among PLHIV *(12)* and also recommends the use of Xpert MTB/RIF *(19,20)* in HIV infected patients as described in Box 8.1.

BOX 8.1 SUMMARY OF WHO RECOMMENDATIONS OF USE OF XPERT MTB/RIF

The WHO evidence synthesis process confirmed a solid evidence base to support widespread use of Xpert MTB/RIF for detection of TB and rifampicin resistance and resulted in the following main recommendations.

- **Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB. (strong recommendation)**
- **Xpert MTB/RIF may be considered as a follow-on test to microscopy in settings where MDR-TB or HIV is of lesser concern, especially in further testing of smear-negative specimens. (conditional recommendation acknowledging major resource implications)**

Remarks:

- These recommendations apply to the use of Xpert MTB/RIF in sputum specimens (including pellets from decontaminated specimens). Data on the utility of Xpert MTB/RIF in extrapulmonary specimens are still limited.
- These recommendations support the use of one sputum specimen for diagnostic testing, acknowledging that multiple specimens increase the sensitivity of Xpert MTB/RIF but have major resource implications.
- These recommendations also apply to children, based on the generalization of data from adults and acknowledging the limitations of microbiological diagnosis of TB (including MDR-TB) in children.
- Access to conventional microscopy, culture and DST is still needed for monitoring of therapy, for prevalence surveys and/or surveillance, and for recovering isolates for drug susceptibility testing other than rifampicin (including second-line anti-TB drugs).

The algorithms in these WHO documents *(12,20)* emphasize the use of clinical criteria especially for seriously sick patients, and the prompt utilization of all available investigations including molecular tests (Xpert MTB/RIF), culture and radiography. These algorithms *(12)* are proven to shorten the number of days needed to diagnose TB in smear negative and seriously sick patients by increasing the sensitivity and significantly reducing mortality *(21,22)*. For patients with advanced HIV disease, molecular tests and/or mycobacterial culture of other fluids (e.g. blood, pleural fluid, ascitic fluid, cerebrospinal fluid, and bone-marrow aspirates) and histopathology (e.g. lymph node biopsies) may be helpful in diagnosis.

In many programmes and areas, all PLHIV with TB are screened for drug resistance with DST. Rapid DST is preferable since this allows prompt diagnosis of MDR-TB, decreasing the time the patient may be on an inadequate regimen and the period during which the patient may be spreading drug-resistant TB. Programmes without facilities or resources to screen all HIV-infected patients for drug-resistant TB should put significant efforts into increasing laboratory capacity, since universal access to DST is the long-term goal. In the meantime, empiric MDR-TB treatment is particularly important for high-risk MDR suspects (see Chapter 4) who are HIV-positive *(22)*. Co-infected patients have the most to gain from a strategy that decreases time to effective TB treatment.

8.4 Drug-resistant TB and HIV co-treatment

The treatment of drug-resistant TB in patients with HIV is very similar to that in patients without HIV as described in Chapter 5, with the following exceptions.

- ART plays a crucial role (see Section 8.4.1), as mortality in those with MDR-TB and HIV without the use of ART is extremely high (91% to 100% as reported in one analysis of MDR-TB outbreaks in nine different institutions) *(23)*. Other observational cohort studies have shown that ART improves survival of HIV-infected patients with MDR-TB *(24)* and XDR-TB *(25)*. However, drug-resistant-TB patients may often have advanced clinical disease that puts patients at increased risk of immune reconstitution inflammatory syndrome (IRIS) in addition to frequent drug interactions and cotoxicities if ART is started early.
- Drug–drug interactions with second-line anti-TB drugs do exist (see Section 8.4.2).
- Adverse effects are more common in PLHIV. The multiple medicines involved in drug-resistant TB with recognized high toxicity risks, often combined with ART, results in a high incidence of adverse effects. Some toxicities are common to both anti-TB treatment and ART, which may result in added rates of adverse events (See Section 8.4.3 and Table 8.1).
- Monitoring needs to be more intense for both response to therapy and adverse effects (see Section 8.4.4 and Chapter 11).
- The use of thioacetazone is not recommended for patients with HIV *(26)* or for routine use in populations with high rates of HIV.
- IRIS may complicate therapy (see Section 8.4.5).

8.4.1 ART in patients with drug-resistant TB

ART in HIV-infected patients with TB improves survival for both drug-resistant and susceptible disease *(3,27)*. Cohorts of patients treated for MDR- and XDR-TB without the benefit of ART have experienced mortality rates often greater than 90% *(2,22)*. Undue delay in the start of ART could result in significant risk of HIV-related death among patients with advanced disease *(28)*.

For drug-susceptible TB, it is now well established through randomized clinical trials that earlier initiation of ART is associated with a decrease in mortality *(29)*. This decrease in mortality is more pronounced among patients with a CD4 count less than 50 cells/mm *(1,30,31)*. Similar randomized clinical trials have not been performed with drug-resistant TB patients, but clinical experience supports the strategy of early ART initiation in MDR- and

XDR-TB patients *(32,33)*. Furthermore, evidence reviewed from 10 studies by the WHO *(34)* to assess patient treatment outcomes when ART and second-line anti-TB drugs were used together resulted in the following recommendation:

> ***Antiretroviral therapy is recommended for all patients with HIV and drug-resistant-TB requiring second-line anti-TB drugs, irrespective of CD4 cell-count, as early as possible (within the first 8 weeks) following initiation of anti-TB treatment (strong recommendation/very low quality evidence)*** *(33)*.

Initiating ART "as soon as possible" with second-line anti-TB drugs may be challenging because many second-line anti-TB drugs can produce serious side-effects, but a well-trained clinical team can usually initiate ART within 2–4 weeks of starting MDR-TB treatment *(34)*.

The recommended standard first-line ART regimen for drug-susceptible TB is described in other WHO documents and is beyond the scope of this Handbook. While there are few drug–drug interactions with second-line TB drugs and ART regimens, the problem of overlapping drug toxicities is an ever-present concern. A common first-line ART regimen used in MDR-TB treatment is AZT + 3TC + EFV. TDF is generally avoided because of the possibility of overlapping renal toxicity with the injectables, but AZT (anaemia) and d4T (peripheral neuropathy) have even more common side-effects that may make them unsuitable for some MDR- and XDR-TB patients. If TDF is used, additional monitoring of renal function and electrolytes is indicated (see Chapter 11).

8.4.2 Important drug–drug interactions in the treatment of HIV and drug-resistant TB

Currently, little is known about drug–drug interactions between second-line anti-TB drugs and ART. There are several known interactions between drugs used to treat HIV and TB.

- **Rifamycin derivatives**. While rifamycin derivatives are not used in MDR-TB treatment, they are used in the treatment of rifampicin-sensitive poly- and mono-resistant TB. Guidance on use of rifamycin derivative-based regimens and ART (including with protease inhibitor-based regimens) is available elsewhere.
- **Bedaquiline.** This drug is metabolized by the CYP3A4 and has multiple drug interactions with protease inhibitors and non-nucleoside reverse-transcriptase inhibitors (NNRTI). (See Annex 4.1 for a full description of the use of bedaquiline with ART.)
- **Delamanid.** CYP3A4 is the metabolizer of delamanid. Many drugs can either induce or inhibit the CYP3A4 system, resulting in drug–drug interactions. (See Annex 4.2 for a full description of the use of delamanid with ART).
- **Quinolones and didanosine**. Buffered didanosine contains an aluminium/magnesium-based antacid and if given jointly with fluoroquinolones may result in decreased fluoroquinolone absorption *(35)*; it should be avoided, but if it is necessary it should be given six hours before or two hours after fluoroquinolone administration. The enteric-coated formulation of didanosine can be used concomitantly without this precaution.
- **Ethionamide/prothionamide**. Based on limited existing information of the metabolism of thiamides (ethionamide and prothionamide), this drug class may have interactions with

antiretroviral drugs. Ethionamide/prothionamide are metabolized by the CYP450 system, though it is not known which of the CYP enzymes are responsible. Whether doses of ethionamide/prothionamide and/or certain antiretroviral drugs should be modified during the concomitant treatment of drug-resistant TB and HIV is completely unknown *(36)*.

- **Clarithromycin**. Clarithromycin is a substrate and inhibitor of CYP3A and has multiple drug interactions with protease inhibitors and NNRTIs. If possible avoid the use of clarithromycin in patients co-infected with drug-resistant TB and HIV because of both its weak efficacy against *Mycobacterium tuberculosis*, multiple drug interactions, and added adverse events.

8.4.3 Potential drug toxicities and overlapping adverse effects in the treatment of HIV and drug-resistant TB

There is limited evidence on the frequency and severity of toxicities and adverse events from ART and second-line anti-TB drugs. In general, HIV patients have a higher rate of adverse drug reactions to both TB and non-TB medications, and the risk of adverse drug reaction increases with the degree of immunosuppression *(37,38)*. Identifying the source of adverse effects in patients receiving concomitant therapy for drug-resistant TB and HIV is difficult. Many of the medications used to treat drug-resistant TB and HIV have overlapping, or in some cases additive, toxicities. Often it may not be possible to link side-effects to a single drug, as the risk of resistance for ART precludes the typical medical challenge of stopping all medications and starting them one by one *(39)*.

Adverse effects that are common to both antiretroviral and anti-TB drugs are listed in Table 8.1 (drug abbreviations for antiretrovirals and anti-TB drugs are in the front of the Handbook). When possible, avoid the use of agents with shared side-effect profiles. Often, however, the benefit of using drugs that have overlying toxicities outweighs the risk. Therefore, if two drugs with overlapping toxicities are determined to be essential in a patient's regimen, it is recommended with increased monitoring of adverse effects rather than disallowing a certain combination.

TABLE 8.1 **Potential overlapping and additive toxicities of ART and anti-TB treatment**

TOXICITY	ANTIRETROVIRAL AGENT	ANTI-TB AGENT	COMMENTS
Skin rash	**ABC, NVP, EFV, d4T** and others	**H, R, Z, PAS, Fluoro-quinolones**, and others	Do not re-challenge with ABC (can result in life-threatening anaphylaxis). Do not re-challenge with any agent that may have caused Stevens-Johnson syndrome. **Also consider co-trimoxazole as a cause of skin rash if the patient is receiving this medication.** Thioacetazone is contraindicated in HIV because of the risk of life-threatening rash.

TOXICITY	ANTIRETROVIRAL AGENT	ANTI-TB AGENT	COMMENTS
Peripheral neuropathy	**d4T, ddI**	**Lzd, Cs, H,** aminoglycosides Eto/Pto, E	Avoid use of D4T or ddI in combination with Cs or Lzd because of an increased risk of peripheral neuropathy; If these agents must be used in combination and peripheral neuropathy does develop, replace antiretrovirals with a less neurotoxic agent. Patients taking H, Cs or Lzd should receive prophylactic pyridoxine.
Central nervous system (CNS) toxicity	**EFV**	**Cs,** H, Eto/Pto, FQ	EFV has a high rate of CNS side effects (dizziness, impaired concentration, depersonalization, abnormal dreams, insomnia and confusion) in the first 2–3 weeks of use, but typically resolve on their own. If these effects do not resolve, consider substitution of the agent. At present, there are limited data on the use of EFV with Cs; concurrent use is the accepted practice as long as there is frequent monitoring for central nervous system toxicity. Frank psychosis can occur with Cs but is rare with EFV alone; other causes should always be ruled out.
Depression	**EFV**	**Cs,** FQ, H, Eto/Pto	Severe depression can be seen in 2.4% of patients receiving EFV. Consider substitution of EFV if severe depression develops.
Headache	**AZT, EFV**	**Cs, Bdq**	Rule out more serious causes of headache, such as bacterial meningitis, cryptococcal meningitis, central nervous system toxoplasmosis, etc. Use of analgesics (ibuprofen, paracetamol) and good hydration may help. Headaches secondary to AZT, EFV and Cs are usually self-limited.
Nausea and vomiting	**RTV, d4T,** NVP, and most others	**Eto/Pto, PAS, H, Bdq, Dlm, E, Z** and others	Persistent vomiting and abdominal pain may be a result of developing lactic acidosis (especially common with long-term d4T use) and/or hepatitis secondary to medications.

TOXICITY	ANTIRETROVIRAL AGENT	ANTI-TB AGENT	COMMENTS
Abdominal pain	**All antiretrovirals have been associated with abdominal pain**	**Eto/Pto, PAS**	Abdominal pain is a common adverse effect and often benign; however, abdominal pain may be an early symptom of severe side-effects, such as pancreatitis, hepatitis or lactic acidosis (especially common with long-term d4T use.
Pancreatitis	**d4T, ddI**	**Lzd**	Avoid use of these agents together. If an agent causes pancreatitis, suspend it permanently and do not use any of the potentially pancreatitis-producing antiretrovirals (d4T or ddI) in the future. Also consider gallstones or excessive alcohol use as potential causes of pancreatitis.
Diarrhoea	**All protease inhibitors, ddI (buffered formulation)**	**Eto/Pto, PAS,** FQ	Diarrhoea is a common adverse effect. Also consider opportunistic infections as a cause of diarrhoea, or C*lostridium difficile* (pseudomembranous colitis).
Hepatotoxicity	**NVP, EFV, all protease inhibitors** (RTV > others), **all NRTIs**	**H, R, E, Z, Bdq, PAS,** Eto/ Pto, FQ	Also see Section on hepatotoxicity treatment related to second-line anti-TB drugs. When severe, stop both the ART and TB medications, and restart the TB medications first. (Also see Chapter 9 on managing drug-induced hepatotoxicity). Also consider co-trimoxazole as a cause of hepatotoxicity if the patient is receiving this medication. Also rule out viral aetiologies as cause of hepatitis (hepatitis A, B, C, and CMV).
Lactic acidosis	**d4T, ddI,** AZT, 3TC	Lzd	If an agent has caused hyperlactataemia (i.e. high lactate) or lactic acidosis, replace it with an agent less likely to cause lactic acidosis. Note: the goal should always be early detection and management of hyperlactataemia to prevent development of lactic acidosis.

TOXICITY	ANTIRETROVIRAL AGENT	ANTI-TB AGENT	COMMENTS
Renal toxicity	TDF (rare)	**Amino-glycosides, Cm**	TDF may cause renal injury with the characteristic features of Fanconi syndrome, hypophosphataemia, hypouricaemia, proteinuria, normoglycaemic glycosuria and, in some cases, acute renal failure. **Avoid TDF in patients receiving aminoglycosides or Cm. If TDF is absolutely necessary, serum creatinine and electrolytes should be monitored frequently (at least every two weeks).** Even without the concurrent use of TDF, HIV-infected patients have an increased risk of renal toxicity secondary to aminoglycosides and Cm. Frequent creatinine and electrolyte monitoring is recommended. In the presence of renal insufficiency, antiretrovirals and anti-TB medications need to have their doses adjusted.
Nephrolithiasis	**IDV**	None	No overlapping toxicities regarding nephrolithiasis have been documented between ART and anti-TB medications. Adequate hydration prevents nephrolithiasis in patients taking IDV. If nephrolithiasis develops while on IDV, substitute with another protease inhibitor.
Electrolyte disturbances	TDF (rare)	**Cm, amino-glycosides**	Diarrhoea and/or vomiting can contribute to electrolyte disturbances. Even without the concurrent use of TDF, HIV-infected patients have an increased risk of both renal toxicity and electrolyte disturbances secondary to aminoglycosides and Cm.
Bone marrow suppression	AZT	**Lzd**, R, Rfb, H	Monitor blood counts regularly. Replace AZT if bone marrow suppression develops. Consider suspension of Lzd. Also consider co-trimoxazole as a cause if the patient is receiving this medication. Consider adding folinic acid supplements, especially if the patient is receiving co-trimoxazole.

TOXICITY	ANTIRETROVIRAL AGENT	ANTI-TB AGENT	COMMENTS
Optic neuritis	ddI	**E**, Eto/Pto (rare)	Suspend agent responsible for optic neuritis permanently and replace with an agent that does not cause optic neuritis.
Hyperlipidaemia	**Protease inhibitors, EFV**	None	No overlapping toxicities regarding hyperlipidaemia have been documented between antiretrovirals and anti-TB drugs.
Lipodystrophy	**NRTIs** (especially d4T and ddI	None	No overlapping toxicities regarding lipodystrophy have been documented between antiretrovirals and anti-TB drugs.
Dysglycaemia (disturbed blood sugar regulation)	**Protease inhibitors**	**Gfx**, Eto/Pto	Protease inhibitors tend to cause insulin resistance and hyperglycaemia. Eto/Pto tends to make insulin control in diabetics more difficult, and can result in hypoglycaemia and poor glucose regulation.
Hypothyroidism	d4T	**Eto/Pto, PAS**	There is potential for overlying toxicity, but evidence is mixed. Several studies show subclinical hypothyroidism associated with some antiretrovirals, particularly stavudine (d4T). PAS and Eto/Pto, especially in combination, can commonly cause hypothyroidism.
Arthralgia	**Indinavir, other protease inhibitors**	**Z, Bdq**	Protease inhibitors can cause arthralgia and there have been case reports of more severe rheumatologic pathology *(40)*. Arthralgias are very common with Z and has been reported as one of the most frequent adverse effects (>10%) in controlled clinical trials with Bdq *(41)*.
QT Prolongation	ART has been associated with QTc prolongation	**Bdq, Dlm, Mfx, Gfx, Cfz,** Lfx, Ofx	ARV therapy does appear to confer a significant increased risk of QTc prolongation in HIV-positive patients *(42)* but data is sparse. The additive effects of combining ART with the known second-line anti-TB drugs in respect to QTc prolongation is not known.

Note: Drugs that are more strongly associated with the listed toxicities appear in bold lettering.

8.4.4 Monitoring of drug-resistant TB and HIV therapy in co-infected patients

HIV treatment must be taken daily without exception to prevent the evolution of drug resistance. Since direct observation of treatment with patient-centred care is an important component of drug-resistant TB therapy, programmes would be advised to explore the provision of TB medications and antiretrovirals through concomitant direct observation of treatment or other methods of adherence support (see Chapter 12). This is particularly important in the setting of second-line anti-TB drugs, since it can result in a large pill burden and numerous side-effects that make taking antiretrovirals more difficult.

The complexity of antiretroviral regimens and second-line TB treatment, each with its own toxicity profiles and some of which may be potentiated by concomitant therapy, demands rigorous clinical monitoring *(43)*. Chapter 11, Table 11.1 describes the monitoring requirements while on drug-resistant TB therapy and indicates where any extra monitoring is required for patients co-infected with HIV and/or on ART.

If the patient shows signs of TB treatment failure, the same evaluation described in Chapter 10 is warranted. In addition, the ART regimen should be evaluated for possible treatment failure as described in other WHO guidelines.

Given that the regimens together are particularly difficult to take, the stigma of both diseases can result in serious discrimination, and the risk of mortality is very high, patients with HIV-associated drug-resistant TB may require special socioeconomic, nutritional and psychosocial support to successfully complete treatment.

8.4.5 Immune reconstitution inflammatory syndrome (IRIS)

IRIS has emerged as an important complication of ART. IRIS is relatively common in mild to moderate forms in patients with TB started on ART (seen in up to one third of patients in some studies *(44,45)*; however, it is relatively rare in its severe forms. This syndrome can present as a paradoxical worsening of the patient's clinical status, often due to a previously subclinical and unrecognized opportunistic infection *(42,46)*. These reactions may present as fever, enlarging lymph nodes, worsening pulmonary infiltrates, respiratory distress, or exacerbation of inflammatory changes at other sites. It generally presents within three months of the initiation of ART and is more common with a low CD4 cell count (<50 cells/mm^3) *(47)*.

It is important to note that IRIS is a diagnosis of exclusion. Patients with advanced AIDS may show clinical deterioration for a number of other reasons. New opportunistic infections or previously subclinical infections may be unmasked following immune reconstitution and cause clinical worsening *(14)*. IRIS can also be confused with TB treatment failure, and co-infected patients may be demonstrating progression of TB disease due to drug resistance.

The management of IRIS is complex and depends on the clinical status of the patient and the site and extent of involvement. Various treatment modalities have been employed, including nonsteroidal anti-inflammatory drugs (NSAIDs) in mild disease and corticosteroids in moderate to severe disease. Most patients can be treated without interruption of ART.

8.4.6 Integration of drug-resistant TB and HIV services

Integrated delivery of drug-resistant TB and HIV services offers an opportunity to provide quality and seamless care for drug-resistant TB patients living with HIV both at the facility and community level *(6,48)*. The models of service delivery can be referral with systematic linkages, partial integration of services either in the drug-resistant TB or HIV services or full integration of co-location of drug-resistant TB and HIV services into one facility so that services are provided at the same time and place *(6)*. However, few studies have reported on patient-relevant impacts – such as outcomes of treatment or on programme outcomes such as early diagnosis of HIV and TB, early initiation of ART, prompt TB diagnosis and treatment, and retention into care – hindering a direc.t comparison of the various models. The models for integration mentioned above are not exhaustive or prescriptive. Models of delivery of treatment and direct observation of treatment described in Chapter 18 can be applied to co-infected HIV and MDR-TB patients.

Emphasis has to be given to the implementation of proper infection control measures throughout health facilities in high-burden settings to minimize the risk of nosocomial spread of drug-resistant TB to immunosuppressed PLHIV *(16,17)*.

Integrated delivery of services supports early detection and treatment of undiagnosed infectious TB, including drug-resistant TB and may result in a reduction of TB risk compared with separate services.

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CHAPTER 9

Initiating treatment

9.1 Introduction

This chapter describes the activities for proper treatment initiation. Often there are long unnecessary delays between diagnosing multidrug-resistant TB (MDR-TB) and the start of treatment. Section 9.2 describes the needed systems to enrol patients in a timely fashion. Proper treatment initiation includes: (i) an initial baseline evaluation, comprising assessment of any relevant pre-existing comorbidities and/or risks for adverse effects due to anti-TB drugs; and (ii) excellent patient and family education.

9.2 Flow of patients into treatment

Once a patient has been diagnosed with MDR-TB or has been identified to belong to a group with a high enough risk of MDR-TB that warrants enrolment, the patient should be promptly evaluated and initiated on treatment, while awaiting drug susceptibility testing (DST). A physician trained in the management of MDR-TB usually performs the initial evaluation. A quick flow of patients into MDR-TB treatment requires:

- the general health system to be aware of where and how patients with MDR-TB receive treatment;
- the timely return of laboratory results to the facility that requested the diagnostic test;
- the regular review of the Laboratory register (at least weekly) and documentation of all positive cases of drug-resistant TB that have initiated treatment in the Treatment register;
- established protocols of who should be admitted to the hospital for the start of treatment versus who should be started as an outpatient;
- a well-defined place of care where the patient will get regular follow-up visits and all monitoring tests;

- the identification of the directly observed therapy (DOT) provider, who will support and accompany the patient through treatment and perform direct observation of treatment with a patient-centred approach;
- ensuring treatment delivery and social support, as described in Chapter 12; and
- monitoring the average time from diagnosis to start of treatment and making suitable programme adjustments when delays of even a few days exist.

9.3 Initial evaluation and pretreatment screening

Pretreatment assessment should be systematically conducted on all patients to identify those at greatest risk of adverse effects and poor outcomes, and to establish a baseline. The required initial pretreatment clinical investigation includes a thorough medical history and physical examination. The conditions to be screened for at initial medical evaluation are presented in Box 9.1. The monitoring of treatment and the management of adverse effects may have to be more intensive in patients with pre-existing conditions or conditions identified at the initial evaluation.

BOX 9.1 CONDITIONS TO BE SCREENED FOR AT INITIAL MEDICAL EVALUATION[a]

- HIV infection (option of HIV testing)
- Diabetes mellitus
- Hypertension
- Renal insufficiency
- Acute or chronic liver disease
- Mental illness
- Drug or alcohol dependency
- Pregnancy
- Breastfeeding
- Seizures
- Malnutrition
- Thyroid disease

[a] The management of drug-resistant TB for the conditions listed above is described in Chapter 7.

The recommended initial laboratory evaluations are summarized in Annex 6. All patients starting MDR-TB treatment should have the following tests.

- Acid-fast smear, mycobacterial cultures and DST to rifampicin and isoniazid. Whenever possible, cases of rifampicin-resistant TB (RR-TB) and MDR-TB should undergo DST to second-line drugs (see Chapters 3 and 4).
- Baseline potassium, creatinine, serum glucose and serum glutamic-pyruvic transaminase (SGPT; alanine transaminase (ALT)).
- HIV rapid testing (repeat if negative and suspicion of HIV is high).
- If HIV positive, refer for full blood count and CD4 (CD4% in children).
- Baseline full blood count should be performed if anaemia is suspected.
- Pregnancy test for women of childbearing age.
- If symptoms of hypothyroidism or goitre are present or the patient is of advanced age, perform baseline free thyroxine (FT4) and thyroid stimulating hormone (TSH) test. Routine baseline FT4 and TSH test can be done on all patients if resources permit.
- Audiometry.
- Chest radiograph.

- Electrocardiogram if bedaquiline or delamanid is to be included in the regimen or the patient has a history of cardiac disease (see Annexes 4.1 and 4.2).
- Baseline psychosocial assessment by trained personnel in the skills of psychosocial management during MDR-TB treatment.

Methods of preventing pregnancy during treatment for women of childbearing age should be discussed and agreed upon with the patient during the initial visit.

Weight and height should be recorded at the onset of treatment in the Treatment card; this helps calculate the body mass index (BMI) and assess nutrition status.

The initial evaluation may require a repeat or confirmation DST, or further DST for other anti-TB drugs. The indications for confirming drug susceptibility in patients identified with RR-TB with Xpert MTB/RIF are discussed in Chapters 3 and 4. For a patient to be considered bacteriologically positive, a culture, or molecular test or sputum smear must be positive at the start of drug-resistant TB treatment. The collection date of the sample should be less than 30 days before, or maximum seven days after the initiation of drug-resistant TB treatment. Specimens collected prior to start of treatment are preferred.

While a full medical history should be taken at every initial evaluation, Box 9.2 lists the minimum screening questions required to assess if a second-line drug regimen may need modification, to diagnose comorbidities that went undetected, and to plan subsequent measures to maintain patient safety through early detection of adverse drug reactions.

Ideally, DOT provider(s) will have already been identified and be present at the initial evaluation as they play a crucial role in the activities aimed at providing patient-centred care throughout treatment. Information on the selection and responsibilities of a DOT provider are found in Chapters 12 and 18.

BOX 9.2 MINIMUM CRITERIA TO START THE STANDARD MDR-TB REGIMEN *(1)*

Address the following questions before starting the standard MDR-TB regimen.

1. Is the patient pregnant?
2. Is there jaundice or a known liver problem? Is there an antecedent of alcohol abuse?
3. Is there chronic illness, such as HIV, diabetes mellitus, heart or kidney disease, etc. (see Box 9.1)?
4. Is the patient a household contact of a patient with confirmed extensively drug-resistant TB?
5. Has the patient ever taken second-line anti-TB drugs?

NO to all? ➡ No modifications to the programme's empiric MDR-TB regimen or monitoring schedule are needed.

YES to any question? ➡ Patient will need further evaluation and adjustments may be needed to the programme's empiric MDR-TB regimen and monitoring needs to be increased.

9.4 Preparing the patient for treatment and education

Preparing the patient for treatment involves educating the patient and family, including the drugs used, length of treatment, possible side-effects and support that will be available for the patient. It also includes information on how the patient can protect his/her family and household members from getting TB. Educating the patient should ultimately help the patient obtain better adherence. (Patient education is further discussed in Chapter 12 on Social support and adherence to treatment).

Box 9.3 provides a short checklist for the health care provider to help best prepare the patient for treatment. Patient education takes place over several visits with different health care providers (from the DOT provider right up to the physician). There should be a well-formulated plan on how to educate both the patient and their family/caregivers so that they have complete information. Educational pamphlets with reminders of the main points, in the local language and in pictures, are helpful.

BOX 9.3 CLINICIAN CHECKLIST TO GO OVER WITH THE PATIENT BEFORE TREATMENT STARTS

- Discuss where treatment will start. If at a hospital, estimate the approximate length of stay. If at home ask about the home living situation and whether or not the patient feels home treatment will be possible.
- Inform the patient the about the length of treatment; that it will be for at least 20 months but may be longer.
- Teach the patient about the drugs: there are at least five anti-TB drugs, of which one is an injectable agent.
- Teach the patient about monitoring requirements for smear, culture and laboratory tests for side-effects.
- Make a follow-up plan for seeing the doctor and inform the patient if he/she has problems they should be seen sooner. Make sure they know how to make an appointment if they need to be seen before the next routine visit.
- Instruct them what to do in case of an emergency (like severe shortness of breath).
- Teach patients about possible side-effects.
- Inform patients that they must report any side-effects to the medications; remind them to notify you right away if there is any hearing loss or ringing in the ears.
- Teach patients how drug-resistant TB can be transmitted and some basics about household infection control. The patient is most infectious during the first few days or weeks of treatment when he/she is still smear positive.
- Windows and doors should be left open in the home to increase ventilation.
- A smear positive patient should wear a surgical or cloth mask at all possible times.
- It is safer to visit with family and friends if the patient is outdoors in the open air.
- Seek an informed consent, in writing if local law requires to do so, if bedaquiline or delamanid are going to be part of the treatment regimen.

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CHAPTER 10

Monitoring treatment response

10.1 Introduction

This chapter focuses on monitoring the progress of treatment and identifying failure of treatment that indicates the need for a change in treatment strategy. The response to second-line anti-TB drugs is often slow with the median time to conversion being three months *(1)*. Performing monthly culture tests is the best strategy in identifying failures earlier. Sputum smear microscopy alone results in delayed detection of failure. The WHO 2011 *Guidelines for programme management of drug-resistant tuberculosis* made the following recommendation:

> **The use of sputum smear microscopy and culture rather than sputum smear microscopy alone is recommended for the monitoring of patients with multidrug-resistant TB (MDR-TB) during treatment (conditional recommendation/very low quality evidence)** *(2)*.

Initial culture conversion is not always maintained. In one study approximately 15% of patients experienced initial culture conversion and at least one subsequent culture reversion to positive. In the same study, about three quarters of the patients had an initial conversion and sustained it *(1)*.

Molecular tests such as Xpert MTB/RIF and line probe assays should not be used to monitor response to treatment (see Chapter 3).

10.2 Monitoring the progress of treatment

Patients should be monitored closely for signs of treatment failure. Monitoring response to treatment is done through regular history taking, physical examination, chest radiograph and laboratory monitoring. The classic symptoms of TB – cough, sputum production, fever and weight loss – generally improve within the first few weeks. Cough and sputum production can

persist after sputum conversion in patients with extensive lung damage, but even in those with extensive lung damage improvement is often seen within a month or two of effective treatment. Persistent fever, weight loss or recurrence of any of the classic symptoms of TB should prompt investigation of treatment failure or untreated comorbidities. The recurrence of TB symptoms after sputum conversion may be the first sign of treatment failure. For children, height and weight should be measured monthly to ensure that they are growing normally. Normal growth rate usually resumes after a few months of successful treatment. For adults too weight should be recorded monthly (height is only recorded at the start of treatment).

The chest radiograph may appear unchanged in the first few months of treatment or show only slight improvement, especially in patients with chronic pulmonary lesions. Chest radiographs should be taken at least every six months to document progress and to use for comparison if the patient's clinical condition changes. Chest radiographs are also done when a surgical intervention is being considered, or whenever the patient's clinical situation has worsened. A chest radiograph at the end of treatment is useful to later manage TB pulmonary sequelae post-treatment.

The most important evidence of improvement is conversion of the sputum culture to negative. While sputum smear is useful because of its much shorter turnaround time, sputum culture is much more sensitive to detect ongoing active disease and/or treatment failure *(2)*. Therefore, culture is necessary to monitor the progress of treatment. Sputum smear and culture examinations are also dependent on the quality of the sputum produced, so care should be taken to obtain adequate specimens and transporting them to the laboratory according to standard procedures to maintain viability of the bacilli to get a valid culture result (also see Chapter 3).

Persistently positive sputums and cultures for acid-fast bacilli (AFB) should be assessed for non-TB mycobacteria (NTM) as colonization or infection with NTM in a damaged lung secondary to TB is not uncommon. In such cases, though drug-resistant TB may be adequately treated, treatment may need to be directed towards the NTM as well.

Culture conversion should not be considered to be equivalent to cure. A certain proportion of patients may initially convert and later revert to positive sputum culture. These patients can either go on to have a sustained re-conversion or eventually be declared treatment failures.

Monthly monitoring of sputum smears and cultures throughout treatment enables the programme to identify conversion or failure to convert in a timely way, which has major implications on both clinical management and the use of resources by the programme. Programmes that still do not have the culture capacity needed may have to do cultures less frequently, e.g. monthly until conversion and then every two months. It should be acknowledged that with culture monitoring every other month, there is a small to moderate degree of delay in the detection of failure. Delayed detection of failure can increase transmission and increase the probability of acquisition of resistance to the patient's strain, making it harder to cure the patient after failure *(2)*.

Single 'on the spot' specimens can be submitted for monitoring cultures and two "on the spot" specimens for smear monitoring should be submitted. Alternatively, if logistics permit, the culture and one of the smears can be a first-morning sputum.

Drug susceptibility testing (DST) can be repeated for patients who remain smear and culture positive or who are suspects for treatment failure. In such cases, it is usually not necessary to repeat DST within less than two to three months of the previous DST.

A key component of monitoring the progress of treatment is patient-centred directly observed therapy (DOT). All treatment should be given under direct observation and DOT providers should be trained on the signs of treatment failure. Systemic reviews have shown that DOT for MDR-TB patients is an independent predictor of success *(3)*; DOT provider(s) responsibilities are discussed in Chapter 18.

Table 10.1 summarizes the activities for monitoring treatment response. Annex 6 summarizes all monitoring tests for both response to treatment and monitoring for adverse events.

TABLE 10.1 **Activities for monitoring treatment response**

MONITORING EVALUATION	RECOMMENDED FREQUENCY
Evaluation by clinician	*During the intensive phase*: Every day during the first weeks if hospitalized and at least every week if treated as outpatient, until the treatment is well tolerated. Once stable, the patient is seen twice a month or once a month. *During the continuation phase*: Monthly assessments unless there is a medical necessity to see the patient more often. The DOT supporter sees the patient daily between consultations and signals any concerns to the clinician.
Treatment adherence and tolerance	Daily at every DOT encounter by the DOT provider.
Sputum smears and culture	Monitoring smears and culture monthly throughout treatment. (Note: programmes with limited resources may choose to do monthly smears and cultures until conversion and then monthly smears with every other month cultures.)
Weight	At baseline, then every two weeks for first three months and then monthly.
Height	At start of treatment for all (to be able to assess BMI throughout treatment); monthly for children (to assess growth).
Drug susceptibility testing	At baseline for first- and second-line anti-TB drugs. Repeat DST for patients who remain culture-positive or revert after month four (see Chapter 3 for more information on DST).
Chest radiograph	At baseline, and then every six months.

10.3 Assessment of patients when treatment failure is suspected

Any patient not clinically responding to therapy after several weeks should be considered at risk for failure. In particular, patients who had at least four months of full adherence to what was deemed to be an effective treatment regimen with quality-assured drugs that show either clinical, radiographical or bacteriological evidence of active disease, or reappearance of disease, should be considered as being at high risk for treatment failure. The following steps are recommended in such a situation.

- **The treatment card should be reviewed to confirm that the patient has fully adhered to treatment.** The supervisor of the DOT provider should confirm that the patient has taken all the prescribed medicines. A non-confrontational interview with the patient should be undertaken with and without the DOT provider being present. Questions should be asked to rule out the possible manipulation of the DOT provider by the patient, or of the DOT provider(s) not fulfilling their duties. If manipulation is suspected, the DOT provider should be removed of DOT responsibilities with the patient, receive additional training and get closer supervision whenever he/she is assigned another DOT provider role. If the DOT provider is not fulfilling his/her duties even then, removal from the job may be requried.
- **Look for undetected comorbidities.** Some undetected comorbidities mimic treatment failure through clinical and chest radiographical deterioration that occurs simultaneously with repeated culture- and smear-negative results. These comorbidities, such as NTMs, fungal infections, lung infections, or a pulmonary malignancy should be diagnosed and treated appropriately. Illnesses that may decrease absorption of medicines (e.g. chronic diarrhoea) or may result in immune suppression (e.g. HIV infection) should also be excluded.
- **The bacteriological data should be reviewed.** One single positive culture in the presence of an otherwise good clinical response can be caused by a laboratory contaminant or error. In this case, subsequent cultures that are negative help prove that the apparently positive result did not reflect treatment failure. Positive smears with negative cultures may be caused by the presence of dead bacilli and therefore may not indicate treatment failure.
- **Review the DST.** If there is evidence of acquired resistance to fluoroquinolones or second-line injectable drugs while on the MDR regimen, treatment failure is probable and a new regimen may need to be started.
- **Review treatment regimen.** The treatment regimen should be reviewed in relation to medical history, contacts and all DST reports. If the regimen does not meet the WHO standards of an adequate regimen, a new regimen should be designed following the principles presented in Chapter 5.

Patients who have persistent positive smears or cultures late into the continuation phase but who are doing well clinically and radiographically may not require a regimen change. Treatment failure is defined in Chapter 2. Whenever a regimen change is indicated because of treatment failure, a new regimen is started (with at least four likely effective drugs) and options for adjunctive treatment – most commonly surgery – can be considered. Adding one drug to a failing regimen is always to be avoided.

10.4 Indications for suspending treatment[7]

If the patient continues to deteriorate despite the measures described in the previous section, treatment failure should be considered. There is no single set of parameters to indicate that cure is possible (or impossible) or an absolute time frame to determine whether a treatment regimen is failing. Although there is no simple definition to determine failure, sometimes it becomes clear that the patient is not going to improve despite the treatment delivered. Signs suggesting treatment failure with no further options to available cure include the concurrence of several of the following.

- Persistent positive smears or cultures in the past eight to 10 months of treatment.
- Progressive extensive and bilateral lung disease on chest radiography with no option for surgery.
- High-grade resistance (often extensively drug-resistant TB (XDR-TB) with additional resistance) with no option to add at least two additional effective agents.
- Severe drug intolerance that does not respond to all existing measures to prevent and alleviate it.
- Overall deteriorating clinical condition that usually includes weight loss and respiratory insufficiency.

The ways to approach the patient and family on suspending therapy and the provision of end-of-life care, especially when treatment options have been exhausted, is addressed in Chapter 13.

10.5 Follow-up after successful completion of MDR-TB treatment

Patients should be followed up post treatment. Even though a patient has been cured of drug-resistant TB they may have sequelae from the disease that needs regular follow-up for care *(4)*. For example, they may have parenchymal damage in the lung and be at risk for bacterial pneumonias. Second, all cured patients are at risk for relapse of TB. Scheduled visits for the patient at three, six and 12 months post treatment is suggested, at a minimum. Also, instruct the patient to return to the clinic if there is cough of more than two weeks, or persistent fever and weight loss or for any medical concerns. Check sputum culture at six and 12 months after treatment completion date to evaluate for possible recurrence or whenever relapse is suspected.

There have been reports that molecular tests can be positive for genetic material even after cure has been reached. Further research is needed in the role of diagnosing relapse with molecular testing. Caution is warranted in the interpretation of a positive Xpert MTB/RIF or other molecular test following successful treatment.

[7] The definition of treatment failure (see Chapter 2) is different from that used in the process of suspending therapy in a patient when the therapy is failing. The clinical decision to suspend therapy is made after a clinical search for all other options has been exhausted and cure of the patient is considered to be highly unlikely.

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CHAPTER 11

Management of adverse effects and pharmacovigilance

11.1 Introduction

MDR-TB can be deadly but the drugs used to treat the disease can be harmful in many ways. This chapter focuses on the measures to promote patient safety that contribute to improving quality of care during the treatment of multidrug-resistant TB (MDR-TB), relieving unnecessary suffering. It provides information on early identification and proper management of adverse effects caused by second-line anti-TB drugs. It also introduces pharmacovigilance of anti-TB drugs, which can be part of routine monitoring in drug- resistant TB treatment programmes and is especially warranted with the introduction of new anti-TB drugs. Adverse effects in HIV coinfected patients are addressed in Chapter 8.

11.2 Monitoring for adverse effects during treatment

Close monitoring of patients is necessary to ensure that the adverse effects of second-line anti-TB drugs are recognized quickly (management and treatment of adverse effects is covered in Section 9.7). The ability to monitor patients for adverse effects daily is one of the major advantages of directly observed therapy (DOT) over self-administration of drug-resistant TB treatment. Box 11.1 lists some common adverse effects of second-line anti-TB drugs for the treatment of drug-resistant TB *(1)*.

BOX 11.1 COMMON OR RELEVANT ADVERSE EFFECTS OF DRUG-RESISTANT TB THERAPY

Nausea/vomiting	Abdominal pain	Visual disturbances
Diarrhoea	Anorexia	Seizures
Arthralgia	Gastritis	Hypothyroidism
Dizziness/vertigo	Peripheral neuropathy	Psychosis
Hearing disturbances	Depression	Suicidal ideation
Headache	Tinnitus	Hepatitis (hepatotoxicity)
Sleep disturbances	Allergic reaction	Renal failure (nephrotoxicity)
Electrolyte disturbances	Rash	QT prolongation

The majority of adverse effects are easy to recognize and patients usually voice the effects they are experiencing. However, it is important to have a systematic method for patient interview since some patients may be reticent about reporting even severe adverse effects. Other patients may be distracted by one adverse effect and forget to tell the health care provider about others. All DOT providers, including hospital, clinic or community health workers should be trained to screen patients regularly for symptoms of common adverse effects. Likewise physicians may be reluctant to report adverse events, especially serious ones, as this may reflect badly on their practise. DOT providers should be trained in simple adverse effect management and on when to refer patients to a nurse or physician.

Laboratory screening is invaluable for detecting certain adverse effects that are not often detectable by the patient and DOT provider. The schedule of monitoring in Table 11.1 is the minimal recommended frequency. More frequent screenings may be advisable, particularly for high-risk patients. Table 11.1 does not include evaluations to monitor response to therapy (see Chapter 10). Monitoring requirements for HIV patients are included in Table 11.1.

TABLE 11.1 **Baseline and routine monitoring for patients on MDR-TB regimens**

MONITORING EVALUATION	RECOMMENDED FREQUENCY
Serum creatinine	At baseline; then monthly if possible while receiving an injectable agent. Every one to three weeks in HIV infected patients, diabetics and other high-risk patients.
Serum potassium	Monthly while receiving an injectable agent. Every one to three weeks in HIV infected patients, diabetics and other high-risk patients.
Serum magnesium and calcium	Check magnesium and calcium blood levels whenever hypokalaemia is diagnosed. At baseline and then monthly if on bedaquiline or delamanid. Repeat if any electrocardiogram (ECG) abnormalities develop (prolonged QT interval).

MONITORING EVALUATION	RECOMMENDED FREQUENCY
Thyroid stimulating hormone (TSH)	Every three months if receiving ethionamide/prothionamide and *p*- aminosalicylic acid (PAS). Every six months if receiving ethionamide/ prothionamide or PAS, but not both together. TSH is sufficient for screening for hypothyroidism and it is not necessary to measure hormone thyroid levels. Monthly monitoring for clinical signs/symptoms of hypothyroidism is also necessary.
Liver serum enzymes (SGOT, SGPT)	Periodic monitoring (every 1–3 months) in patients receiving pyrazinamide for extended periods or for patients at risk for, or with symptoms of hepatitis. For HIV-infected patients monthly monitoring is recommended. For patients on bedaquiline, monitor monthly. For patients with viral hepatitis, monitor every one to two weeks for the first month and then every one to four weeks.
HIV testing	At baseline, and repeat if clinically indicated.
Pregnancy tests	At baseline for women of childbearing age, and repeat if indicated.
Haemoglobin and white blood cell count	If on linezolid, monitor weekly at first, then monthly or as needed based on symptoms; there is little clinical experience with prolonged use of linezolid. For HIV-infected patients on zidovudine, monitor monthly initially and then as needed based on symptoms.
Lipase	Indicated for work-up of abdominal pain to rule out pancreatitis in patients on linezolid, bedaquiline, D4T, ddI or ddc.
Lactic acid	Indicated for work up of lactic acidosis in patients on linezolid or antiretroviral treatment (ART).
Serum glucose	If receiving gatifloxacin, monitor fasting blood glucose at baseline and monitor monthly. Educate/remind patients on signs and symptoms of hypoglycaemia and hyperglycaemia monthly.
Audiometry (hearing test)	Baseline audiogram and then monthly while on an injectable agent. Ask patients about changes in hearing at every clinic visit and evaluate their ability to participate in normal conversation.
Vision tests	For patients on long-term ethambutol or linezolid perform at least a visual acuity test with Snellen charts and colour vision test at baseline (as a small percentage of the population has colour blindness). Repeat the test for any suspicion of change in acuity or colour vision.
Educational, psychological and social consultation	At baseline by personnel trained in health education, psychological and social issues relevant to TB management; during treatment and repeat as indicated. Refer to social worker, psychologist or psychiatrist when indicated.
ECG	An ECG should be obtained before initiation of treatment with bedaquiline or delamanid, and at least 2, 4, 8, 12, and 24 weeks after starting treatment. Monitoring ECGs should be done monthly if taking other QT prolonging drugs (i.e moxifloxacin, clofazimin) (see Annexes 4.1 and 4.2 for details).

There are a number of relatively common toxicities that are complicated to monitor, and can be life threatening or very disabling to the patient; they necessitate extra attention in monitoring and include the following.

- **Nephrotoxicity**. This is a known complication of injectable drugs, both aminoglycosides and capreomycin. The adverse effect is occult (not obviously noted by taking the history of the patient or by physical examination) in onset and can be fatal. The optimal timing for checking serum creatinine is unknown, but most current treatment programmes for drug-resistant TB check serum creatinine at least monthly. In addition, patients with a history of renal disease (including comorbidities such as HIV and diabetes), advanced age or any renal symptoms should be monitored more closely, particularly at the start of treatment. An estimate of the glomerular filtration rate (GFR) may help to further stratify the risk of nephrotoxicity in these patients (see Chapter 7, Section 7.7), patients with a low baseline GFR should be monitored closely for nephrotoxicity.
- **Electrolyte wasting.** Electrolyte loss through the kidneys is a known complication of anti-TB injectable drugs, most frequently with capreomycin. It is generally a late effect occurring after months of treatment, and is reversible once the injectable drug is suspended. Since electrolyte wasting is often occult in the early stages and can be easily managed with electrolyte replacement, serum potassium should be checked at least monthly in all patients while they receive an injectable agent.
- **Hypothyroidism.** Hypothyroidism is an effect provoked by PAS and/or ethionamide/prothionamide. It is suspected by clinical assessment and confirmed by testing serum TSH. These agents produced hypothyroidism in 3.5% of patients in one study *(3),* while in a different study the rate was greater than 50% *(4).* The higher rate in the second cohort may be a result of high rates of advanced disease, HIV and/or malnutrition. Since symptoms can be subtle, it is recommended that patients be screened for hypothyroidism with a serum TSH every three months for the first six months and then every six months thereafter. Screening with TSH should occur sooner if symptoms of hypothyroidism arise. The dosing of thyroid replacement therapy should be guided using serum TSH levels every month until a stable dose in thyroid replacement hormone is reached. Goitres can develop due to the toxic effects of PAS, ethionamide and/or prothionamide. In areas where iodine deficiency goitres are endemic, treatment with iodine is indicated, in addition to assessment and treatment for hypothyroidism.
- **Liver toxicity.** Chemical hepatitis can result from pyrazinamide, PAS and less commonly with other second-line drugs. Liver enzymes should be checked for all patients who exhibit signs of hepatotoxicity. It is recommended to check serum liver enzymes monthly for HIV positive patients on pyrazinamide.
- **Ototoxicity**. Ototoxicity refers to damage to the auditory cranial nerve (VIII), usually manifested by hearing loss, tinnitus (ringing in the ear), and/or other vestibular symptoms, such as nystagmus, ataxia; disequilibrium can also occur. Presentation is most commonly observed in patients receiving large cumulative doses of aminoglycosides and/or capreomycin. Concomitant use of furosemide, particularly in the setting of renal insufficiency, may exacerbate ototoxic effects of these medications. Patients starting therapy with hearing loss at baseline from prior aminoglycoside use are at the highest risk. Hearing loss is generally not reversible upon discontinuation of therapy. Hearing loss begins at higher frequencies and progresses to low frequencies. This often manifests as tinnitus in early stages.

Audiological surveillance reveals that even patients without any audiological complaints (tinnitus or hearing loss) may show audiological characteristics of ototoxic hearing loss at higher frequencies. As speech frequencies are affected late in the disease, complaints of difficulty in hearing often indicate a later stage in the progression of ototoxic hearing loss. Thus, audiometry for baseline and/or follow-up testing is required to pick up early hearing loss. It is recommended to do audiometry every month while on the injectable agent. If hearing loss is detected, it is usually best to stop the injectable agent and replace with an alternative agent(s) (a Group 4 drug previously not part of the regimen but thought to be effective, or a Group 5 drug such as linezolid, bedaquiline or delamanid. Often when the injectable is being replaced clinicians may use two drugs, especially if high resistance is present). If the injectable agent is felt to be critical to cure, close monitoring (weekly audiometry) and decreasing the frequency of the injectable agent to thrice a week can be tried; however, if hearing loss or vestibular disturbances continue the injectable agent should be stopped and drug replacement should be done.

- **Psychiatric disturbances.** Psychosis and depression can result in thoughts of suicide and even suicide. Assessment of the patient's psychosocial condition, including the specific question, "Are you having thoughts of suicide?," should be done routinely at the monthly visit. Similarly, signs of psychosis, anxiety, agitation and depression should be looked for monthly.
- **QT prolongation.** See Annex 4.1 on bedaquiline and Annex 4.2 on delamanid for more information on management of QT prolongation.

11.3 Management of adverse effects

Second-line anti-TB drugs have many more adverse effects than the first-line anti-TB drugs. Proper management of adverse effects begins with education of all stakeholders involved in treatment and care (see Section 11.2). Before starting treatment, the patient, DOT providers and health care workers should be instructed in detail about the potential adverse effects due to the prescribed drug regimen, the relevant early signs and symptoms associated with it, and if and when to notify the appropriate responsible authority.

Prompt evaluation, diagnosis and treatment of adverse effects are extremely important, even if the adverse effect is not particularly dangerous. Patients may have significant fear and anxiety about an adverse effect if they do not understand why it is happening. These emotions in turn may augment the severity of the adverse effect, as in the case of nausea and vomiting. Long periods of time without medical evaluation also promote feelings of isolation and abandonment by the health care system.

Table 11.2 reports the number and percentage of patients who had a particular adverse event, observed in the first five MDR-TB control sites that followed internationally endorsed recommendations on the treatment of MDR-TB *(2)*. The percentage of events may vary depending on the regimens used and prevalence of other factors such as malnutrition and HIV disease. Complete discontinuation of therapy because of adverse effects is rare and applied to only 2% of the patients in this series.

The data presented in Table 11.2 refer to patients not infected with HIV. Although data are limited, adverse effects are higher in the HIV-infected patients receiving MDR regimens *(4,5)*.

TABLE 11.2 **Prevalence of common adverse effects among 818 patients from five drug-resistant TB control programme sites *(2)***

ADVERSE EVENT	NO. AFFECTED (%)
Nausea/vomiting	268 (32.8)
Diarrhoea	173 (21.1)
Arthralgia	134 (16.4)
Dizziness/vertigo	117 (14.3)
Hearing disturbances	98 (12.0)
Headache	96 (11.7)
Sleep disturbances	95 (11.6)
Electrolyte disturbances	94 (11.5)
Abdominal pain	88 (10.8)
Anorexia	75 (9.2)
Gastritis	70 (8.6)
Peripheral neuropathy	65 (7.9)
Depression	51 (6.2)
Tinnitus	42 (5.1)
Allergic reaction	42 (5.1)
Rash	38 (4.6)
Visual disturbances	36 (4.4)
Seizures	33 (4.0)
Hypothyroidism	29 (3.5)
Psychosis	28 (3.4)
Hepatitis	18 (2.2)
Renal failure/nephrotoxicity	9 (1.1)

If the adverse effect is mild and not dangerous, continuing the treatment regimen with the help of ancillary drugs if needed is often the best option. In TB patients with advanced resistance patterns, a satisfactory replacement drug may not be available, and thus suspending a drug will make the treatment regimen less potent. Some adverse effects may disappear or diminish with time, and patients may be able to continue receiving the drug if sufficiently motivated.

It is extremely important that patients realize that an MDR-TB regimen may be their last opportunity for cure. If the MDR-TB regimen is not taken in full the strain may develop resistance to some of the drugs in the regimen, making any future regimen rely on less effective and more toxic drugs.

The adverse effects of a number of second-line drugs are highly dose dependent. Reducing the dosage of the offending drug is another method of managing adverse effects but only in cases

where the reduced dose is still expected to produce adequate serum levels and not compromise the regimen. With cycloserine and ethionamide, for example, a patient may be completely intolerant at one dose and completely tolerant at a slightly lower dose. Unfortunately, given the narrow therapeutic margins of these drugs, lowering the dose may also affect efficacy, so every effort should be made to maintain an adequate dose of the drug according to body weight. Lowering the dose by more than one weight class should be avoided (see Annex 2 and 3 for weight classes and dosing).

Pyridoxine (vitamin B6) should be given to all patients receiving cycloserine or terizidone to help prevent neurological adverse effects. The recommended dose is 50 mg for every 250 mg of cycloserine (or terizidone) prescribed.

Psychosocial support is an important component for the management of adverse effects. This is one of the most important roles played by DOT providers, who educate patients about adverse effects and encourage them to continue treatment. Patient support groups are another means of providing psychosocial support to patients.

Table 11.3 summarizes the common adverse effects, the likely responsible anti-TB drugs and the suggested management strategies. Overlapping toxicities for HIV-infected patients on ART and drug-resistant TB treatment are addressed in Chapter 10.

Management often requires the use of ancillary medications to eliminate or lessen the adverse effects. Drug-resistant TB control programmes should, if at all possible, have a stock of ancillary medications available for health care providers to prescribe to patients free of charge. Table 11.4 is a list of indications and commonly used medications for the management of adverse reactions. The list is an example of a formulary that programmes may want to have available and will assist programmes in planning respective drug management and budgeting. However, programmes may choose to have alternative medications available in the same class as those in the list, or other medications not listed here, depending on the treatment methods followed in the particular country.

It is recommended that all laboratory testing for the monitoring of therapy, pregnancy testing, HIV screening and contraceptive methods be offered free of charge.

TABLE 11.3 **Adverse effects, suspected agent(s) and management strategies**[a]

ADVERSE EFFECT	SUSPECTED AGENT(S)[b]	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Rash, allergic reaction and anaphylaxis	**Any drug**	1. For serious allergic reactions, stop all therapy pending resolution of reaction. In the case of anaphylaxis manage with standard emergency protocols. 2. Eliminate other potential causes of allergic skin reactions (like scabies or other environmental agents). 3. For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They include • Antihistamines • Hydrocortisone cream for localized rash • Prednisone in a low dose of 10 to 20 mg per day for several weeks can be tried if other measures are not helpful • Phototoxicity may respond to sunscreens, but these can also cause rash • Dry skin may cause itching (especially in diabetics), liberal use of moisturizing lotion is recommended. Dry skin is a common and significant problem with clofazimine. 4. Once the rash resolves, reintroduce remaining drugs, one at a time with the one most likely to cause the reaction last. Consider not reintroducing even as a challenge any drug that is highly likely to be the cause. 5. Suspend permanently any drug identified to be the cause of a serious reaction.	1. History of previous drug allergies should be carefully reviewed. Any known drug allergies should be noted on the treatment card. 2. Flushing reaction to rifampicin or pyrazinamide is usually mild and resolves with time. Antihistamines can be used. Hot flushes, itching, palpitations can be caused with isoniazid and tyramine-containing foods (cheese, red wine). If this occurs advise patients to avoid foods that precipitate the reaction. 3. Any of the drugs can cause hives (urticaria). To identify the drug, introduce the drugs one at a time. In the case of hives a desensitization attempt can be made (methods are described elsewhere *(6)*. 4. Any drug that resulted in anaphylaxis or Stevens–Johnson syndrome should never be reintroduced, not even as a challenge.

ADVERSE EFFECT	SUSPECTED AGENT(S)[b]	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Nausea and vomiting	**Eto, Pto, PAS, Bdq** H, E, Z, Amx/Clv, Cfz, Dlm	1. Assess for danger signs including dehydration, electrolyte disturbances and hepatitis. Initiate rehydration therapy if indicated and correct any electrolyte disturbances. If there is blood in the vomit, check haemoglobin and treat for possible bleeding ulcers. 2. Initiate a step-wise approach to manage nausea and vomiting. · **Phase 1: Adjust medications and conditions without lowering the overall dose**: –Give Eto/Pto at night –Give Eto or PAS twice or thrice daily –Give a light snack (biscuits, bread, rice, tea) before the medications –Give PAS two hours after other anti-TB drugs. **Phase 2: Start antiemetic(s):** –Metoclopramide 10 mg, 30 minutes before anti-TB medications. –Ondansetron 8 mg, 30 minutes before the anti-TB drugs and again eight hours after. Ondansetron can either be used on its own or with metoclopramide. (If ondansetron is not available, promethazine can be used.) For refractory nausea give 24 mg, 30 minutes before the dose can be tried. **Phase 3: Decrease dose of the suspected drug** by one weight class if this can be done without compromising the regimen. It is rarely necessary to suspend the drug completely.	1. Nausea and vomiting are universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy. Some nausea and even vomiting may need to be tolerated at least in the initial period. 2. Creatinine and electrolytes should be checked if vomiting is severe. Give intravenous fluids and replace electrolytes as needed. 3. Another strategy is to stop the responsible medicine for two or three days and then add it back gradually increasing the dose (advise the patient that the medicine will be increased back to a therapeutic dose in a manner that will be better tolerated). 4. Odansetron is a serotonin 5-HT3 receptor antagonist and considered to have strong antiemetic properties. It is on the WHO essential drug list. A number of other antiemetics from this class of serotonin 5-HT3 receptor antagonists exist. Trying different antiemetics, even if from the same class may be helpful for some patients. Odansetron prolongs the QT interval; avoid the use of odansetron with bedaquiline or delamanid. 5. For patients particularly anxious about the nausea, (and with “anticipatory nausea and vomiting”) a small dose of an anti-anxiety medicine (5 mg of diazepam) can help when given 30 minutes prior to the intake of anti-TB drugs.

ADVERSE EFFECT	SUSPECTED AGENT(S)[b]	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Gastritis and abdominal pain	**PAS, Eto, Pto, Cfz,** FQs, H, E, and Z	1. Abdominal pain can also be associated with serious adverse effects, such as pancreatitis, lactic acidosis and hepatitis. If any of these are suspected, obtain appropriate laboratory tests to confirm and suspend the suspected agent. 2. If symptoms are associated consistent with gastritis (epigastric burning or discomfort, a sour taste in mouth associated with reflux) initiate medical therapy with the use of H2-blockers (ranitidine 150 mg twice daily or 300 mg once daily) or proton-pump inhibitors (omeprazole 20 mg once daily). Avoid the use of antacids as they decrease absorption of fluoroquinolones. 3. For severe abdominal pain stop suspected agent(s) for short periods of time (one to seven days). 4. Lower the dose of the suspected agent, if this can be done without compromising the regimen. 5. Discontinue the suspected agent if this can be done without compromising the regimen.	1. Severe gastritis, as manifested by blood in the vomit or stool is relatively rare, but should be always treated to facilitate adherence to treatment. 2. If antacids must be used, they should be carefully timed so as to not interfere with the absorption of fluoroquinolones (take two hours before or three hours after anti-TB drugs). 3. Stop any nonsteroidal anti-inflammatory drugs the patient may be taking. 4. Diagnose and treat for *Helicobacter pylori* infections. 5. Severe abdominal distress has been reported with the use of clofazimine. Although these reports are rare, if this occurs, clofazimine should be suspended.

ADVERSE EFFECT	SUSPECTED AGENT(S)[b]	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Diarrhoea and/ or flatulence	**PAS,** Eto/Pto	1. Encourage patients to tolerate some degree of loose stools and flatulence. 2. Encourage fluid intake. 3. Treat uncomplicated diarrhoea (no blood in stool and no fever) with loperamide 4 mg by mouth initially followed by 2 mg after each loose stool to a maximum of 10 mg per 24 hours. 4. Check serum electrolytes (especially potassium) and dehydration status if diarrhoea is severe. 5. Fever and diarrhoea and/or blood in the stools indicate that diarrhoea may be secondary to something other than the simple adverse effect of anti-TB drugs.	1. Consider other causes of diarrhoea: • Pseudo-membranous colitis related to broad-spectrum antibiotics (such as the fluoroquinolones) is a serious and even life threatening condition. Fever, bloody diarrhoea, intense abdominal pain and increased white blood cells are warning signs of possible pseudo-membranous colitis. • Parasites and common waterborne pathogens in the area should be evaluated in the patient and treated. • Lactose intolerance, especially if patient has been exposed to new foods in a hospital not normally part of their diet. 2. Loperamide can be used in children over two years of age.
Hepatitis	**Z, H, R, Pto / Eto,** and PAS	1. If enzymes are more than five times the upper limit of normal, stop all hepatotoxic drugs and continue with at least three non hepatotoxic medications (for example, the injectable agent, fluoroquinolone and cycloserine). If hepatitis worsens or does not resolve with the three-drug regimen, then stop all drugs. 2. Eliminate other potential causes of hepatitis (viral hepatitis and alcohol induced hepatitis being the two most common causes) and treat any that is identified. 3. Consider suspending the most likely agent permanently. Reintroduce remaining drugs, one at a time with the least hepatotoxic agents first, while monitoring liver function by testing the enzymes every three days, and if the most likely agent is not essential consider not reintroducing it.	1. History of previous drug hepatitis should be carefully analysed to determine the most likely causative agent(s); these drugs should be avoided in future regimens. 2. Viral serology should be done to rule out other aetiologies of hepatitis if available, especially to hepatitis A, B and C. 3. Alcohol use should be investigated and alcoholism addressed. 4. Generally, hepatitis due to medications resolves upon discontinuation of the suspected drug.

ADVERSE EFFECT	SUSPECTED AGENT(S)[b]	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Hypo-thyroidism	**Eto/Pto, PAS**	1. Most adults will require 100–150 mcg of levothyroxine daily. Start levothyroxine in the following manner: • Young healthy adults can be started on 75–100 mcg daily • Older patients should begin treatment with 50 mcg daily • Patients with significant cardiovascular disease should start at 25 mcg daily. 2. Monitor TSH every one to two months and increase the dose by 12.5–25 mcg until TSH normalizes. Adjust the dose more slowly in the elderly and in patients with cardiac conditions.	1. Symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, as well as occasional depression and inability to concentrate. 2. Do not start treatment unless TSH is above 1.5–2.0 times of the upper normal limit. 3. It is completely reversible upon discontinuation of PAS and/or ethionamide/protionamide. 4. The combination of ethionamide/protionamide with PAS is more frequently associated with hypothyroidism than when each individual drug is used.
Arthralgia	**Z,** Bdq, Fluoroquinolones	1. Initiate therapy with nonsteroidal anti-inflammatory drugs (indomethacin 50 mg twice daily or ibuprofen 400 to 800 mg three times a day). 2. Lower the dose of the suspected agent (most commonly pyrazinamide) if this can be done without compromising the regimen. 3. Discontinue the suspected agent if this can be done without compromising the regimen.	1. Symptoms of arthralgia generally diminish over time, even without intervention. 2. Uric acid levels may be elevated in patients on pyrazinamide. There is little evidence to support the addition of allopurinol for arthralgias, although if gout is present it should be used. 3. If acute swelling, redness and warmth are present in a joint, consider aspiration for diagnosis of gout, infections, autoimmune diseases, etc.

ADVERSE EFFECT	SUSPECTED AGENT(S)[b]	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Tendonitis and tendon rupture	Fluoroquinolones	1. If significant inflammation of tendons or tendon sheaths occur: • Consider stopping fluoroquinolones • Give a non steroidal anti-inflammatory drug (ibuprofen 400 mg four times daily) • Rest the joint. 2. If treatment failure is likely without the fluoroquinolone • Reduce dose if possible • Ensure joint is strictly rested • Inform patient of the possible risk of tendon rupture and discuss the risks and benefits of ongoing use of the fluoroquinolone.	1. Tendon rupture with fluoroquinolone use is more likely in patients doing new physical activities and more common among older patients and diabetics. 2. Tendon rupture is relatively rare in patients on MDR-TB regimens with fluoroquinolones.
Electrolyte disturbances (hypokalaemia and hypomagne-saemia)	**Cm, Km, Am, S**	1. Check potassium. 2. If potassium is low, also check for magnesium and calcium (if unable to check for magnesium, consider empiric treatment with magnesium in all cases of hypokalaemia). 3. Replace electrolytes as needed. Dose oral electrolytes apart from fluoroquinolone as they can interfere with fluoroquinolone absorption. **Also see Annex 7 – Management of electrolyte disturbances**	1. If severe hypokalaemia is present, consider hospitalization. 2. Amiloride, 5–10 mg daily, or spironolactone, 25 mg daily, may decrease potassium and magnesium wasting, and thus useful in refractory cases. 3. Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhoea. 4. See Annexes 4.1 and 4.2 for management of hypokalaemia when the patient receives bedaquiline or delamanid.

ADVERSE EFFECT	SUSPECTED AGENT(S)[b]	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Nephrotoxicity (renal toxicity)	**S, Km, Am, Cm**	1. Discontinue the suspected agent. 2. Consider using capreomycin if an aminoglycoside had been the prior injectable drug in the regimen. 3. Consider other contributing aetiologies (non steroidal anti-inflammatory drugs, diabetes, other medications, dehydration, congestive heart failure, urinary obstruction, etc.) and address as indicated. 4. Follow creatinine (and electrolyte) levels closely, every one to two weeks. 5. Consider dosing the injectable agent two to three times a week if the drug is essential to the regimen and the patient can tolerate (close monitoring of creatinine). If the creatinine continues to rise despite twice/thrice a week dosing, suspend the injectable agent. 5. Adjust all TB medications according to the creatinine clearance (see Chapter 7, Table 7.2 and Box 7.2).	1. History of diabetes or renal disease is not a contraindication to the use of agents listed here, although patients with these comorbidities may be at increased risk for developing renal failure. 2. An example of how to calculate a creatinine clearance based on the serum creatinine is provided in Chapter 7, Box 7.2. 3. Renal impairment may be permanent.
Vestibular toxicity (tinnitus and dizziness)	**S, Km, Am, Cm,** Cs, FQs, H Eto, Lzd	1. If early symptoms of vestibular toxicity appear, change the dosing of the injectable agent to twice/thrice a week. Also, consider using capreomycin if an aminoglycoside had been the prior injectable in the regimen. 3. If tinnitus and unsteadiness worsen with the above adjustment, stop the injectable agent. **This is one of the few adverse reactions that cause permanent intolerable toxicity and can necessitate discontinuation of a class of agents.**	1. Ask the patient about tinnitus and unsteadiness every week. 2. Fullness in the ears and intermittent ringing are early symptoms of vestibular toxicity. 3. A degree of disequilibrium can be caused by Cs, FQs, Eto/Pto, INH or linezolid. Some clinicians will stop all drugs for several days to see if symptoms are attributed to these drugs. Symptoms of vestibular toxicity generally do not improve on withholding medications.

ADVERSE EFFECT	SUSPECTED AGENT(S)[b]	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Hearing loss (also see vestibular toxicity above)	**S, Km, Am, Cm,** Clr	1. Document hearing loss and compare with baseline audiogram if available. (Some degree of hearing loss occurs with most patients starting with high frequency loss.) 2. If early symptoms of hearing loss are documented, change the dosing of the injectable agent to twice/thrice a week. Also, consider using capreomycin if an aminoglycoside had been the prior injectable in the regimen. 3. Discontinue the injectable agent if hearing loss continues despite dose adjustment and add additional drugs to reinforce the regimen. Even when additional drugs are not available, stopping the injectable agent can be considered based on the patient's desire to maintain hearing. **Also see Annex 7 – Management of hearing loss**	1. Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of MDR-TB therapy. 2. Hearing loss is almost always permanent. **Continuing the injectable agent despite hearing loss almost always results in irreversible deafness**. 3. While the benefit of hearing aids is minimal to moderate in auditory toxicity, consider a trial use to determine if a patient with hearing loss can benefit from their use.

ADVERSE EFFECT	SUSPECTED AGENT(S)[b]	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Peripheral neuropathy	**Cs, Lzd, H,** S, Km, Amk, Cm, H, Fluoroquinolones, rarely Pto/Eto, E	1. Correct any vitamin or nutritional deficiencies. Increase pyridoxine to the maximum daily dose (200 mg per day). 2. Consider whether the dose of cycloserine can be reduced without compromising the regimen. If isoniazid is being used (especially high dose isoniazid), consider stopping it. If possible, switching the aminoglycoside to capreomycin may also be helpful. 3. Initiate medical therapy: • Nonsteroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms. • Therapy with tricyclic antidepressants such as amitriptyline (start with 25 mg at bedtime, the dose may be increased to a maximum of 150 mg) can be tried. Do not use tricyclic antidepressants with selective serotonin reuptake inhibitors and anti depressant drugs. • Carbamazepine, an anticonvulsant, at 100 to 400 mg twice daily can be tried. • Gabapentin (used off-label) at 300 mg thrice a day; it can be used at a maximum dose of 3600 mg/day in three or four divided doses. 4. Rarely, medication may be discontinued, but only if an alternative drug is available and the regimen is not compromised.	1. Patients with comorbid disease (e.g. diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here. 2. Neuropathy may be irreversible but many patients experience improvement when the offending agents are suspended. The neuropathy associated with linezolid is common after prolonged use and often permanent. For this reason, suspension of this drug should be strongly considered when neuropathy develops due to linezolid.

ADVERSE EFFECT	SUSPECTED AGENT(S)[b]	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Headache	**Cs, Bdq,**	Rule out more serious causes of headache including meningitis, and other infections of the central nervous system. (HIV co-infected patients should receive a head computed tomography scan and cerebrospinal fluid analysis). Start analgesics like ibuprofen or paracetamol. Also encourage good hydration. Consider low dose tricyclic antidepressants for refractory headaches.	1. Headaches are common during the initial months of MDR-TB therapy. They can present as migraine or cluster headaches. 2. To minimize headaches at the start of therapy, cycloserine can be started at lower doses of 250–500 mg and gradually increased over one to two weeks to achieve the target dose. 3. Headaches due to cycloserine and bedaquiline are usually self-limited. 4. Pyridoxine (vitamin B6) should be given to all patients receiving cycloserine to help prevent neurotoxicity. The recommended dose is 50 mg for every 250 mg of cycloserine prescribed.
Depression	**Psychological and socioeconomic circumstances, chronic disease, Cs,** fluoroquinolones, H, Eto/Pto	1. Assess and address underlying emotional and socioeconomic issues (see Chapter 12 on Social support). 2. Assess patients for coexisting substance abuse and refer to treatment if appropriate. 3. Initiate individual counselling (or group counselling if the patient is sputum smear and culture negative). 3. When depression is more significant, initiate antidepressant therapy (amitryptiline, fluoxetine or similar). Tricyclic antidepressants and selective serotonin reuptake inhibitors should be given together and should not be given to patients on linezolid. 4. Lower the dose of the suspected agent if this can be done without compromising the regimen. (Reducing the dose of cycloserine and ethionamide to 500 mg daily to see if the depression is lessened is a common strategy). 5. Discontinue the suspected agent if this can be done without compromising the regimen.	1. Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression. 2. Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated. 3. History of previous depression is not a contraindication to the use of agents listed but may increase the likelihood of depression developing during treatment. If significant depression is present at the start of treatment, avoid a regimen with cycloserine, if possible. 4. Question the patient regarding suicidal ideation any time the depression is judged to be more than mild.

ADVERSE EFFECT	SUSPECTED AGENT(S)[b]	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Suicidal ideation	**CS,** H, Eto/Pto	1. Hospitalize the patient and put under 24-hour surveillance. 2. Discontinue cycloserine. 3. Request psychiatric consultation. 4. Initiate antidepressant therapy. 5. Lower the dose of Eto/Pto to 500 mg daily until the patient is stable.	1. Keep the patient in the hospital until risk of suicide has passed. 2. If no improvement occurs after holding cycloserine, hold H and/or Eto/Pto.
Psychotic symptoms	**Cs, H,** fluoroquinolones	1. Stop the suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control. The most likely drug is cycloserine followed by high dose isonizaid. 2. If moderate to severe symptoms persist, initiate antipsychotic therapy (haloperidol). 3. Hospitalize in a ward with psychiatric expertise if patient is at risk to himself/herself or others. 4. Increase pyridoxine to the maximum daily dose (200 mg per day). 5. Lower the dose of the suspected agent (most commonly cycloserine to 500 mg a day) if this can be done without compromising the regimen. 6. Discontinue the suspected agent if this can be done without compromising the regimen. 7. Once all symptoms resolve and patient is off cycloserine, antipsychotic therapy can be tapered off. If cycloserine is continued at a lower dose, antipsychotic therapy may need to be continued and any attempts of tapering off should be done after referring to a psychiatrist trained in the adverse effects of second-line anti-TB drugs.	1. Some patients will need to continue antipsychotic treatment throughout MDR-TB treatment (and discontinued upon completion of treatment). 2. Previous history of psychiatric disease is not a contraindication to cycloserine, but its use may increase the likelihood of psychotic symptoms developing during treatment. 3. Some patients will tolerate cycloserine with an antipsychotic drug but this should be done in consultation with a psychiatrist, as these patients will need to be under special observation; this should only be done when there is no other alternative. 4. Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent. 5. Always check creatinine in patients with new onset psychosis. A decrease in renal function can result in high blood levels of cycloserine, which can cause psychosis.

ADVERSE EFFECT	SUSPECTED AGENT(S)[b]	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Seizures	**Cs, H, fluoro-quinolones**	1. Hold cycloserine, fluoroquinolones and isoniazid pending resolution of seizures. 2. Initiate anticonvulsant therapy (carbamazepine, phenytoin or valproic acid are most commonly used). 3. Increase pyridoxine to the maximum daily dose (200 mg per day). 4. Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium and chloride. 5. When seizures have resolved, restart medications one at a time. Cycloserine should not be restarted unless it is absolutely essential to the regimen. If cycloserine is reinitiated, start a dose one weight band lower.	1. An anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agent is discontinued. 2. History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well controlled and/or the patient is receiving anticonvulsant therapy. (Do not include cycloserine if an alternative drug is available.) 3. Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy. 5. Always check creatinine in patients with new onset seizures. A decrease in renal function can result in high blood levels of cycloserine, which can cause seizures. Adjusting the dose of cycloserine in the presence of low creatinine may be all that is needed to control the seizures.
Optic neuritis	**E,** Eto/Pto, Lzd, Cfz, rifabutin, H, S	1. Stop ethambutol. Do not restart. 2. Refer patient to an ophthalmologist.	1. The most common drug responsible is ethambutol and it usually reverses with cessation of the drug. 2. Improve diabetes control in diabetic patients.
Metallic taste	**Eto/Pto**, Clr, FQs	1. Encourage the patient to tolerate this side effect. 2. Sucking hard candy or chewing gum can be helpful.	1. Normal taste returns when treatment is stopped.
Gynaecomastia	**Eto/Pto**	1. Breast enlargement can be a troublesome side effect of Eto/Pto therapy, especially for male patients. Galactorrhoea has also been reported. 2. Encourage patients to tolerate this side effect.	1. Resolution occurs after treatment is stopped.

ADVERSE EFFECT	SUSPECTED AGENT(S)[b]	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Alopecia	**H, Eto/Pto**	1. Hair loss can occur or there can be significant thinning of the hair, but this is temporary and not progressive during treatment. 2. Encourage patients to tolerate this side effect.	1. Significant cosmetic change has not been reported.
Superficial fungal infection and thrush	**Fluoroquinolones** and other antibiotics with antibacterial properties	1. Topical antifungal agents or short-course oral antifungal drugs are helpful. 2. Exclude other diseases if response to treatment is not prompt (such as HIV).	1. Vaginal or penile candidiasis, oral thrush or cutaneous candidiasis in skin folds may occur with antibiotic treatment.
Lactic acidosis	**Lzd**	1. Stop linezolid if lactic acidosis occurs.	1. Lactic acidosis can be monitored with a blood test that measures lactic acid.
Dysglycaemia and hyperglycaemia	**Gfx,** Eto/Pto	1. Stop gatifloxacin and replace with different later-generation fluoroquinolone like moxifloxacin. 2. Treat diabetes as needed. Good glucose control is important during treatment.	

ADVERSE EFFECT	SUSPECTED AGENT(S)[b]	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
QT prolongation	**Bdq, Dlm, fluoroquinolones,** clarithromycin clofazimine	Any patient found to have a QTc value greater than 500ms should be managed carefully. • Repeat ECG and confirm the prolongation. • Bedaquiline and delamanid are drugs that should be stopped for QTc value greater than 500ms. Consider stopping other drugs that prolong the QT interval. • Check potassium, calcium and magnesium levels. Electrolyte levels should be maintained in the normal range in any patients with an elevated QT interval. • It is suggested to maintain potassium levels of more than 4 mEq/l and magnesium levels of more than 1.8 mg/dl. • Avoid other drugs that increase the QT interval. Monitor the patient's renal and hepatic function and adjust the dose of fluoroquinolones if impairment is present. Consider suspension of fluoroquinolone if risk of torsades de pointes outweighs the benefits of the drug. **Also see Annexes 4.1 and 4.2 for more information on QT interval monitoring with bedaquiline and delamanid**	1. The QT interval is measured from the end of the QRS complex to the beginning of the T wave on a standard ECG. The QT is corrected for heart rate, which is referred to as the QTc and calculated by most ECG machines. A normal QTc is generally <440ms. 2. Values above QTc 440ms are referred to as prolonged. Patients with prolonged QTc are at risk for developing cardiac arrhythmias like torsades de pointes, which can be life threatening. Patients with QTc greater than 500ms are at the greatest risk for developing these arrhythmias. 3. The fluoroquinolones cause prolongation of the QTc. Moxifloxacin and gatifloxacin cause the greatest QTc prolongation, while levofloxacin and ofloxacin have a lower risk. 4. Currently, ECG monitoring prior to initiation and during MDR-TB therapy is only required with the use of bedaquiline, delamanid, or when two drugs known to prolong QT (e.g.moxifloxacin, clofazimine) are combined in the same regimen.
Haematological abnormalities	**Lzd**	Stop linezolid if myelosuppression (suppression of white blood cells, red blood cells or platelets) occurs. Consider restarting with a lower dose of linezolid (300 mg instead of 600 mg) if myelosupression resolves and if linezolid is considered essential to the regimen. Consider nondrug related causes of the haematological abnormality. Consider blood transfusion for severe anaemia.	1. Haematological abnormalities (leukopenia, thrombocytopenia, anaemia, red cell aplasia, coagulation abnormalities, and eosinophilia) can rarely occur with a number of other anti-TB drugs. (See individual drug sheets, Part 3.) 2. There is little experience with prolonged use of linezolid.

[a] Adapted from *(5)* and *(6)*.

[b] Bolded agents are more likely to cause the indicated adverse effect.

TABLE 11.4 **Commonly used ancillary medications *(5)***

INDICATION	DRUG
Nausea, vomiting, upset stomach	Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, odansetron (and other serotonin 5-HT3 receptor antagonist)
Heartburn, acid indigestion, sour stomach, ulcer	H2-blockers (ranitidine, cimetidine, famotidine, etc.), proton pump inhibitors (omeprazole, lansoprazole, etc.). Avoid antacids because they can decrease absorption of fluoroquinolone
Oral candidiasis	Fluconazole, clotrimazole lozenges, nystatin suspension
Diarrhoea	Loperamide
Depression	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)
Severe anxiety	Lorazepam, diazepam
Insomnia	Dimenhydrinate
Psychosis	Haloperidol, thorazine, risperidone (Also include stocks of benzotropine or biperiden to prevent extrapyramidal effects.)
Seizures	Phenytoin, carbamazepine, valproic acid, phenobarbital
Prophylaxis of neurological complications of cycloserine and isoniazid	Pyridoxine (vitamin B6)
Peripheral neuropathy	Amitriptyline, gabapentin
Vestibular symptoms	Meclizine, dimenhydrinate, prochlorperazine, promethazine
Musculoskeletal pain, arthralgia, headaches	Ibuprofen, paracetamol, codeine
Cutaneous reactions, itching	Hydrocortisone cream, calamine, caladryl lotions
Systemic hypersensitivity reactions	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, prednisolone, dexamethasone)
Bronchospasm	Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisone, prednisolone), injectable steroids (dexamethasone, methylprednisolone)
Hypothyroidism	Levothyroxine
Electrolyte wasting	Potassium, magnesium and calcium replacement therapy (oral and intravenous formulations)

11.4 Active TB drug-safety monitoring and management (aDSM) for treatment of drug-resistant TB

Pharmacovigilance is defined by WHO as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem". It is a fundamental public health surveillance activity to inform the management of patient safety measures in healthcare. Pharmacovigilance is a facet of programme monitoring, not too different from the way many countries operate routine surveillance of TB drug resistance based on diagnostic testing. Patients can be better served if monitoring of drug safety is implemented in tandem with management of adverse events (AEs) and adverse drug reactions (ADRs). Many of the second-line anti-TB drugs are more likely to cause toxic reactions in patients than first-line drugs, making pharmacovigilance more important in the programmatic management of drug-resistant TB. By recording the occurrence of ADRs for patients on treatment, many programmes are already collecting basic data inherent to pharmacovigilance. However, the collection of such data and the measurement of indicators on pharmacovigilance are not part of the standard parameters used in monitoring of TB patients on treatment. Consequently, in most programmes, the nature and frequency of harm caused by the drugs themselves are poorly profiled and can only be inferred indirectly from interruption or failure of treatment. As programmes start to incorporate newly released drugs into treatment regimens, WHO recommends that they also improve their capacity to undertake pharmacovigilance, which is fundamental to ensure the safety of patients and the updating of patient safety standards, drug safety profiles and TB treatment guidelines.

In November 2014, a WHO workshop with broad representation from stakeholders and experts was held in Viet Nam to define the methods for active surveillance of drug-safety concerns in TB programmes *(7)*. In order to improve understanding and arrive at a broad consensus on the ways to address patient safety, the WHO Global TB Programme (WHO/GTB) convened key technical partners to a consultation meeting in Geneva, Switzerland on 28–29 July 2015 *(8)*. The technical partners discussed essential requirements for the implementation of active pharmacovigilance and proper management of AEs and ADRs (which is one of the conditions included in the WHO interim policies on the use of new anti-TB medicines or novel MDR-TB regimens). The consensus reached during this meeting and in subsequent discussions is presented in the framework for the implementation of active TB drug-safety monitoring and management (aDSM) *(9)*. The framework document outlines the agreed essential requirements for aDSM in patients on treatment for drug-resistant TB and proposes key terms that were adapted to the specific context of TB drug-safety monitoring. This section provides advice on implementing the WHO policy on aDSM for the treatment of MDR-TB. TB practitioners, health officials, planners, public health teams, drug regulatory authorities and others should become familiar with other publications relating to the subject *(10,11)*.

11.4.1 Definitions used in aDSM *(9)*[8]

Active TB drug-safety monitoring and management (aDSM)* is the active and systematic clinical and laboratory assessment of patients on treatment with new anti-TB drugs, novel MDR-TB regimens, or XDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities. While all detected AEs need to be managed, the core package of aDSM requires the reporting of serious AEs (SAEs) only. M/XDR-TB treatment sites with additional resources may also monitor other AEs that are of clinical significance or of special interest to the programme, as part of comprehensive aDSM.

Adverse drug reaction (ADR) is a response to a TB medicine which is noxious and unintended, and which occurs at doses normally used in humans.

Adverse event (AE) is any untoward medical occurrence that may present in a TB patient during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment.

Serious adverse event (SAE) is an AE that leads to: death or a life-threatening experience; hospitalization or prolongation of hospitalization; persistent or significant disability; or a congenital anomaly. SAEs that do not immediately result in one of these outcomes but may require an intervention to prevent it from happening are included *(12)*. SAEs may require a drastic intervention, such as termination of the drug suspected of having caused the event.

Adverse event of special interest* is an AE documented to have occurred during clinical trials and for which the monitoring programme is specifically sensitized to report regardless of its seriousness, severity or causal relationship to the TB treatment. The centres that offer intermediate and advanced packages of aDSM will include all AEs of special interest in their reporting.

Adverse event of clinical significance* is an AE which is either (i) serious, (ii) of special interest, (iii) leads to a discontinuation or change in the treatment, or (iv) judged as otherwise clinically significant by the clinician. The centres that offer the advanced package of aDSM will include all AEs of clinical significance in their reporting.

Adverse event leading to treatment discontinuation or change in drug dosage* is that which leads a clinician to stop, interrupt temporarily or change the dosage of one or more drugs, regardless of its seriousness, severity, or causal relationship to the TB treatment.

Causal relationship is a relationship between an exposure (A) and an event (B) in which A precedes and causes B. This may refer to the causal association between an exposure to a TB medicine and the occurrence of an adverse reaction.

Causality assessment is the evaluation of the likelihood that a TB medicine was the causative agent of an observed adverse reaction.

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[8] The definitions of some terms have been modified from the ones in general usage in order to fit better the context of national TB programmes.

Drug-safety profile* is a description of the benefits, risks and toxicity of a given TB drug or regimen, specifying any known or likely safety concerns, contraindications, cautions, preventive measures and other features which the user should be aware of to protect the health of a TB patient.

Sentinel sites* are centres which in addition to the core package of aDSM also undertake intermediate or advanced levels of drug-safety monitoring.

Signal is reported information on a possible causal relationship between an adverse event and a TB medicine, the relationship being unknown or incompletely documented previously or representing a new aspect of a known association. The information may arise from one or multiple sources that is judged to be of sufficient likelihood to justify verification *(14)*.

11.4.2 What to monitor for aDSM

The detection of SAEs, which lead to hospitalization, or prolongation of hospitalization, a persistent significant disability, a congenital anomaly, a life-threatening condition, or death, will be a priority for monitoring. Reporting of SAEs as per ICH[9] definition is a necessity. All deaths are to be reported and as much relevant information on ascertainment of the cause of death should be consistently collected. This may require recovering information from vital registration coding. Reporting of AEs and other events (e.g. pregnancy, lactation exposure) may be required, primarily based on what is known about the safety profile of the new agent and also for other possible harms which have not yet been described. Some countries (e.g. Kenya) have developed utilities for the electronic reporting of suspected adverse drug reactions.[10]

A cohort-based monitoring is the best method in pharmacovigilance for new anti-TB drugs and novel regimens. WHO recommends this for conducting pharmacovigilance on the new drugs bedaquiline and delamanid (see Annexes 4.1 and 4.2). Independent experts who reviewed the available information on safety of bedaquiline and delamanid supported this recommendation in the Guideline Development Group meetings held in 2013 and 2014, respectively. Both these medicines are still relatively new and only a limited number of patients have been treated with them. Their conditional marketing approval by stringent drug regulatory authorities ahead of the completion of Phase III trials took into account the serious nature of MDR-TB and the unsatisfactory outcomes obtained when regimens composed solely of older second-line drugs were used. All reasonable measures are thus needed to ensure that patient safety is monitored alongside the effectiveness of treatment. In this situation, spontaneous reporting is not expected to represent an appropriate level of care, and active and cohort-based drug-safety monitoring approaches are considered necessary to improve early and systematic detection, and management of harms. Conversely, it is also important to collect safety data accurately to ensure that any AE is properly investigated and no hasty conclusions are drawn on the causative medicine. A cohort approach is essential to avoid bias in the selection of patients or in the

[9] Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 25 August 2007. Guideline for Industry – Clinical safety data management: definitions and standards for expedited reporting. FDA Center for Drug Evaluation and Research; 1995 (http:// www.fda.gov/downloads/Drugs/Guidances/ucm073087.pdf, accessed February 24, 2014).

[10] http://pharmacyboardkenya.org/downloads/?file=MIPV_Newsletter_4th_Edition.pdf, accessed February 24, 2016.

measurement of events. It is also best suited to infer on the potential association of an event with the given exposure. Lastly, the cohort approach provides denominators and baseline data for analysis.

The term aDSM defines the active and systematic clinical and laboratory assessment of patients while on treatment. aDSM applies to patients on treatment with new anti-TB drugs, novel MDR-TB regimens or XDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities. The appropriate and timely management of all AEs and ADRs is an integral component of aDSM and patient care.

The recording and reporting of aDSM primarily target SAEs as a core requirement. Programmatic management of drug-resistant TB (PMDT) sites with additional resources may also monitor other AEs that are of clinical significance or of special interest to the PMDT programme as part of an extended aDSM approach.

aDSM is currently being recommended by WHO for MDR-TB and XDR-TB patients treated with new medicines (such as bedaquiline or delamanid), MDR-TB patients enrolled on treatment with novel regimens (such as shorter (9-month) MDR-TB regimen recently recommended by WHO), and all other XDR-TB patients on second-line treatment (as these regimens often include multiple repurposed drugs). Once these groups of patients are covered, aDSM can be extended to other patients on treatment with conventional MDR-TB regimens, depending on the resources available.

aDSM is important when patients are treated with a medicine for which the drug safety profile is as yet incomplete. This does not depend on the number of patients enrolled. Monitoring needs to be closely associated with early action to prevent and manage any serious consequences to the individual patient. A national programme should also strive to capture data in the private sector and through public–private partnerships.

aDSM is intended to pick up not only the known reactions associated with a drug but also any unexpected effect of treatment (some of these may actually be beneficial to the patient). For aDSM, a non-severe event may be the early manifestation of a more consequential process (e.g. a dose-dependent effect). Where it is feasible for the programme, such events should be captured on the data collection forms. To reduce the workload, entering of this information into the aDSM database is kept optional.

Objectives of aDSM

The overall objectives of aDSM are to reduce risks from drug-related harms in patients on second-line treatment for drug-resistant TB and to generate standardized aDSM data to inform future policy updates on the use of such medicines. To achieve these objectives, the aDSM includes three essential activities:

i. Patients targeted for aDSM should undergo active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs.
ii. All AEs detected should be managed in a timely manner in order to deliver the best possible patient care (as described in section 11.3).

iii. Standardized data should be systematically collected and reported for any SAE detected:[11] these will eventually be used to characterize the types of SAEs, assess the safety of treatment and inform future policy on the use of these medicines.

Levels of monitoring in aDSM

There are three levels of monitoring in aDSM.

i. Core package that requires monitoring for and reporting of all SAEs.
ii. Intermediate package that includes SAEs as well as AEs of special interest (see 11.4.1).
iii. Advanced package that includes all AEs of clinical significance (see 11.4.1).

All PMDT sites treating eligible patients with new anti-TB drugs, novel MDR-TB regimens or for XDR-TB require the core package. These treatment centres should, as a minimum, also be taking part in spontaneous reporting of ADRs as required by local regulations. Expansion of aDSM should be implemented in a phased approach as and when resources permit.

All SAEs detected should be reported to the national authority responsible for pharmacovigilance according to individual country requirements (including time limits for reporting) and should be regularly assessed for causality.

It is recommended to regularly check the WHO website (http://www.who.int/entity/tb/areas-of-work/drug-resistant-tb/treatment/pharmacovigilance/en/index.html) for updated information on aDSM.

11.4.3 Implementing aDSM

The implementation of aDSM will require the following eight essential steps.

i. Create a national coordinating mechanism for aDSM
ii. Develop a plan for aDSM
iii. Define management and supervisory roles and responsibilities
iv. Create standard data collection materials
v. Train staff on the collection of data
vi. Define schedules and routes for data collection and reporting
vii. Consolidate aDSM data electronically
viii. Develop capacity for signal detection and causality assessment.

Ideally, all eight steps should be in place before patients are enrolled on treatment with new drugs, novel MDR-TB regimens or XDR-TB treatment. As this may not always be feasible, the following two steps – step (iv) create standard data collection materials; and step (v) train staff on the collection of data – are essential ahead of any patient enrolment.

A fully functional aDSM is not required at the time of ordering drugs or starting patients on treatment. However, certain key elements need to be in place so that essential safety data

[11] Countries and stakeholders may also monitor other AEs of special interest or clinical significance (see next section).

are collected for all patients the moment they are started on a new drug or new regimen. The capacity for aDSM could be built over the following months.

The aDSM plan would clearly define the activities and standard operating procedures, including the plan for data collection, reporting of indicators, analysis and communication. The final document would be incorporated within the national TB or PMDT guidelines. Local and/or international experts in drug safety as well as the national pharmacovigilance centre (if functional) should be engaged.

While some of the data collection tools for aDSM are separate from those used for routine PMDT monitoring, the process could be integrated with other cohort-based monitoring for bacteriological response and outcomes that have been a standard feature of the PMDT component of TB control programmes for several years (see Chapter 2 of this book and the corresponding annexes). WHO is working closely with partners towards further integration of aDSM within routine PMDT programme monitoring.

In the core package of aDSM, clinical and laboratory test records at baseline and during regular reviews (e.g. monthly intervals) would be integrated in an expanded version of the programmatic MDR-TB (second-line TB) Treatment Card (see Annex 11.1 for an example).

A standard form (in paper or electronic format) to alert the programme when any SAE occurs will need to be developed (see Annex 11.2 for an example), with content similar to that used by the national pharmacovigilance centre for spontaneous reporting.

Staff at the different levels of health services would be informed and trained on the use of new anti-TB drugs or novel regimens ahead of any patient enrolment. This training would need to include instruction on the completion of aDSM forms. It is important that this activity is completed ahead of any patient enrolment to ensure timely identification of AEs that need to be managed as well as proper and complete collection of information.

All AEs detected during routine clinical patient care should lead to an appropriate and timely management response to limit potential harms to the patient. In terms of monitoring, the minimum requirement for aDSM is that all SAEs be registered and reported, regardless of their severity or having been caused by any of medicines to which the patient is exposed.

Some centres with sufficient resources may be designated as "sentinel sites" and undertake monitoring additional to that required by the core package of aDSM, such as the reporting of AEs of special interest or AEs of clinical significance (see above). In many countries the law mandates the reporting of ADRs to the national pharmacovigilance centre. In all public and private health services, TB practitioners should comply with the national legal requirements for such reporting.

The creation of an electronic database – or preferably the adaptation of an existing TB patient database to accommodate the additional data fields required – is an important step in aDSM implementation. It will ensure the standardization and safekeeping of data. If data are collected on paper forms these need to be entered regularly into the electronic database. The management

of data in electronic format is indispensable for facilitating data sharing and data analysis, as well as generating indicators

Measures would be taken to avoid duplication of work by revising existing databases, ensuring interoperability of data management systems, consulting with local pharmacovigilance authorities and granting access rights to users for different data as needed (Figure 11.1). The roles and responsibilities for data management and analysis would be specified in the aDSM plan in an effort to avoid the creation of parallel systems of ADR reporting and make use of the best possible expertise on drug safety in the country.

In addition to the identification of signals and causality assessment, indicators will be useful to assess the coverage of aDSM activities and to summarize the overall AE experience of monitored patients. For these purposes Table 11.5 and Table 11.6 respectively present the indicators and a "drug-safety profile" as proposed at the WHO workshop held in Hanoi, Viet Nam in 2014 *(7)*. The essential laboratory tests and examinations that need to be conducted will be determined by the programme protocol. A minimum list of variables and a data dictionary for an aDSM database can be accessed at http://www.who.int/entity/tb/areas-of-work/drug-resistant-tb/treatment/pharmacovigilance/en/index.html.

Development of a schedule for screening of adverse events as well as for laboratory, clinical and radiological testing is also recommended (see Annexes 13.1. and 13.2. for examples relating to a bedaquiline-based regimen and a shorter MDR-TB regimen). Both the list of data elements and the frequency of testing would be validated and customized based on local needs before they are integrated in the aDSM protocol of the programme.

11.4.4 Roles, responsibilities and support for the implementation of aDSM

The responsibility for the coordination of aDSM at national level should be assigned to an existing TB expert body, such as the MDR-TB committee (or consilium) or the technical working group on new drugs. These committees should primarily have scientific and clinical expertise for MDR-TB care and drug safety monitoring and could also include expertise important for coordination and advocacy (e.g. funding, communication, patient representation). Until such a group is tasked with this role the NTP needs to assign someone to coordinate the necessary aDSM activities and ensure that the two key steps mentioned above are in place prior to patient enrolment.

The ultimate purpose of systematic data collection within aDSM is to enable causality assessment for SAEs, determine their frequency (rates) and detect signals. Physicians skilled in MDR-TB management already attempt to assess relationships between drugs and ADRs and take appropriate clinical action. Nevertheless, formal causality assessment is a separate process that requires involvement of other experts. In a number of countries, the capacity of national pharmacovigilance centres to conduct formal causality assessment is very limited. However, where such capacity exists it would be availed of.

NTP staff are required to acquire the skills necessary to undertake essential activities related to aDSM. This is a long-term goal but needs to be started as part of the plan to introduce new anti-TB drugs and novel MDR-TB regimens. Local and/or international expertise in causality assessment needs to be sought by the programme to carry out such capacity building. WHO is also working with partners to accelerate such capacity building efforts.

The implementation of aDSM at the NTP level will be greatly facilitated by familiarity with the concept of cohort-based follow-up of patients, which is the basis for monitoring and evaluation of TB and MDR-TB treatment programmes. To date a number of countries have already successfully integrated clinical and laboratory testing schedules for active drug-safety monitoring within the TB patient cohort framework which they use to monitor treatment response and outcomes *(12,13)*. The testing schedules used in these projects have largely followed those generally recommended when second-line TB drugs are used (such as the one in Annex 13.2).

Experience from observational studies of shorter regimens for MDR-TB has shown that active drug-safety monitoring can be feasibly implemented within programmes if dedicated funding is provided. Most of the additional resources are needed to undertake clinical testing (e.g. electrocardiography, audiometry) and laboratory analyses, as well as for the added work of collecting drug-safety data.

It is envisaged that once the right skills have been acquired, and links established with appropriate experts in drug safety, causality assessment and signal detection could be organized within the PMDT programme with appropriate capacity building and support from drug-safety experts (if such capacity is missing at the national pharmacovigilance system). More work is needed to quantify the costs of aDSM and these will eventually be reflected in the tools that would be provided to help users with budgeting.

Clinicians treating patients with second-line anti-TB drugs are usually familiar with clinical monitoring for AEs; and this knowledge may not be available to many other healthcare workers within the programme. The monitoring component of aDSM is also likely to be novel to many healthcare workers. WHO/GTB and technical partners will be supporting national TB programmes to build such capacity and to integrate aDSM into routine PMDT monitoring. A training plan and resources for building capacity will be created in 2016.

The creation of a global central database to pool anti-TB drug-safety data collected through aDSM projects in different countries is envisaged from mid-2016. This could increase the likelihood of detecting rare AEs. Separate guidance will be prepared to help national programmes on how to submit their data to the global database. WHO will work with partners to establish a global database for aDSM to enhance the detection of new signals and to inform future updates of global policies on the use of anti-TB drugs and novel regimens. This is distinct from existing mechanisms for the global coordination of spontaneous reports from national pharmacovigilance systems.

Figure 11.1 Generic model of aDSM within drug-safety structures at the national level

aDSM adapted to the local situation to avoid the creation of parallel systems of reporting

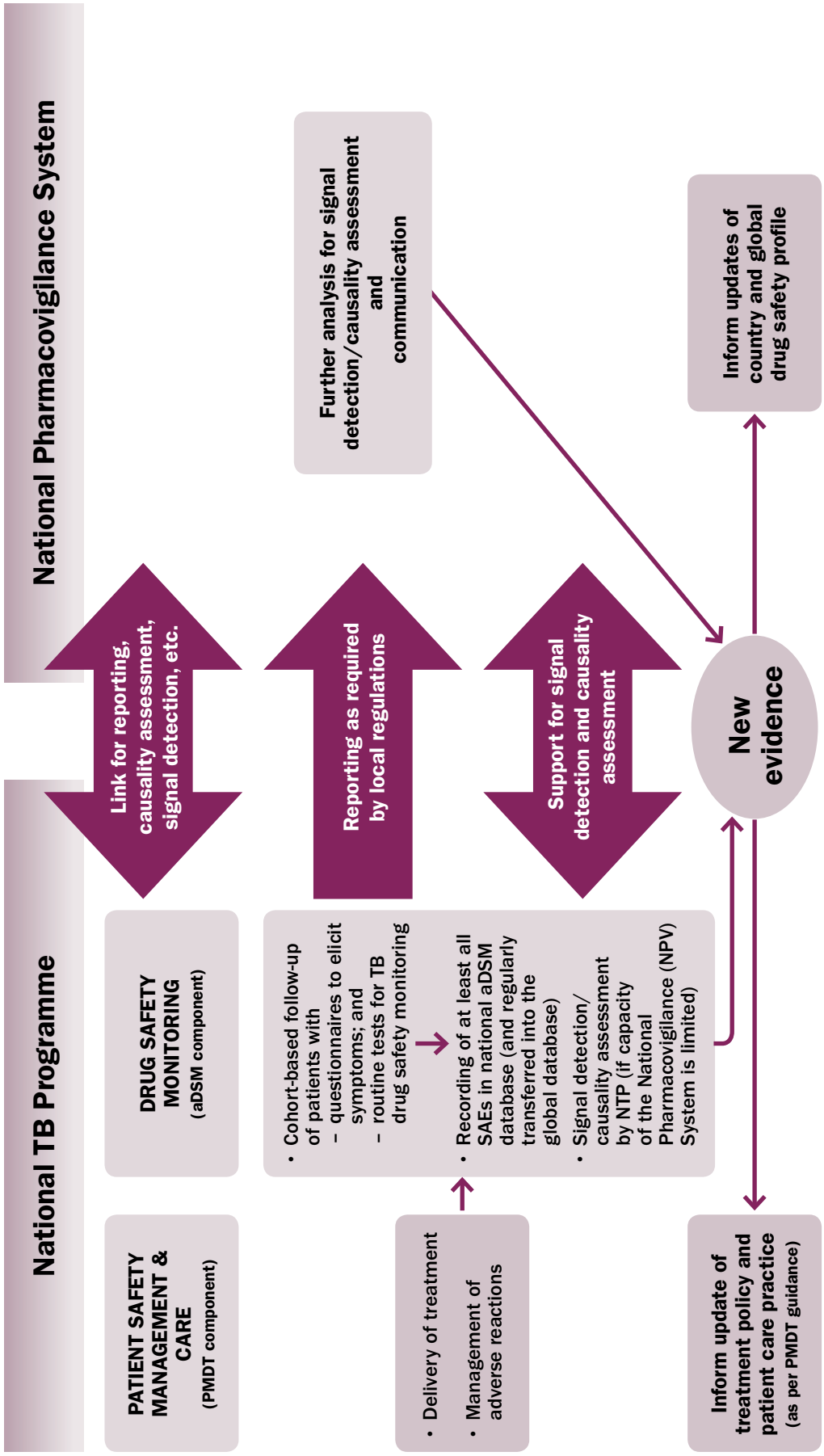

TABLE 11.5 **Programmatic indicators for aDSM**

CLASS	IMPORTANCE	INDICATOR NUMBER AND NAME	CALCULATION	STRATIFICATION	EXPRESSED AS	DATA SOURCES	LEVEL	PERIOD OF ASSESSMENT	NOTES
Coverage (process)	Essential	1) Target RR-/MDR-TB patients included in cohort event monitoring	Numerator: Number of TB cases started on target treatment included in aDSM during the period of assessment. Denominator: Number of TB cases started on target treatment during the period of assessment and who were eligible for aDSM.	None	Absolute numbers, proportion	Numerator: aDSM register. Denominator: Second-line TB treatment register.	National; NTP and national pharma-covigilance centre (NPV)	3 months	To be computed during the period of recruitment but not in the post-treatment observation phase
Completeness (process)	Optional	2) Time to stopping target drug	The difference in days between the date of start of treatment with a target drug and the date of the stopping the target drug. The calculation is done for each member of the cohort.	Reason for stopping	Number of patients included in the calcula-tion; median interval and interquartile range in days	aDSM register	National; NTP & NPV	12 months	Stratify by reason for stopping (e.g. success, died, treatment failed, loss to follow up, exclusion criterion developing after start of treatment such as pregnancy).
Serious adverse events	Essential (but stratification optional)	3) RR-/ MDR-TB patients included in aDSM with any serious adverse event	Numerator: Number of TB cases included in aDSM during the period of assessment with one or more serious adverse events. Denominator: Number of TB cases included in aDSM during the period of assessment.	By organ group; by outcome	Absolute numbers, proportion	Numerator: aDSM register. Denominator: aDSM register.	NTP & NPV	3 months	To be computed during the period of patient recruitment and during the post-treatment observation phase. Indicate outcome (deaths, hospitalisations, disability)

CLASS	IMPORTANCE	INDICATOR NUMBER AND NAME	CALCULATION	STRATIFICATION	EXPRESSED AS	DATA SOURCES	LEVEL	PERIOD OF ASSESSMENT	NOTES
Adverse reactions associated with target treatment	Optional	4) Frequency of ADRs associated with the target treatment	Numerator: Number of ADRs attributed to target treatment among patients on aDSM. Denominator: Number of TB cases included in aDSM during the period of assessment.	By organ group; by seriousness/ severity	Absolute numbers, proportion	aDSM register	NTP & NPV	3 months	To be computed during the period of patient recruitment and during the post-treatment observation phase. Only to be reported after causality assessment (e.g. dechallenge, rechallenge) suggests the target treatment as as the causative agent (certain, probable or possible). The same patient may have several ADRs (therefore the unit of measurement is the ADR and not the patients).

CLASS	IMPORTANCE	INDICATOR NUMBER AND NAME	CALCULATION	STRATIFICATION	EXPRESSED AS	DATA SOURCES	LEVEL	PERIOD OF ASSESSMENT	NOTES
Adverse reactions associated with target treatment	Optional	5) Time to development of ADRs associated with the target treatment	The difference in days between the date of start of the target treatment and the date of the first detected onset of the ADR attributed to it	By organ group	Number of ADRs included in the calculation; median interval and interquartile range in days	aDSM register	aDSM centre	6 months	To be computed during the period of patient recruitment and during the post-treatment observation phase. The calculation is done for each reaction attributed to the target treatment; the same patient may have several ADRs computed (the unit of measurement is the ADR and not the patients); if a particular ADR recurs in the same patient during the aDSM it is not calculated again. Only to be reported after causality assessment (e.g. dechallenge, rechallenge) suggests the target treatment as as the causative agent (certain, probable or possible).

TABLE 11.6 **Elements for a summary profile of drug safety/toxicity**

Draft framework for the harmonized and standardized summarization of both added benefit and risk associated with an intervention (8)

DIMENSION	ADDITIONAL NOTES
The benefit: toxicity profile of the baseline MDR-TB regimen	The MDR-TB regimen which constitutes the most widely used standard of care is described in terms of its effectiveness and associated harms; this dimension of the profile uses information originating from the published literature; trials (un-/published); observational studies and cohorts (including nested case-controls); prospective aDSM data and also other PV findings based on spontaneous reporting
Safety concerns associated with a specific drug or regimen	The characteristics (organ class), risk, severity, drug-drug interactions (DDI) and other safety concerns are summarized from the literature as well as local data (including aDSM). The known concerns are described, such as increased mortality or prolonged QTc in Bdq users; suspected reasons for lack of efficacy such as resistance or drug quality issues
Quantifying risk & benefit	As much as possible the safety concerns are also expressed in terms of risk, such as per 100 or 1000 exposures and as relative risks. The effectiveness is generally expressed in terms of % successful outcome or cure
Risk factors	These include host-related predispositions to harms, such as comorbidities, severity of TB disease, DDI, subpopulations (age-group/sex). These could form the basis of contraindications or caution in use of the regimen or drug
Signal detection	The procedure followed for relationship and causality assessments and detection of signals in the cohort is described and any departures from agreed methodologies described. Signal detection is attempted both at country- and supranational level. Any preliminary signals are discussed with the regulators and manufacturer before wide communication
Preventive measures	Advice on avoidance of harm/toxicity, precautions, contraindications

Figure 11.1 outlines the main lead responsibilities for the different components of aDSM and could be useful in assigning the complementary functions and associated funding needs. This construct is subject to adjustment based on local circumstances (e.g. if the NPV has limited capacity for running a aDSM project in the country, it may be agreed for the NTP or a technical agency to lead certain functions). Technical agencies could for instance catalyze the establishment of a committee or the protocol, organize training or provide technical assistance. Donors could have a role in supporting grant proposals for pharmacovigilance and facilitating the process for accessing the resources at country level.

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CHAPTER 12

Patient-centred care, social support and adherence to treatment

12.1 Introduction

Multidrug-resistant TB (MDR-TB) often affects the poorest and most marginalized members of a society. Their quality of life and financial situation are further aggravated by the disease, due to the adverse drug reactions produced by its treatment, the catastrophic costs they incur while seeking care and adhering to treatment, and the stigma attached to the disease and subsequent discrimination *(1,2)*. The delivery of social support services is essential in any programmatic management of drug-resistant TB that is grounded in the consideration of human rights, ethical standards, financial risk protection, and that pursues high effectiveness in efforts to prevent and treat MDR-TB. Social support may also contribute to improving the quality of life of patients. In many cases it also makes a difference to enable the patient and family to access health care. In this chapter, the patient-centred care approach to direct observation of therapy and the social support framework for programmatic management of drug-resistant TB, both aimed at improving quality of life of MDR-TB patients and enabling their adherence to treatment, are discussed.

12.2 Patient-centred care and its role in directly observed therapy (DOT)

Full adherence to drug-resistant TB treatment is essential in preventing the amplification of resistance and in increasing the chances of cure. Adherence to MDR-TB therapy is particularly difficult because of the current lengthy recommended treatment regimens, the daily high pill burden, the frequent and serious drug adverse reactions, and the indirect social and economic costs to patients associated with access to care. Thus, MDR-TB patients are at increased risk of poor adherence to treatment.

The patient-centred approach of the WHO TB strategy consists of enabling patients to exercise their rights and fulfill their responsibilities with transparency, respect and dignity, by giving due consideration to their values and needs. A patient-centred approach to programmatic management of drug-resistant TB may increase the chances of successful treatment outcomes, and improve well-being and financial risk protection by improving adherence to treatment, benefiting patients and society as a whole *(3,4)*.

Given that MDR-TB and extensively drug-resistant TB (XDR-TB) treatment are often the last therapeutic option for many patients and that there are serious public health consequences if treatment fails, it is advisable that *all* patients receive medicines under DOT as a way to ensure full adherence to treatment, with a strict patient-centred approach based on sound ethics and with due respect for human rights *(5)* (see Box 12.1 for Standard 9 of the International standards for TB care).

BOX 12.1 STANDARD 9 OF THE INTERNATIONAL STANDARDS FOR TB CARE *(5)*

"patient-centered approach to treatment should be developed for all patients in order to promote adherence, improve quality of life, and relieve suffering. This approach should be based on the patient's needs and mutual respect between the patient and the provider."

The DOT provider should maintain strict confidentiality regarding the patient's disease and treatment. In some cases, this may entail working out a system whereby the patient can receive medication without the knowledge of others. The DOT provider should be a person whom the patient is comfortable with. The provider should have the appropriate training, skills and support. In some settings and circumstances DOT may be provided by health workers and in others by community members trained to deliver second-line anti-TB medicines (see Chapter 18). While family-based DOT has shown effectiveness in several settings, health workers should be aware that family relationships are often complicated for the MDR-TB patient, and as a result either the patient or the family supporter may encounter subtle manipulation or abuse that can jeopardize adherence to treatment, management of adverse drug reactions and access to social support services.

Adherence to treatment, even under DOT, is influenced by factors at the individual (knowledge about, attitudes to, and beliefs about the disease, treatment and the health care

system, among other factors), economic (patient's access to means to cover the costs associated with DOT), health system (capacity of the system to make adherence easier and affordable for the patient) and social levels (resources available in the community to prevent the stigma and discrimination of patients) among others. Most if not all the factors associated with poor adherence to treatment can be addressed by ensuring that patients have access to social support.

12.3 Social support in MDR-TB management

Social support refers to the person's perception and confirmation that he/she is part of a social network that cares for him/her. A large body of evidence has confirmed that social support is a predictor of health status and mortality *(6)*. Social support is determined by access to four resources:

(i) *Informational support* refers to any useful information that helps a person to solve problems and address sources of stress; it includes training and education.

(ii) *Emotional support* refers to all expressions of care that contribute to strengthen self-esteem through empathy, trust, encouragement and care, among others, and that helps to deal with the psychological challenges in life.

(iii) *Companionship support* refers to the help that makes a person feel that he or she belongs to the social network, and that he or she can rely on it for certain needs.

(iv) *Material support* refers to all commodities, including financial products that a person receives through the social network as assistance to deal with daily hurdles.

Thus, establishing an effective, age- and gender-sensitive mechanism for the TB control programme and other health care providers to deliver, at least to the MDR-TB patients, the four social support functions described above, are fundamental for a patient-centred approach to promote patient well-being, and to underpin DOT that ensures adherence to treatment *(7)*. The principles of social support described here apply as well to the care to be provided to vulnerable populations, such as elders, prisoners, refugees and internally displaced persons, substance users, indigenous communities and ethnic minorities. In this Handbook we will not discuss the specifics of the management of social support to these groups, some of which are discussed elsewhere *(8)*.

12.3.1 Information support on the disease

All patients and their primary caretaker(s) should receive education about drug-resistant TB and its treatment and the need for adherence to therapy. Information and education interventions should commence as soon as diagnosis is made and continue throughout the course of treatment. Education can be provided by: physicians, nurses, community health workers and other health care providers. Materials should be appropriate to the literacy levels of the patient and should be gender, age and culturally sensitive. The national TB control programme (NTP) and all health care providers should adopt methods of 'communicating with' (and not 'talking at') patients and their caretakers, in a manner that builds a positive partnership towards successful improved quality of life and treatment completion. For patients

with literacy limitations, efforts should be undertaken to use e-health tools based on audio or visual support.

Although implementing a patient-centred high-quality TB care as outlined in the *International standards of TB care (5)* will often require additional human resources, a lot can be achieved with simple adjustments in the attitudes and language used by health care providers and by delivering key information about the disease (see Box 12.2).

BOX 12.2 TIPS FOR DELIVERING KEY INFORMATION TO THE MDR-TB PATIENT

- Always use a venue that guarantees confidentiality in communication.
- Use language that reassures mutual respect and esteem between the patient, caregivers and health care providers.
- Do not make promises that the health care service cannot keep.
- Avoid arguments and any discriminatory remarks for whatever conditions the patient has.
- Respect the patient's right to choose.
- Teach the patient how drug-resistant TB can be transmitted (long exposure to contaminated air in crowded conditions), how it cannot be transmitted (sexual relations, kisses, sharing cutlery and clothes, etc.), and teach the essentials about household infection control measures.
- While respecting patient's religious beliefs, explore proactively and clarify wrong notions the patient may have about the disease and its treatment, especially those that may become barriers to adherence to treatment.
- Enable the patient to counteract stigma and discrimination by reassuring that his/her disease is not the result of any socially or morally inappropriate behaviour that he/she has made in the past; and that many other patients have passed successfully through a similar experience.

A patient-centred approach in programmatic management of drug-resistant TB has to be reflected as well in the language used by health care providers, as language is a well-known mechanism to exert power and control. Words like 'defaulter', 'suspect' and 'control' contribute to disempowering TB patients despite the good intentions of the health care providers. It is still not uncommon to find expressions such as 'patient failed treatment', which puts the blame exclusively on the patient as if he or she was singly responsible for failure of treatment. A proposal to replace that language with words that are more respectful of patients and reflect better the values of the patient-centred approach to care is gaining momentum in the TB community *(9)*. This proposal suggests to replace 'defaulter' with 'person lost to follow-up'; 'TB suspect' with 'person with suspected TB', or 'person to be evaluated for TB'; and 'control' with 'prevention and care'. This Handbook and future TB documents of WHO are taking note of this suggestion to prevent derogative and judgmental tones in the language used to address patients and to refer to in TB prevention, diagnosis, treatment and care.

12.3.2 Information support on MDR-TB treatment

There should be a well-formulated plan for preparing the patient for treatment. This includes educating the patient and caretaker on the use of drugs, length of treatment, possible side-effects, and mechanisms to access support that will be available to the patient. Box 12.3 provides a short checklist for the health care provider to best help prepare the patient for treatment. Patient information and education takes place over several visits with different health care providers (from the DOT provider to the physician). Information and educational pamphlets with reminders of the main points, in the local language, are helpful.

Chapter 9 provides further details on medical information (patient education) to be provided to the patient and family when starting treatment.

Patients should be provided with a copy of the *Patients' Charter (10,11)* in their local language. This charter outlines the rights and responsibilities of patients, and its distribution will assist the provider in educating the patient on the disease and treatment.

BOX 12.3 CHECKLIST OF INFORMATION AND EDUCATION ISSUES TO PROVIDE TO PATIENT AND FAMILY CAREGIVERS BEFORE STARTING MDR-TB TREATMENT

- Inform the patient about the length of treatment according to the regimen selected – often at least 20 months, but it may be shorter or longer.
- Discuss where treatment will start. If at a hospital, estimate the approximate length of time. If at home ask about the home living situation and whether or not the patient feels home treatment will be possible.
- Teach the patient about the drugs in general terms: i.e. there are at least five different anti-TB drugs, which the patient will take, of which one is an injectable agent. Try to teach the names of the drugs and show what the pills look like.
- Teach the patient about possible side-effects and the actions to take once detected, including reporting to the DOT provider, especially those with serious consequences like any hearing loss, ringing in the ears or suicidal ideation.
- Teach the patient about monitoring requirements for smear, culture and laboratory tests for early detection of side-effects.
- Make sure that patients and caregivers know how to make an appointment if they need to be seen before the next routine visit.
- Make sure they know that the DOT provider can contact a doctor urgently at any time of the day.
- Instruct them what to do in case of an emergency (like severe shortness of breath, seizure, etc.)
- Always provide a copy of the TB Patient Charter, informing the patients about their rights and responsibilities related with the treatment and prevention and control of TB;
- Inform patient and family caregivers on social support and social protection options the patient is eligible for according to the existing law in the country, including palliative and end-of-life care as needed.

12.3.3 Emotional support

Having MDR-TB can be an emotionally devastating experience for patients and their social networks. Considerable stigma is attached to the disease, and this may interfere with adherence to therapy, and may badly affect the quality of life of patients in view of the discrimination that follows stigma. The provision of emotional support services to patients may increase the likelihood of therapy adherence, and the acquisition of skills to deal with stigma and discrimination. This support may be organized in the form of support groups or in one-to-one counselling by trained providers (see Box 12.4). Informal support can also be provided by physicians, nurses *(12),* DOT providers, drug-resistant TB supporters and family members. Most programmes use a multidisciplinary 'support to adherence' team (social workers, nurses, health educators, community patient supporters and doctors). Support may focus on problems related to different stages of treatment, social stigma of the illness, treatment adherence, side -effects, socioeconomic difficulties, concurrent illnesses/special situations and death. The establishment of support groups may allow patients with drug-resistant TB to meet and socialize with other patients and provide emotional support to each other.

BOX 12.4 PSYCHOLOGICAL SUPPORT TO MDR-TB PATIENTS THROUGH PEER-TO-PEER AND GROUP SUPPORT *(13,14)*

- A counsellor, social worker or someone trained in facilitating support groups should facilitate the meeting.
  A trained drug-resistant TB community nurse or health worker may cofacilitate the group.
- Clear eligibility criteria should be created for participation in each support group:
  - Participation should be generally reserved for patients who are sputum negative and are no longer infectious, especially if the meeting cannot take place in an open space.
  - Cured patients may also be invited to support groups, as they provide hope to patients who are still on treatment.
  - Some groups may be reserved for patients with serious psychosocial issues and may require a facilitator with psychiatric training.
  - Other groups may be largely self-organized and appropriate only for patients without psychiatric issues.
- Support groups may need help in inviting participants, finding a safe meeting place and other organizational issues.
- At the end of each support group meeting, the facilitator and co-facilitator should stay behind to discuss and analyse the lessons learned in the process and plan the next session.

12.3.4 Material support

Poverty, depression, stigmatization, discrimination and perceived isolation are common among drug-resistant TB patients. Socioeconomic problems – not only hunger, homelessness and unemployment, but also family responsibilities – should be addressed to enable patients and their families to adhere to MDR-TB treatment and reduce the impact that the disease and treatment have on their quality of life. These challenges can be successfully tackled through socioeconomic interventions that enable patients to adhere to treatment, such as food baskets or transportation vouchers, which usually work best in combinations tailored to specific needs *(15)*. Some NTPs and health care providers have used these and other commodities as incentives, that is, as a means to encourage patients to adhere to therapy. While incentives may have a positive impact, priority is on delivering enablers to address barriers that otherwise would be insurmountable for patients.

At the onset of treatment, an assessment of the means and financial resources of the patient should be conducted with a view to supporting those in need of assistance, using enablers. Maximal interventions should be given to patients with the most need. Social workers or other designated professionals can help assess needs and monitor their delivery. Cash transfer and microfinance interventions can positively improve household food security, which has shown to increase access to health care *(16)*. When prolonged hospitalization is necessary, financially supporting the patient and their family with a minimum 'living-allowance' would be a proactive step under the patient-centred care approach. The involvement of civil society, such as patient support groups, nongovernmental organizations, as well as community- or faith-based organizations, is fundamental for providing social support services. A more sustained mechanism for delivering material support to MDR-TB patients is the inclusion of all patients in need to the eligible list of social protection schemes that many countries have for vulnerable populations.

12.3.5 Companionship support

On-site social support for patients and their support networks through peer counselling can help to contribute to the effectiveness of TB programmes *(15)*. TB programmes can develop a comprehensive component that identifies a cured patient ('community champion/expert patient'), and provides them with training to function as a peer supporter. This worker engages in support, treatment literacy and communicating with peers under treatment. These community champions/expert patients would follow each patient from diagnosis through to cure, and they would act as both friend and educator. From the patient's perspective, having this companion available greatly reduces the psychological burden of the long duration of treatment and provides them with skills to cope with TB stigma and discrimination.

All those involved in the management of drug-resistant TB should be made familiar with the *International Standards (5)* and the *Patients' Charter (10)*. Copies of these documents should be made available in local languages, and staff should review the content as part of their continuing education. Training materials are available on request from WHO, and technical assistance can also be provided. Peer support groups, community champions/expert patients and trained health workers can offer information-sharing sessions to educate patients, assist

with better detection of risk factors for default (e.g. understanding adverse effects) and identify other warning signs that can affect treatment outcome.

Companionship support provides the groundwork for the development of a social network within the care facility, which can play an essential role in galvanizing adherence and decreasing default. Working together, a health worker, a peer supporter and the patient can facilitate wider participation, fostering a spirit of collaboration and innovation towards reducing stigma, and reaffirming that drug-resistant TB can be successfully treated within a framework of mutual respect among all stakeholders.

12.4 Planning patient-centred care for MDR-TB patients

In order to support people with drug-resistant TB during their treatment, health policy and practice must appreciate that TB affects all aspects of patients' lives. A focus on caring for each patient as an individual should underlie all aspects of treatment and care. Box 12.5 summarizes all the main areas for support during treatment and care as described above. Overall, the following principles can be followed for patient-centred care and support:

1. Develop a treatment partnership with your patient and ensure that he or she is aware of rights and responsibilities regarding TB treatment and care.
2. Focus on your patient's concerns and priorities.
3. Use the 5 A's: Assess, Advise, Agree, Assist and Arrange (see Box 12.5) *(9)*
4. Link the patient with a DOT provider for MDR-TB regimens (also called a drug-resistant TB treatment supporter, see Chapter 18).
5. Support patient self-management, as it relates to personal care and needs.
6. Organize proactive follow-up care.
7. Involve expert patients, peer educators and support staff in your health facility.
8. Link the patient to community-based resources and support and to the government social protection scheme for which the patient is eligible according to local law.
9. Use written information – registers, treatment plans, treatment cards and written information for patients – for documenting, monitoring and reminding.
10. Work as a team.
11. Assure continuity of care.

12.5 Adherence monitoring and the follow-up of the non-adherent patient

When a patient fails to attend a DOT appointment or refuses to take their medicines, a system should be in place that allows prompt patient follow-up. Most commonly, this system will involve the drug-resistant TB clinic or community nurse, doctor or supervisor assisting the drug-resistant TB DOT supporter by visiting the patient's home the same day to find out why the patient has defaulted and ensure that treatment is resumed promptly and effectively. The situation should be addressed in a sympathetic, friendly and nonjudgmental manner. Every effort should be made to listen to the patient's reasons for missing a dose(s) and to work with the patient and the family to ensure continuation of treatment.

BOX 12.5 THE 5 A'S: ASSESS, ADVISE, AGREE, ASSIST AND ARRANGE

ASSESS

- Assess patient's goals at the start of any consultation
- Assess patient's clinical status, classify/identify relevant treatments and/or advise and counsel
- Assess patient's adherence to their medications
- Assess factors associated with the patient's lifestyle that might prevent adherence to therapy
- Assess for the presence of adverse effects
- Assess the financial situation (job, education, dependents)
- Assess patient's knowledge, beliefs, concerns and daily behaviours related to drug-resistant TB and its treatment

ADVISE

- Use neutral and nonjudgmental language
- Correct any inaccurate knowledge (as assessed above) and complete gaps in the patient's understanding of his/her conditions and/or risk factors and treatments
- Considerations for developing the treatment plan:
  - Discuss the options (different treatment delivery options, regimens, infection control, palliative care) that are available to the patient to adhere to treatment
  - Discuss any proposed changes in the treatment plan, relating them to the patient's concerns (as assessed above)
  - Evaluate the importance the patient gives to the indicated treatment
  - Advise on the social protection schemes the patient is eligible to benefit from
  - Evaluate the patient's confidence and readiness to adopt the indicated treatment

AGREE

- Negotiate selection from the different options
- Agree upon options that reflect patient's priorities

ASSIST

- Provide a written or pictorial summary of the plan
- Provide a DOT provider and/or drug-resistant TB treatment supporter
- Provide treatments/medication
- Provide other medical treatments
- Provide skills and tools to assist with self-management and adherence
- Provide with sickness certificate to facilitate access to social protection schemes
- Provide adherence equipment (e.g. pill box by day of week/should stay with drug-resistant TB treatment supporter)

- Provide self-monitoring tools (e.g. calendar or other ways to remind and record treatment plan and next appointment)
- Address obstacles
- Provide psychological support as needed
- Help patients anticipate barriers to implementing the plan and identify strategies to overcome them
- If the patient is depressed, treat the depression; if the patient is a substance user then link with appropriate care services
- Link to available support:
  - Drug-resistant TB treatment supporter
  - Friends and family
  - Expert patients/Community champions
  - Peer support groups
  - Community services

ARRANGE

- Arrange follow-up care and a follow-up visit to monitor treatment progress and to reinforce key messages
- Arrange a way for the patient to contact you if problems arise before the next patient visit
- Schedule for group appointments or relevant support groups, if available
- Record what happened during the visit
- Refer to existing social services for enablers and other social support measures
- Ensure patients' preferred options to adhere to treatment

The following steps should be taken for patients showing any signs of possible poor adherence *(17)*:

- **Home visit by the health care provider involved in the drug-resistant TB programme:** The drug-resistant TB clinic or community nurse, doctor or supervisor should visit the home of the patient together with, or in addition to, the drug-resistant TB DOT supporter, as during the home visit it may be possible to identify more clinical problems than during the monthly clinic evaluation.
- **Manage side-effects:** This is one of the most common reasons for the MDR-TB patient to be lost to follow-up.
- **Counselling**: The patient may no longer want to continue treatment because he/she feels better, and therefore, feels treatment is no longer necessary. Additionally, the patient's perspective about his/her care should be assessed. The patient may have greater confidence in alternative or folk medicine. If this is the case, the drug-resistant TB DOT supporter, along with a nurse, doctor or community supervisor, should explore ways in which to meet the patient's needs, all the while putting them back on treatment.

- **Address economic problems**: Many patients are unable to work when they are ill, and may be the primary wage earners for their family. An assessment related to basic housing, food and clothing needs should be explored and ways to assist with these issues addressed.
- **Address addiction or other social problems**: Alcohol consumption and drug use are known issues that affect treatment adherence. Patients should be encouraged to stop or decrease consumption if it interferes with their treatment. Address problems with health personnel or the drug-resistant TB supporter. Social problems can affect adherence, such that the patient may be or feel mistreated by the health care facility. The drug-resistant TB supporter may arrive late which depreciates the patient. The patient should feel respected by the drug-resistant TB team and be able to communicate with them freely.
- **Involve the family**: Family is the most important source of psychosocial support for the patient. When a patient has no family, have the patient identify a person who can act as a caregiver.
- **Involve community leaders:** Community and religious leaders can be helpful if there are community-wide issues, such as stigma towards drug-resistant TB patients. This option is not always available if the patient desires to keep his or her health status confidential.

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CHAPTER 13

Palliative and end-of-life care

13.1 Introduction

The management of patients when drug-resistant TB treatment has failed and all treatment options have been exhausted is particularly challenging. A proper assessment of cases in which treatment failure is suspected, and a due process for suspending therapy are essential to protect patients and public health interests. For patients where the therapy with second-line anti-TB drugs is being stopped, there is still a need to continue providing care to alleviate the suffering *and* to prevent ongoing transmission. The psychosocial considerations in the management of multi-drug-resistant TB (MDR-TB) are even more relevant when it comes to suspending treatment. Delivering palliative care to alleviate the suffering of patients during MDR-TB treatment, but especially when all possibilities of treatment have failed, is an ethical imperative. Respiratory infection control measures are a crucial element of care for patients that remain infectious, even more when all treatment options have been exhausted and end-of-life care is being provided.

13.2 Approach to suspending therapy

MDR-TB treatment often consists of a treatment cycle; if no response is seen, reassessment of the regimen and treatment plan as well as formulation of a new plan of action are necessary. Suspension of drug therapy is recommended in cases where the medical personnel involved are confident that all the prescribed drugs have been ingested and there is no possibility of adding other drugs or carrying out surgery (see Chapter 10).

There are at least three important considerations in suspending anti-TB therapy and changing it to palliative/end-of-life care: (i) *the patient's quality of life*: the drugs used in MDR-TB treatment have significant adverse effects, and continuing them while the treatment is failing may cause additional unnecessary suffering; (ii) *the public health interest*: continuing a treatment that is failing can amplify resistance in the patient's strain, and will result in a waste of resources. Patients in whom drug-resistant TB regimens fail are likely to already have highly

resistant strains, and ongoing therapy can result in resistance to all the drugs in Groups 1–4 and multiple drugs in Group 5. These highly resistant strains may subsequently infect others and be extremely difficult to treat; (iii) *the model of care available* to provide end-of-life care *and* proper TB infection control to patients who have no effective treatment alternatives, while remaining a source of TB infection (see chapter 18 for more information on the different models for MDR-TB care).

A drug-resistant TB retreatment regimen for a patient in whom treatment is failing should not be withheld for fear of drug resistance amplification alone. When it is determined that a regimen being used is at a high risk for amplification (any regimen with less than four second-line anti-TB drugs that meet the definition of 'an effective drug' is at risk for amplification), some clinicians may prefer to continue with the regimen (especially if there is no clinical deterioration), however under strict respiratory infection control (see Section 13.4).

The approach to suspending therapy should start with discussions among the clinical team, including all physicians, nurses and directly observed therapy (DOT) providers involved in the patient's care. Once the clinical team decides that treatment should be suspended, a clear plan should be prepared for approaching the patient and the family. This process usually requires a number of visits and may take several weeks. Home visits during the process offer an excellent opportunity to talk with family members and the patient in a familiar environment. It is not recommended to suspend therapy before the patient understands and accepts the reasons to do so, and agrees with the supportive care offered. TB programmes that have planned in advance and have the resources needed to provide continued care to patients in whom all treatment alternatives have failed are in a good position to provide timely and effective care.

13.3 Palliative and end-of-life care for patients in whom all the possibilities of effective treatment have failed

WHO defines palliative care as an "approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" *(1)*. While high MDR-TB cure rates are being reported by some programmes, in many others MDR-TB remains a life-threatening condition with high mortality and poor cure rates. There is also significant suffering associated with MDR-TB illness and its treatment. These burdens add to the possibility that TB patients will not be able to adhere to treatment, and as a result treatment fails to cure them. Thus, the need for palliative and end-of-life care is being increasingly recognized as an important part of the continuum of care for all MDR-TB patients *(1–3)*.

All measures to relieve the patient of suffering caused by the disease and its treatment begins at the time of diagnosis, and continues regardless of whether or not the patient is expected to be cured or fail treatment. Thus, all the measures mentioned in this chapter are appropriate for patients in all stages of MDR-TB disease, especially among those who are less likely to be cured as well as patients who are nearing the end of life. Nonetheless, in patients with drug-resistant TB who have no anti-TB regimen options, the only realistic choice is support in the form of palliative/end-of-life care and proper infection control measures being in place.

For those in whom treatment alternatives have been exhausted there is a moral obligation to continue providing care through to the end of life *(4)*. Effective support at the end of life requires a broad multidisciplinary approach that includes the family and makes use of available community resources. It can be successfully implemented even if resources are limited. It can be provided in tertiary care facilities, in hospices, in community health centres and even in the patient's home. Proper collaboration and coordination of the national TB control programme (NTP) with other units in the health ministry responsible for cancer or HIV care, and with nongovernmental organizations working in palliative care, can facilitate the access to services for MDR-TB patients that otherwise the NTP is not set up to provide. However, the primary responsibility for the care of the patient should remain with the NTP, especially when the patient remains a source of infection.

The benefits for MDR-TB patients to receive palliative care are that it:

- provides relief from respiratory distress, pain and other symptoms;
- affirms life and regards dying as a normal process;
- intends neither to hasten nor to postpone death;
- integrates the psychological and spiritual aspects of patient care;
- offers a support system to help patients live as actively as possible until death;
- offers a support system to help the family cope during the patient's illness and in their own bereavement;
- uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated;
- enhances quality of life, and may also positively influence the course of illness; and
- is applicable early in the course of illness, in conjunction with second-line anti-TB medications, with the main therapy intended to prolong life through cure.

A number of supportive measures can be used once the therapy has been suspended. The overall supportive measures are summarized in Box 13.1. It is very important that medical care continues and that the patient is not abandoned. Several supportive measures are described in detail elsewhere *(5)*. Dyspnoea, and to a much lesser extent pain, are among the most distressing symptoms in the last stages of the disease. Thus, access to opioids and other controlled medicines is fundamental for delivering high standards of palliative and end-of-life care to patients with MDR-TB *(6)*. Many misconceptions about the use of opioids held by health care workers and caregivers result in depriving patients from the relief of suffering that these medications can provide, and contribute to create or perpetuate unethical medical practices *(7)*. The WHO Access to Controlled Medications Programme offers policy guidance, technical assistance and guidance to improve access to opioids *(8)*. NTPs may consider establishing collaboration with the corresponding officer responsible for access to controlled medicines at the health ministry, in order to guarantee access to the products needed for palliative care of MDR-TB patients according to international standards.

BOX 13.1 END-OF-LIFE SUPPORTIVE MEASURES

- **Relief from dyspnoea.** Oxygen may be used to alleviate shortness of breath in some cases but there is no significant evidence to generalize its practice. Morphine provides significant relief from respiratory insufficiency and should be offered according to established clinical protocols available in the medical literature.
- **Relief from pain and other symptoms.** Paracetamol, or codeine with paracetamol, gives relief from moderate pain. If possible, stronger analgesics, including morphine, should be used when appropriate to keep the patient adequately comfortable *(9).* The WHO has developed analgesic guides, pain scales and a three-step 'ladder' for pain relief *(10).*
- **Infection control measures.** The patient who is taken off anti-TB treatment because of failure often remains infectious. Infection control measures should be continued (see Chapter 14) with reinforcement of environmental and personal measures, including N-95 mask use for caregivers.
- **Nutritional support.** Small and frequent meals are often best for a person at the end of life. It should be accepted that the intake will reduce as the patient's condition deteriorates and during end-of-life care. Nausea and vomiting or any other conditions that interfere with nutritional support should be treated.
- **Regular medical visits.** When MDR-TB treatment stops, regular visits by health care providers and the support team should be continued to address medical needs and ensure that infection control practices are being followed.
- **Continuation of ancillary medicines.** All necessary ancillary medications should be continued as needed. Codeine helps control cough, as well as pain. Other cough suppressants can be added. Bronchospasms can be controlled with a metre-dosed inhaler with a spacer or mask. Depression and anxiety, if present, should be addressed. Antiemetics may still be needed and fever treated if the patient is uncomfortable.
- **Hospitalization, hospice care or nursing home care.** Having a patient die at home can be difficult for the family and the other way around. Home-based care should be offered to patients and families who want to keep the patient at home, whenever appropriate infection control practices can be followed. Institutionally based end-of-life care should be available to those for whom home care is not feasible or desirable. Availability of respiratory isolation facilities is essential when a patient is transferred to institutionally based palliative care for medical reasons and the patient remains infectious.
- **Preventive measures.** Oral care, prevention of bedsores, bathing and prevention of muscle contractures are indicated in all patients. Regular scheduled movement of the bedridden patient is very important. Encourage patients to move their bodies in bed if able. Keeping beds dry and clean are also important.
- **Provide psychological support.** Psychological counselling to the patient and family caregivers is critical at this stage, especially to assist patients in the planning of decisions related with the end of life, and provide emotional support, especially in settings in which strong stigma is attached to the disease.
- **Respect for patient's beliefs and values during treatment, and especially at the end of life.** It is common for the patient and family caregivers to develop or increase their interest in spiritual and religious matters once they perceive that the end of life is approaching. The health-care providers should respect have a life-threatening condition or they those beliefs and should not impose personal values and practices that prevent the patient to seek and find comfort in the services delivered by faith-based organizations.

13.4 Infection control measures and domicile considerations for the end-of-life MDR-TB patient

The patient who is taken off anti-TB treatment because of failure often remains infectious. Infection control measures should be continued, including both environmental controls and personal protection. Health workers and family members at high risk, who are providing close patient care should use particulate respirators (N95 masks or equivalent) over the nose and mouth and other infection control interventions when caring for patients who remain infectious, especially for those who have been taken off therapy (also see Chapter 14 for details on infection control). For those patients without medical reasons for hospitalization, the refurbishment of the household should be considered in order to facilitate implementation of TB infection control measures.

When patient isolation is done, strong measures to prevent loneliness, boredom and the sense of abandonment are needed to be in place. These consist of daily access to family and friends under proper infection control conditions, interaction with staff, and access to activities according to the patient's condition (radio, television, hobbies, etc.).

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CHAPTER 14

Drug resistance and infection control

14.1 Introduction

Evidence indicates that drug-resistant TB is similar in transmissibility to drug-susceptible TB *(1)*. Thus, infection control policies and strategies are not much different for drug-resistant TB. However, it does demand that every programme attempting to treat multidrug-resistant TB (MDR-TB) also undertake a systematic assessment of current policies and strategies to ensure methodical implementation of infection control policy in all health-care facilities, at public/private/household level, and in congregate settings (correctional facilities, military barracks, homeless shelters, refugee camps, student dormitories, nursing homes, among others). Infection control measures should be prioritized in settings where capacity for early detection and immediate enrolment on effective treatment is not yet readily available.

The WHO TB infection control policy is discussed in detail in another WHO document *(2)*. Unlike previous WHO guidelines that were targeted at health facilities, this policy guides WHO Member States on what to do and how to prioritize TB infection control measures at the national level, in congregate settings and at the household level. To implement this policy in low-resource settings TB CARE – one of the main global mechanisms for implementing USAID's TB strategy and developed a website (http://www.tbcare1.org/publications/toolbox/ic/) that provides a comprehensive set of examples, tools, fact sheets and case studies for adaptation and use *(3)*. Recently, a guide for monitoring the incidence of TB disease among health-care workers was developed by TB CARE partners to assist countries in strengthening their TB notification system *(4)*.

14.2 The WHO global TB infection control policy

A proper infection control assessment should be conducted taking into consideration in particular the local TB and HIV epidemiological context, climatic conditions and resources available to implement the activities described in Box 14.1, and discussed elsewhere *(1,2)*. Activities to implement the WHO global infection control policy are summarized in Box 14.1.

BOX 14.1 ACTIVITIES TO IMPLEMENT FOR THE WHO GLOBAL TB INFECTION CONTROL POLICY *(1)*

Activities for national and sub-national TB infection control

1. Identify and strengthen a coordinating body for TB infection control, ensuring that TB infection control is part of a general infection prevention and control programme.
2. Develop a comprehensive budgeted plan that includes human resource requirements for implementation of TB infection control at all levels.
3. Ensure that health facility design, construction, renovation and use are as per prescribed criteria.
4. Conduct surveillance of TB disease among health workers, and conduct assessment at all levels of the health system and in congregate settings.
5. Address TB infection control advocacy, communication and social mobilization, including engagement of civil society.
6. Monitor and evaluate the set of TB infection control measures.
7. Enable and conduct operational research.

Measures for facility-level TB infection control

1. Identify and strengthen local coordinating bodies for TB infection control as part of the facility-wide comprehensive infection prevention and control programme, and develop a facility plan (including human resources, and policies and procedures to ensure proper implementation of the controls listed below) for implementation.
2. Rethink the use of available spaces and consider renovation of existing facilities or construction of new ones to optimize implementation of controls.
3. Conduct on-site surveillance of TB disease among health workers and assess the facility.
4. Address advocacy, communication and social mobilization for health workers, patients and visitors.
5. Monitor and evaluate the set of TB infection control measures.
6. Participate in research efforts.

Administrative controls

1. Promptly identify people with TB symptoms (triage), separate infectious patients, control the spread of pathogens (cough etiquette and respiratory hygiene) and minimize time spent in health-care facilities.
2. Provide a package of prevention and care interventions for health workers, including HIV prevention, antiretroviral therapy and isoniazid preventive therapy for HIV-positive health workers.

Environmental controls

1. Use ventilation systems.
2. Use ultraviolet germicidal irradiation fixtures, at least when adequate ventilation cannot be achieved.

Personal protective equipment

1. Use particulate respirators (N95 or equivalent).

In addition to enrolling MDR-TB patients on effective treatment as quickly as possible, it is necessary to observe the following at the household level and any congregate setting whenever the MDR-TB patient remains culture positive:

- Houses should be adequately ventilated, particularly the rooms where people with infectious TB spend considerable time (natural ventilation may be sufficient to provide adequate ventilation).
- Anyone who coughs should be educated on cough etiquette and respiratory hygiene, and should follow such practices at all times.
- Smear positive TB patients should:
  - spend as much time as possible outdoors;
  - sleep alone in a separate, adequately ventilated room; and if possible
  - spend as little time as possible in congregate settings or in public transport.

The following practices should be observed whenever a MDR-TB patient is culture positive *(1)*:

- Cough etiquette and respiratory hygiene (including use of masks) should be practiced.
- Health care providers should wear particulate N95 respirator or equivalent when attending to patients in enclosed spaces.
- Family members living with HIV, or family members with a high likelihood of having HIV infection (for example, the spouse of the patient with HIV and MDR-TB), should not provide care for patients with culture positive MDR-TB. If there is no alternative, HIV-positive family members should wear N95 respirator or equivalent.
- Children below five years of age should spend as little time as possible in the same living spaces as culture positive MDR-TB patients. Such children should be followed up regularly for early detection of TB disease, and if diagnosed with TB, drug susceptibility testing should be conducted to inform treatment design.
- Culture positive extensively drug-resistant TB (XDR-TB) patients should be in respiratory isolation at all times, especially when treatment options have been exhausted, and any person in contact with such a patient should wear a N95 respirator or equivalent. If at all possible, HIV-positive family members, or family members with a strong clinical evidence of HIV infection, should not share a household with culture positive XDR-TB patients.
- If possible, potential renovation of the patient's home should be considered, to improve ventilation (e.g. building of a separate bedroom, or installation of a window or wind catcher, or both).

14.2 Impact of effective treatment on TB transmission

All the measures described above correspond to the traditional framework for TB infection control: administrative, environmental and respiratory protection. They are complex and challenging to fully implement at the institutional and household levels. The most important means of TB transmission control are active case finding, rapid diagnosis, rapid drug susceptibility testing, and prompt implementation of effective treatment (see Chapters 3, 4, 5).

It is important to emphasize effective treatment, because it is routine practice to admit patients to hospital wards without initial drug susceptibility testing and to treat them for

drug-susceptible TB while observing for clinical or bacteriological treatment failure months later, or waiting for months for results from traditional drug susceptibility testing (DST). Only then does the clinician realize that the treatment was not effective and that transmission of drug-resistant TB continued. In general, active case finding through cough surveillance of all admissions in medical and non-TB specialty wards will avoid days or weeks of transmission from unsuspected TB cases, as reported from active surveillance studies (5,6).

The rapid impact of effective chemotherapy on TB transmission, including drug-resistant strains, is the other critical information needed to reprioritize TB transmission control efforts. The impact of effective treatment on TB transmission is extremely rapid and profound, including that for MDR-TB (but transmission is ongoing if an ineffective regimen is used, for example when a first-line regimen is used in a case of MDR-TB or a MDR-TB regimen is used in a case of XDR-TB) *(7)*. This understanding comes at a time when advances in rapid diagnostics will allow the rapid diagnosis of TB and drug resistance, potentially eliminating the admission of unsuspected TB and unsuspected drug resistance, the key sources of institutional TB transmission today.

While a focus on rapid diagnosis and treatment has always been part of administrative controls, the rapid action of effective treatment has to be more fully appreciated, especially now that tools for rapid diagnosis and rapid DST are becoming increasingly available. From an institutional TB transmission control perspective the strategic implementation of each step is critical (see Box 14.2).

BOX 14.2 CRITICAL QUESTIONS TO ADDRESS WHILE LINKING INFECTION CONTROL WITH CASE FINDING AND TREATMENT

Who will do cough surveillance?

How will sputum be obtained?

How can the laboratory turnaround be optimized?

How will effective treatment based on drug susceptibility testing be started within days of presentation?

How will these operational steps be monitored?

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CHAPTER 15

Management of contacts of MDR-TB patients

15.1 Introduction

'Close contacts' of multidrug-resistant TB (MDR-TB) patients are defined as people living in the same household as the index patient, or spending many hours a day together with the patient in the same indoor space. For drug-susceptible TB, contact investigation includes the treatment of active or latent TB. For MDR-TB, however, the programmatic priority in most countries is on finding and treating contacts who have active TB. Contact tracing is an underutilized strategy that can stop the transmission of multidrug-resistant strains. The experience with treatment of latent MDR-TB in close contacts is limited, and therefore routine treatment of latent MDR-TB with second-line anti-TB drugs is not recommended at this time.

15.2 Diagnosis and treatment of contacts with active MDR-TB

Studies have shown that contact investigation is a high-yield strategy that, in many high-burden TB countries, probably merits more resources even for regular, drug-susceptible TB patients *(1)*.

In many countries where MDR-TB diagnosis and treatment are still in the early stages of scale up, MDR-TB patients face long delays before initiation of effective treatment. This means that the family has been in close contact with a highly infectious MDR-TB patient for months or years. The prevalence of active MDR-TB in household contacts is therefore likely to be higher than that of household contacts of drug-susceptible index cases, and that of extensively drug-resistant TB (XDR-TB) even higher *(2)*. Anecdotal stories of TB 'families' are common in many resource-limited settings *(3)*. A contact of an MDR-TB patient, if treated promptly with an effective regimen, is no longer infectious after initiation of effective treatment, thus stopping transmission of this strain to others inside or outside of the home. Early treatment of MDR-TB is cheaper and more effective compared to MDR-TB that is detected late. Finally,

MDR-TB patients are usually fewer in number than drug-susceptible TB patients, meaning that the feasibility and cost of MDR-TB contact investigation is realistic even for resource-limited settings.

15.2.1 Programmatic management of MDR-TB contacts

Contact investigation should be integrated into routine programmatic management of MDR-TB. The difficulty of active case finding among MDR-TB contacts should not be underestimated. MDR-TB patients have often experienced multiple failed courses of TB treatment, and have lost faith in the health care system. Family members may be unwilling to undergo additional testing, or may be reluctant to start another treatment with second-line drugs even after being diagnosed with MDR-TB. Sometimes during contact investigation, an older family member with a history of chronic TB for many years is discovered to be the true index case within the family. It is therefore imperative to address the social barriers to effective treatment so that MDR-TB contacts can be diagnosed and treated promptly.

There are multiple opportunities to investigate contacts of MDR-TB patients, and programme staff at multiple levels should be trained to screen family members for symptoms and signs of active TB.

- **Patient**. Contact investigation starts with the education of the MDR-TB patient. Patients should be educated about the infectiousness of their disease and the high risk of transmission to contacts who share the same living space. While they should not be unduly alarmed, they should be informed that their family members are likely already infected with MDR-TB, so the most important intervention is to monitor them closely for symptoms of active TB.
- **Family**. One of the most important reasons to do a home visit for every MDR-TB patient at the initiation of MDR-TB treatment is to do contact investigation. A community nurse or health care provider should educate the family that they are all likely already infected with MDR-TB, and explain the importance of notifying the community or clinical team quickly about family members who develop symptoms of active TB.
- **Clinical team**. The clinical team has multiple opportunities to inquire about the health of the MDR-TB patient's family contacts. At every clinical evaluation, doctors and nurses should ask the patient whether any family member has developed TB symptoms.
- **Community nurses or health care providers educated on MDR-TB.** During home visits to check adherence or assess the social situation, the community nurse should inquire if there are any family members who have developed symptoms of active TB. The community nurse may also directly interview the family members at their home. Community nurses are also best suited to address fears or doubts about the health system or other social barriers to treatment for MDR-TB contacts.
- **Community health workers.** In community-based programmes that incorporate home-based direct observation of treatment, community health workers are the closest to the family and are most likely to identify family members with TB symptoms. This is particularly true for members of the extended family who visit periodically.

15.2.2 Diagnostic workup of symptomatic adult contacts

Close contacts of MDR-TB patients with TB symptoms should receive a more aggressive diagnostic workup than among those in whom drug-susceptible TB is suspected. This includes:

- an evaluation by a physician, including history and physical examination;
- a chest radiograph examination;
- sputum investigations (ideally a rapid diagnostic method such as Xpert MTB/RIF, or if not available, sputum smear microscopy, culture and drug susceptibility testing (DST)); and
- HIV testing (in areas of high HIV prevalence, or if anyone in the household is known to be HIV-positive).

In contacts suspected of having extrapulmonary TB, bacteriological confirmation is often quite challenging. Sputum culture should always be done, since patients with extrapulmonary TB often have subtle pulmonary involvement. DST should be done for all contacts with a suspicion of extrapulmonary TB.

If the initial investigation is not suggestive of active TB, the household contact should continue to be monitored closely by the clinical team. The chest radiograph should be kept on file by the clinical team because it is often helpful to compare subsequent radiographs for continued symptoms or development of new symptoms in the future.

15.2.3 Diagnostic workup of symptomatic paediatric contacts

Children who live with MDR-TB patients, particularly young children, have a high risk of infection with MDR-TB and of development of active MDR-TB *(4,5)*. The diagnosis of MDR-TB in children is challenging (see Chapter 4, Section 4.8).

The diagnostic workup of child contacts of MDR-TB patients should include the following:

- an evaluation by a physician, including history and physical examination;
- a chest radiograph examination;
- tuberculin skin testing with purified protein derivative;
- sputum investigations (ideally a rapid diagnostic method such as Xpert MTB/RIF, or if not available, sputum smear microscopy, culture and DST); and
- HIV testing (in areas of high HIV prevalence, or if either parent is known to be HIV-positive).

However, if any of the above recommended investigations are not present or are inconclusive, the diagnosis of MDR-TB can still be made clinically in a child contact. Since young children are often unable to produce good sputum samples gastric aspiration using a nasogastric tube is the classic way to obtain sputum samples. Sputum induction is another method that has been shown to be safe and effective in young children *(6)*.

According to *Guidance for national tuberculosis programmes on the management of tuberculosis in children*, the presence of three or more of the following should strongly suggest a diagnosis of TB *(7)*:

- Chronic symptoms suggestive of TB
- Physical signs highly suggestive of TB
- A positive tuberculin skin test
- Chest radiograph suggestive of TB.

15.2.4 Empiric treatment of MDR-TB contacts

Studies show that close contacts of MDR-TB patients who develop active TB almost always have MDR-TB themselves, even if the exact pattern of resistance is not always the same *(8–12)*. Household contacts are therefore excellent candidates for empiric MDR-TB treatment, since delay in the start of appropriate treatment can lead to increased morbidity and mortality, as well as transmission and amplification of drug resistance. As discussed in Section 4.5 (empiric MDR-TB treatment), close contacts of MDR-TB patients should be directly enrolled in MDR-TB treatment when rapid DST is not available.

- **Contacts with bacteriologically confirmed TB, but without confirmation of MDR-TB.** What should be done after the diagnosis of TB – for example, with smear microscopy – but before the laboratory confirmation of drug resistance? If rapid molecular DST is not available, confirmation of drug resistance by culture-based methods may take weeks or months. These patients should be empirically treated with the same regimen as the index patient while DST is pending. Clinical judgment can be used to decide if isoniazid and rifampicin should be added while awaiting DST results. In most cases, however, it is prudent to add these drugs to the empiric MDR-TB regimen. If the DST eventually shows that the contact was infected outside the home by a pan-susceptible strain, the contact can be switched to a regimen of first-line drugs. But in the vast majority of cases, family members are infected with the same MDR strain *(13,14)*. Treatment of MDR strains for weeks or months with ineffective regimens, such as 2HREZ/4HR or 2SHREZ/1HREZ/5HRE, can result in amplification of resistance or worse, death of the contact.
- **Contacts with extrapulmonary TB**. Certain forms of extrapulmonary TB are often culture negative. Contacts with evidence of these forms of extrapulmonary TB should therefore be started empirically on MDR-TB treatment after collecting samples of pleural tissue, as well as peritoneal and cerebrospinal fluid for TB culture. These samples are often culture negative, and there is no need to wait for bacteriological confirmation. Xpert MTB/RIF and other molecular tests can be done on a number of body fluids and tissues (also see Chapters 3 and 4) *(15)*. Close contacts with evidence of extrapulmonary TB should be started on empiric treatment with the same regimen as the index patient, with the possible addition of isoniazid and rifampicin as described above. This is particularly important for HIV-positive contacts who are at risk for developing severe forms of extrapulmonary TB that are rapidly fatal.
- **Contacts with culture negative TB.** While it is important to make an effort to confirm the diagnosis of MDR-TB in close contacts, it is often counterproductive to insist on laboratory confirmation in all patients. This is particularly true for children, who are often unable to produce good sputum samples. These children often receive multiple courses of treatment with first-line drugs and suffer significant and protracted morbidity, with the possibility of lifelong disability or even death. Once a child contact of MDR-TB meets the criteria

for diagnosis with active TB, he/she should be started empirically on treatment with the same regimen as the index patient. Isoniazid and rifampicin can be added to the regimen as described above.

15.3 Management of TB infection in close contacts of MDR-TB patients

The goal of preventive therapy is to stop people with TB infection from developing active TB. An effective preventive therapy for people likely to be infected with MDR-TB from close contacts – such as household or workplace contacts – would be an important intervention with individual and public health benefits. Unfortunately, there have been very few comparative studies of the use of second-line TB drugs to prevent disease in MDR-TB contacts *(10,16).* Ongoing clinical trials are not expected to be finalized before 2019. Recently, some experts have advocated for the treatment of adults and children who were significantly exposed to MDR-TB using a fluoroquinolone-containing regimen for at least 6 months *(17).* A Guideline Development Group convened by WHO in 2014 to revise guidance on treatment of TB infection found serious limitation in the evidence available for MDR-TB preventive therapy and recommended primarily to conduct strict clinical observation and monitoring for the early detection of symptoms of TB among contacts of MDR-TB for at least two years over the provision of preventive treatment *(18).* WHO recommends deferring the decision to start MDR-TB preventive therapy to the clinician based on an assessment of benefits to harms given the individual patient circumstances. Children under five, people living with HIV, and other groups at increased risk would be prioritised for the treatment of MDR-TB infection. The evaluation of exposure is based on clinical assessment and tests for infection and second-line DST of the source case, when available (see also Section 15.2 above). All contacts, regardless whether they receive MDR-TB preventive therapy or not, need a follow up every few months for two years after their last MDR-TB exposure to monitor closely for active disease, and for drug-related harms if prescribed treatment. The testing of all symptomatic contacts for drug resistance (eg, with Xpert MTB/RIF) and the maintenance of a database for MDR-TB contacts identified are advised. If active disease develops, prompt initiation of treatment with a MDR-TB regimen is recommended and adjusted on the basis of the strain DST (as per instructions in Chapter 5).

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CHAPTER 16

The global response to drug-resistant TB

16.1 Introduction

This chapter includes a brief situation analysis of the global drug-resistant TB epidemic, a brief review Global Plan to Stop TB, and the global framework in place to support country efforts to curb the epidemic. Multidrug-resistant TB (MDR-TB) is a global public health threat that requires coordinated efforts between the health sector and other sectors and stakeholders.

16.2 Global epidemiology and the magnitude of the drug-resistant TB problem

Drug-resistant TB today is a recognized significant public health threat with no country or region being spared. In 1994, the WHO, International Union Against Tuberculosis and Lung Disease (IUATLD) and other partners established a Global Project on Anti-TB Drug Resistance Surveillance. The aim of the project is to determine the levels of resistance to first-line TB drugs (primarily isoniazid and rifampicin) in nationally representative populations using standardized methods. In recent years, the project has also started to document the magnitude and distribution of extensively drug-resistant TB (XDR-TB) among MDR-TB cases. Emphasis is placed on epidemiological methods to ensure patient representativeness and differentiating new and retreatment TB cases (for more information see the WHO *Guidelines for the surveillance of drug resistance in tuberculosis*) *(1)*.

A network of Supranational Reference Laboratories (SRLs) has been established over the years and these centres provide quality assurance through validation of drug susceptibility data. For a list and contact details of the members of the SRL network, see the Global Laboratory

Initiative website *(2)*. There has been important progress in recent years in the global coverage of data collection on anti-TB drug resistance.

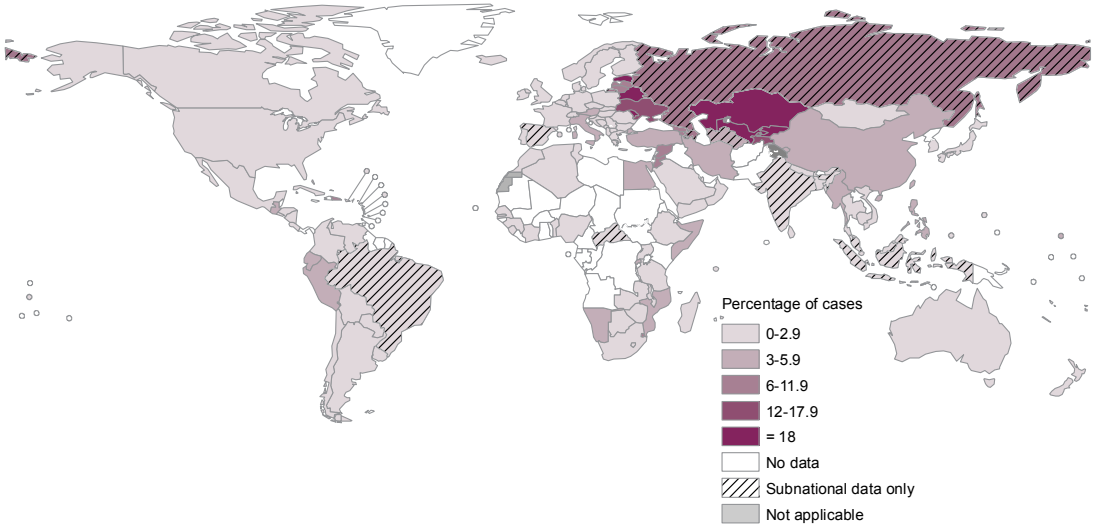
Globally, 3.6% (2.1–5.1%) of new cases and 20% (13–27%) of previously treated cases are estimated to have MDR-TB *(3)*. Each year, about 450 000 (range 300 000–600 000) MDR-TB cases are estimated to emerge, and 170 000 persons with MDR-TB die *(3)*. About 60% of MDR-TB cases are estimated to occur in China, India, the Russian Federation and South Africa alone and over 85% in 27 high MDR-TB burden countries *(1)*. The highest frequencies of MDR-TB ever reported occurred in recent years. In countries, like Belarus and parts of the Russian Federation, more than a quarter of new TB cases now have MDR-TB. Swaziland reported the highest level of primary MDR-TB ever reported in Africa in 2009 (7.7%) *(3)*. Unfortunately, data still preclude from concluding definitively about global or regional MDR-TB trends; for some countries and subnational areas time trends based on observations over several years indicate a decrease in MDR-TB frequency, while in others there appears to be an increase.

The social and economic burden of MDR-TB on patients and the health care system is self-evident, given that it takes more than 20 months of daily therapy in most of the affected patients and that the cost of treating an average MDR-TB patient is 50 to 200 times higher than treating a drug-susceptible TB case. Furthermore, MDR-TB treatment success is low at about 48% globally albeit varying substantially between countries. Of the 107 countries reporting outcomes for 2010 MDR-TB cohorts, only 34 achieved or exceeded 75% success and in many the size of cohorts was very small. Figure 16.1 and Figure 16.2 provide the reported proportions of MDR-TB among new TB cases (2011) and among previously treated TB cases (2011), respectively.

In 2006, the term 'XDR-TB' was coined referring to strains of MDR-TB resistant to fluoroquinolones and second-line injectable drugs. Patients infected with these strains were considered at a greater risk of dying and less likely to complete their treatment successfully. By 2013, 92 countries had reported at least one case of XDR. It is estimated that 9.6% (8–11%) of MDR-TB cases worldwide have XDR-TB *(3)*. Reporting is particularly low in the African continent, probably because the low capacity of drug susceptibility testing (DST) for second-line TB medicines *(4)*.

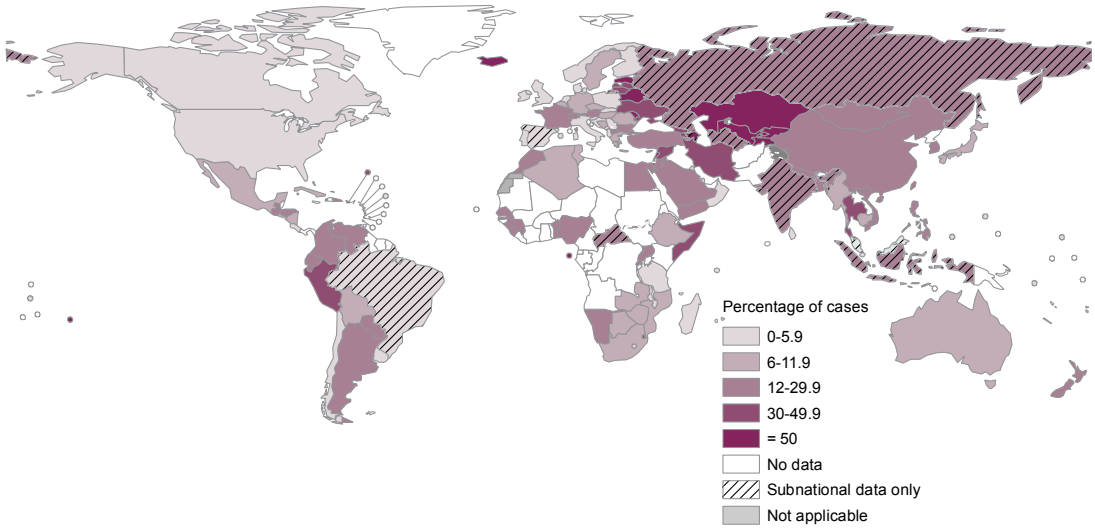
Shortly after XDR-TB was defined, cases were reported from different settings infected with strains resistant to all or most of the first-line and second-line anti-TB drugs that were tested *(5–7)*. While WHO acknowledges that such patients harbouring highly resistant strains present clinicians with a formidable challenge, an expert consultation that it convened in 2012 concluded that a new definition of resistance beyond XDR-TB is not recommended. This conclusion was reached because of the technical difficulties with DST of many anti-TB medicines, the lack of standardized DST methods for several anti-TB drugs (including new investigational compounds), and insufficient evidence to link such DST results to treatment outcomes of patients *(8)*.

Figure 16.1 Proportion of MDR-TB among new TB cases (2012)



* Figures are based on the most recent year for which data have been reported, which varies among countries.

Figure 16.2 Proportion of MDR-TB among previously treated TB cases (2012)[a]



[a] Figures are based on the most recent year for which data have been reported, which varies among countries. The high percentages of previously treated TB cases with MDR-TB in Bahrain, Bonaire – Saint Eustatius and Saba, Cook Islands, Iceland, Sao Tome and Principe, and Lebanon refer to only a small number of notified cases (<10).

* Source: Adapted from graphics from gamapserver.who.int/mapLibrary/app/searchResults.aspx

16.3 The strategy to prevent, diagnose and treat TB and the Global Plan to Stop TB 2011–2015

In order to address the overall burden caused by TB, the WHO's Stop TB Strategy defines specific objectives and components directed towards halting the epidemic *(9)*. This strategy underpins the Stop TB Partnership's *Global Plan to Stop TB 2011–2015 (10)*, which has the target of treating 50 million patients and preventing 14 million TB deaths. This plan sets out the activities oriented towards implementing the Stop TB Strategy and achieving the international targets for TB control set by the Stop TB Partnership, which is in line with the target of the internationally agreed development goal relevant to TB contained in the United Nations Millennium Declaration to "have halted by 2015 and begun to reverse the incidence of major diseases." In short, this partnership aims to halve TB prevalence and death rates by 2015 compared with 1990 levels (see Table 16.1 for the indicators and targets from the *Global Plan to Stop TB 2011–2015* as they relate to drug-resistant TB).

TABLE 16.1 **Global Plan: drug-resistant TB indicators and targets**[a]

DRUG-RESISTANT TB INDICATORS	STATUS IN 2011	TARGETS 2015
Percentage of new bacteriologically-positive TB cases tested for MDR-TB	4%	20%
Percentage of previously treated TB patients tested for MDR-TB	6%	100%
Number of high TB or high MDR-TB burden countries with >1 culture laboratory per 5 million population	18	All (36)
Percentage of confirmed cases of MDR-TB enrolled on treatment according to international guidelines	86%[b]	100%
Number of confirmed cases of MDR-TB enrolled on treatment according to international guidelines	55 600[b]	~270 000
Treatment success rate among confirmed cases of MDR-TB	about 48%[b] (2009 cohort)	≥75%

[a] Source *(13)*.

[b] The proportion treated strictly according to WHO recommendations is not measured.

In order to accelerate progress towards addressing the overall burden caused by TB, the 67th World Health Assembly at its meeting held in May 2014 endorsed a new TB strategy. (*11*). that sets newer ambitious goals to be reached by 2035. A global plan to implement this strategy will be developed by the Stop TB Partnership in 2015.

16.4 The WHO response to MDR-TB and the new framework to support scale up to universal access to quality MDR-TB management

WHO responded to the challenge of MDR–TB through the establishment of the WHO/IUATLD drug resistance surveillance project in 1994, the production of guidance for the clinical treatment of MDR-TB in 1997, and the creation in 1999 of the Working Group on DOTS-Plus for MDR-TB to lead the global efforts to prevent and control MDR-TB, in close collaboration and coordination with major technical partners and donors. WHO and this working group, which later became part of the Stop TB Partnership, created the Green Light Committee (GLC) initiative in 2000 to provide technical assistance to national TB control programmes (NTPs) on MDR-TB management, promote the rational use of second-line anti-TB drugs worldwide to prevent amplification of resistance, and enable access to preferentially priced quality-assured second-line drugs through a pooled procured mechanism via the Global Drug Facility (GDF).

The experiences gained in the GLC pilot projects proved that MDR-TB management under programmatic conditions was feasible and cost-effective, even in low-resource settings. These findings were instrumental for the production of the first ever guidelines on the programmatic management of MDR-TB, and for its inclusion in the Stop TB Strategy launched in 2006. The commitment to achieve universal access to diagnosis and treatment of MDR-TB made by the member states at the Sixty-second World Health Assembly (2009) *(12)* made it necessary to revise the mandate of the GLC. The need to establish a stronger mechanism for countries moving from pilot projects to nationwide expansion of programmatic management of MDR-TB became obvious. Thus, in 2011 the GLC initiative was revised and a new Global Framework to Support Scale Up to Universal Access to Quality Management of MDR-TB was established *(13)*. It included the creation of a global GLC (gGLC) with advisory functions to WHO and partners; and six regional GLC (rGLC) for support to countries and partners.

The **new Global Framework** provides:

1. coordinated, increased level and diverse models of technical support from partners to assist countries to plan, implement, manage and monitor the required scale-up of MDR-TB services;
2. increased access to high-quality, affordable second-line anti-TB drugs for the treatment of MDR-TB;
3. strengthened advocacy for the accelerated scale up of the response to MDR-TB; and
4. regular and supportive monitoring and evaluation of country performance in accelerating access to MDR-TB treatment and care, to inform assessment of global progress, to propose improvements to the global, regional and national approaches, and to pursue advocacy activities tailored to country needs.

The MDR-TB Working Group and gGLC were later revised, and replaced by the Global Drug-resistant TB Initiative (GDI). The main focus of the GDI will be accelerating the global response to drug-resistant TB through a partnership approach with involvement of all key stakeholders. Its mission will be to assist partners in coordinating efforts to support countries

scaling-up programmatic management of drug-resistant TB in the public and private sector (visit http://www.stoptb.org/wg/mdrtb/default.asp for a more detailed description of the strategic priorities and governance of the GDI).

To support the activities and implementation of the new global framework, GLC Committees have been established at regional levels. The rGLCs and their respective secretariats are based in the six WHO Regional Offices. The GLC activities have been decentralized to regional entities – the rGLCs. The rationale of decentralization is to bring GLC activities closer to the countries and benefit from the greater involvement of key national and international partners in the scale-up of MDR-TB services and care in the respective regions. Regional GLCs would also ensure coordination of activities with other ongoing TB, HIV and health system strengthening-related interventions. The name 'GLC' has been retained as a brand name as there is no longer any green light approval for access to second-line drugs; it is also not used as an abbreviation of its prior meaning or of a specific longer form of notation.

For more information regarding technical assistance and access to second-line drugs or any other questions related to the management of drug-resistant TB, the Global GLC Secretariat can be contacted at glc_secretariat@who.int. For technical assistance with the planning, implementation or monitoring of drug-resistant TB related activities or any other drug-resistant TB related questions, the r-GLC Secretariats can be contacted at the following emails:

Regional Office for Africa: glc_africa@afro.who.int

Regional Office for the Americas: rglc.amro@paho.org

Regional Office for the Eastern Mediterranean: EMRGLC@emro.who.int

Regional Office for Europe: glc_europe@euro.who.int

Regional Office for South-East Asia: rglc_searo@searo.who.int

Regional Office for the Western Pacific: glc_pacific@wpro.who.int

The GDF (www.stoptb.org/gdf/) continues to play an important role in increasing access to high-quality, affordable second-line anti-TB drugs. The requirement of having a programme approved by the GLC was removed by the WHO in 2011 to ensure that all programmes interested in scaling up MDR-TB programmes had access to quality-assured medicines, and that the responsibility of ensuring quality programmes is owned by the countries themselves. The revised GLC initiative permits all countries to directly connect with the GDF without first requiring approval from the GLC. However, although no approval is needed, programmes purchasing second-line anti-TB drugs from the GDF, must agree to annual monitoring visits from the GDF (inquires to the GDF can be made at gdf@who.int).

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CHAPTER 17

Managerial aspects of the programmatic management of drug-resistant TB

17.1 Introduction

Diagnosing, treating and caring for a person affected with multidrug-resistant TB (MDR-TB) pose enormous managerial challenges in any health care system, even for those in high-income settings. The programmatic management of drug-resistant TB (PMDT) can be defined as "all associated functions related to providing services based in the TB strategy in order to achieve the targets set for drug-resistant TB in the *Global Plan to Stop TB 2011–2015*" *(1)*. These functions are typically oriented in systems establishment (i.e. budgetary, infrastructure, procurement, communication, management) that assist and facilitate the clinical, laboratory, and social support-related components of drug-resistant TB prevention, diagnosis, treatment and care.

Scaling up the prevention, diagnosis, treatment and care of drug-resistant TB requires detailed planning. Countries need to spell out objectives and how they are to be achieved, the timeframe for scale-up, who is responsible, and how much the implementation will cost. Such a plan can operationalize the MDR-TB sections of a national TB strategy.

In this chapter we introduce the general elements to consider for the management of MDR-TB. For a more detailed description please refer to the *MDR-TB planning toolkit* designed to help

countries develop or strengthen the MDR-TB component within their national TB strategy or plan *(2)*. The toolkit contains key steps for the planning process, identifying current gaps in service coverage, securing funding sources and determining how to monitor progress.

17.2 Management structure of the PMDT

Good management is essential for quality service delivery and achieving desired outcomes. The programmatic management of drug-resistant TB is embedded in the management structure of the national TB control programme (NTP) (see Box 17.1). However, it is often complicated by explicit linkages, and the obvious coordination required, with hospitals, laboratories, other offices in the health ministry and other government sectors, technical partners, health care providers and community-based organizations.

The management structure for drug-resistant TB is very country specific. Well-defined terms of reference and standard operating procedures are the pillars of an effective management structure. Managers are defined as those with primary responsibility for oversight of multi-disciplinary services, resources and partnerships, which may operate at different levels of the programme (central, regional/provincial, and district). In many countries the key managers for PMDT usually occupy one of the below listed positions.

- The national TB control programme manager.
- The manager of the national reference laboratory (and other designated PMDT laboratories).
- Managers or focal points of designated reference hospitals and laboratories.
- Responsible officer/focal point for the PMDT component of the TB control programme.
- Heads of sub-national health services (e.g. district TB medical officers, those in charge of health sub-districts).
- Responsible officer/focal point for PMDT of sub-national health services.

BOX 17.1 ORGANIZATIONAL STRUCTURE OF A TYPICAL NTP[a]

- Central unit, including the national TB reference laboratory, with the NTP manager, technical officers and support staff.
- Regional/provincial coordinators specific for TB control, including the regional reference TB laboratory.
- District (basic management unit) coordinators specific for TB control or with multiple responsibilities, including TB laboratory services.
- Health service delivery points – TB services, including laboratory, integrated into general health services.

[a] Source: *Implementing the Stop TB Strategy – a handbook for national tuberculosis programmes. (3).*

As PMDT expands, especially in large countries, the NTP manager may need a core team that can cover some strategic functions/services (i.e. laboratory, infection control, treatment services, drug management, human resource and training, recording and reporting, pharmacovigilance, social support, etc.). When managing health systems and services, the nature of what has to be

managed is very similar across different settings. PMDT, whether public or private, involves three key components:

1. Planning, implementation and evaluation.
2. Resources allocation (e.g. staff, budgets, drugs, equipment, buildings, information).
3. Engagement of all relevant stakeholders, including patients.

Often managerial competencies to deal with these aspects of PMDT are not readily available within the health system structure and have to be developed.

17.3 Supervisory support to facilities implementing PMDT

Supervisory visits for PMDT should include all the managerial functional areas implementing the PMDT framework. Hence, a multidisciplinary team is ideal to provide quality supervision per site. Supervisory visits to a facility implementing the PMDT give an opportunity to assess the performance and provide technical advice, guidance and moral support to the staff. This will enable the staff to correctly perform activities needed to achieve programme objectives. Regular supervisory visits place emphasis on helping staff identify and solve problems, such that the potential to create a good working relationship between the programme supervisor and district is achieved. Systematic supervision increases efficiency of health workers by developing their knowledge, perfecting their skills, improving their attitudes towards their work and increasing their motivation. Effective supervision is essential to achieve and maintain desired programme performance.

It is important to develop supervisory skills so that supervision is conducted effectively. A skilled supervisor is capable of converting information into action. In order to assist the supervisor with this activity, a simple checklist can help to structure supervision and provide an opportunity for information to be systematically analysed.

17.4 Planning the scale-up of PMDT integrated into the NTP

The PMDT should be fully integrated into the NTP. Box 17.2 depicts the three key steps for integrating the management of drug-resistant TB into NTPs. The political will to deliver treatment to patients with drug-resistant TB, as part of established NTP activities, is an obvious prerequisite before planning the management and implementation of activities.

BOX 17.2 KEY STEPS FOR INTEGRATING THE PMDT INTO NTPs

1. Assessment of the national burden of drug-resistant TB.
2. Needs assessment of capacity already in place to implement PMDT.
3. Design and implementation of a plan for management of drug-resistant TB and its expansion nationally (typically a 3–5 year plan to be reviewed periodically).

While many PMDT services begin in the absence of a thorough assessment of the burden and the needs, the scale-up of PMDT towards universal access does require a comprehensive assessment of the burden and capacity in place to deliver all required services (Box 17.3 lists the most relevant variables to consider in the planning). The needs assessment will facilitate the design and implementation of a plan to meet the gaps identified, in terms of both infrastructure and functioning within the health care system. Often a step-wise approach is taken where drug-resistant TB care is first offered in a small geographical area, where it has the best chance of success (such as the capital or a major city), or where the most number of MDR patients are likely to be found (such as the more urbanized areas of a country). While this is an acceptable approach, programmes are encouraged to have 3–5 year plans that bring drug-resistant TB care to all who are in need, as per the WHA62.15 resolution *(4)*.

BOX 17.3 LIST OF KEY VARIABLES TO CONSIDER WHEN DEVELOPING A COMPREHENSIVE PMDT STRATEGIC PLAN

- *Epidemiology*
  - Magnitude and distribution of drug-resistant TB (geographic and risk groups)
  - Most prevalent drug resistance patterns (including second-line anti-TB drugs) in new and previously treated cases in the catchment area
  - Magnitude of HIV, diabetes and other comorbidities.
- *Likely drivers of the drug resistance epidemic*
  - Performance of NTPs in managing drug-susceptible TB
  - Quality of care of the private sector in TB diagnosis and treatment
  - TB management conditions in prisons and other congregate settings
  - Infection control practices in hospitals and other health care facilities.
- *Policies and existing systems*
  - Availability of national guidelines for the clinical and programmatic management of drug-resistant TB according to WHO and international standards of care
  - Availability of human resources at different levels of the TB programme
  - Legal framework to enable community-based support
  - Existing legal framework for management of second-line drugs, including access to drugs under development
  - Legal framework for the care of patients that refuse treatment
  - Existing TB infection control policy
  - Social protection coverage for TB patients, with preference to MDR-TB patients.
- *Infrastructure*
  - Laboratory network quality assured for performing microscopy, culture and DST for first- and second-line anti-TB drugs, and tests for management of adverse drug reactions
  - Existing primary health care and hospital networks to deliver treatment services with proper infection control protocols in place.

In many cases NTPs may have already initiated PMDT as a pilot or special project. Lessons learnt in these pilot projects need to be used to plan for nationwide expansion. The design and implementation of a drug-resistant TB control programme may vary between and within countries, depending on the local needs and available resources. Despite a wide range of acceptable strategies, essential requirements, such as quality-assured laboratories for diagnosis and monitoring of treatment response, patient centred approach for the delivery of directly observed therapy, use of treatment regimens with quality-assured drugs, and effective social support, all based on sound ethics principles and protection of human rights, should be met under all conditions to ensure proper case management.

17.5 Contributing to health system strengthening

Table 17.1 presents a non-exhaustive list of challenges within the health system for effective TB prevention, care and control; all relevant to drug-resistant TB as well. The contribution of NTP managers, to strengthen health systems, starts with identifying the potential health system barriers that may have a negative impact on TB control. The relevant focus of analysis depends on the country context, including the structure of the general health system, the structure and operation of the NTP within the health system, the structure and operation of other public health programmes, such as national AIDS or diabetes programmes, and links with other sectors responsible for functions related to social support. Identification of health system barriers is a part of routine TB programme planning *(3)*. More information can be found in the Stop TB policy paper *Contributing to health system strengthening: Guiding principles for national tuberculosis programmes (5)*. Identifying opportunities offered and the challenges posed by ongoing and planned health sector development processes, and joining health system partners in addressing these barriers, challenges and opportunities while safeguarding core TB functions are the two next strategic steps to follow, in a broad perspective.

TABLE 17.1 **Health system weaknesses with implications for PMDT[a]**

	CHALLENGES	COUNTRY APPROACH
Financing MDR-TB and extensively drug-resistant TB (XDR-TB) control and care	Funding required for TB care and control was estimated at US$ 8 billion per year, of which 20% required for the treatment of MDR-TB alone (source: Global Plan to Stop TB 2011–2015 and Global Fund Fourth Replenishment (2014–2016) Needs Assessment). While funding mobilized for MDR-TB care has been increasing and is expected to reach US$ 1.8 billion in 2014, additional domestic and international donor funding will be needed to meet the annual Global Plan needs to scale-up MDR-TB implementation.	Maximize use of domestic resources, while targeting resources from the Global Fund to Fight AIDS, Tuberculosis and Malaria, UNITAID and other external funding mechanisms.

	CHALLENGES	COUNTRY APPROACH
Abolishing financial barriers	The cost per patient treated for MDR-TB in 2013 was most often in the range of US$5000–10 000, but on average, it ranged from US$ 9235 in low-income countries to US$ 48 553 in upper middle-income countries. Just the drugs to treat a patient with MDR-TB in the 22 HBC, cost the programme on average US$ 5240 per patient in 2013.	Improve health-financing schemes to strive for universal access to prevention and control of MDR-TB and XDR-TB. Decentralize health services to reduce indirect costs for patients while seeking care; promote enablers and incentives, and social support; subsidize TB care provided in the private sector and reduce costs of second-line anti-TB drugs.
Engaging all care providers in MDR-TB prevention and control	A substantial proportion of patients seek care with health care providers that do not follow internationally recommended standards of care and treatment.	Engage diverse public, voluntary, private and corporate care providers to align TB management practices with International Standards for TB Care.
Optimizing MDR-TB and XDR-TB management and care	Infectious MDR-TB and XDR-TB individuals remain in the community for long periods of time as a result of delayed diagnosis and initiation of second-line anti-TB drug treatment. Hospitalization of MDR-TB and XDR-TB patients poses a number of challenges due to nosocomial transmission, costs and inconveniences to patients.	Ensure timely diagnosis and treatment initiation for MDR-TB cases and implement appropriate models of care, preferably outpatient, to ensure patient centred care, avoid MDR-TB transmission in health care facilities and rational use of financial resources.
Responding to the laboratory crisis	8.5% of new bacteriologically confirmed cases and 17% of previously treated TB cases underwent drug susceptibility testing globally in 2013.	Accelerate access to testing by scaling up new molecular technologies.
Ensuring access to quality assured anti-TB drugs	Use of counterfeit and poor quality anti-TB drugs, which can lead to the development and amplification of drug resistance, is well documented, but there is no accurate estimate of the scale of the problem.	Secure affordable, quality assured anti-TB drugs using national procurement mechanisms, while building up a reliable second-line anti-TB drug market with manufacturers investing in increased volumes and improved quality.
Restricting availability of anti-TB drugs	Wide availability of anti-TB drugs over-the-counter in retail pharmacies encourages self-treatment and the purchase of inadequate quantities and combinations of medicines.	Restrict drug availability to accredited providers by combining government policy, agreement with providers and industry on improved marketing practices, and optimization of the NTP drug management and supply.

	CHALLENGES	COUNTRY APPROACH
Prioritizing TB infection control	Ongoing transmission of MDR-TB in health care facilities and congregate settings due to inadequate infection control measures.	Engage a wide range of stakeholders across the health system (hospital administrators, architects, engineers, health care workers), including those concerned with other airborne infections, such as influenza, to implement infection control policies.
Addressing global health workforce crisis	Shortage of trained staff to effectively manage and treat 1.6 million MDR-TB patients by 2015 exacerbated in many low-income countries by active recruitment of health care workers by industrialized countries.	Revise/update strategic human resource development plans (including private health care providers) to improve basic TB control and scale up MDR-TB control.
Improving surveillance systems	Estimates of the global and country burden of drug-resistant TB are still incomplete and less than accurate.	Establish/strengthen continuous surveillance systems for drug-resistant TB.
Investing in research and development of new diagnostic tests, drugs and vaccines	Tools for prevention, diagnosis and treatment of TB and drug-resistant TB are obsolete.	Ensure collaboration with development and technical agencies to facilitate development and field-testing of new tools for prevention, diagnosis and treatment of TB.

[a] Source: Adapted from *Global tuberculosis report 2012 (7)*.

Having identified health system weaknesses and mapped out ongoing and planned health sector development processes, NTPs should devise health system strengthening actions that balance the following three objectives.

1. To improve the capacity of the general health system to effectively deliver TB control services.
2. To optimize the positive impact on the general health system of specific PMDT activities through adequate coordination and harmonization of financing, planning and service delivery.
3. To ensure core functions, such that effective PMDT is maintained and sustained.

It is essential that the assessments and efforts to address weaknesses are undertaken jointly with health system planners and other public health programmes, so that information is shared and there is common learning from experiences and identification of cross-cutting approaches to solving problems.

17.6 Engaging all care providers

Globally, it is estimated that more patients with drug-resistant TB are being managed outside NTPs, rather than within NTPs. In 2013, just over 30% of estimated MDR-TB patients were enrolled for treatment under the NTPs *(7,8)*. Existing evidence, including results of a recent study on the size and usage of private TB drug markets in 10 high TB burden countries, suggests that a substantial proportion of patients with TB present themselves to a wide array of health care providers not linked to the NTP *(9)*. Most of these patients are not notified to the NTP and as such their treatment outcomes remain unknown.

In many settings MDR-TB management has been undertaken by voluntary, private and corporate sectors, or public care providers outside the NTP *(10)*. Care providers who are not linked to NTPs may be major contributors to the creation and mismanagement of MDR-TB, and to the continued transmission of drug-resistant TB within communities *(11,12)*. However, such providers could, potentially, contribute to the prevention and control of MDR-TB.

To address drug-resistant TB, NTPs in most countries have focused their attention largely on institutions directly under their purview. However, engagement of all relevant care providers is essential for effective scale up of the drug-resistant TB response and to achieve universal access to drug-resistant TB treatment and care. A comprehensive, health system approach, to strengthen the provision of TB care is among the most important measures to "turning off the tap" of MDR-TB *(13)*. This should be possible through a rapid scale-up of public–private mix (PPM) interventions to engage all relevant care providers – private, public, voluntary, corporate or others – in basic TB care and control *(14)*. All these PPM providers need to have capacity for delivering drug-resistant TB services according to international standards *(15)*.

While strengthening their own services for drug-resistant TB, NTPs should also collaborate and support establishing or strengthening capacity of other institutions offering TB care, by providing overall stewardship, financing, guidance, training, supervision and quality assurance. Appropriate tasks of TB control or appropriate partnership models can be assigned to different care providers depending on their interest and technical capacity *(16)*. NTPs should collaborate with professional associations to engage their networks of practitioners, including chest specialists; with voluntary or NGO networks that provide TB care services or provide patients' support; and with corporate or workplace, military and prison health services for the scale-up of PPM interventions for drug-resistant TB in these settings. NTPs should collaborate and strengthen TB care within public health services including general and specialized hospitals or other health institutions offering TB care.

The scale up of PPM for drug-resistant TB needs an assessment on the extent of ongoing PPM and PMDT activities in the country, as well as the preparedness of the NTP and non-NTP sectors for implementation of PPM for drug-resistant TB. PPM for drug-resistant TB should be a part of the PMDT expansion plan and the national strategic plan for TB, including a detailed work plan with a planned budget and activities taking into account the projected increase in drug-resistant TB patients in accordance with the increase in diagnostic capacity; second-line drug requirements; and human resource development, among others. NTPs and partners also need to mobilize sufficient resources for the PPM drug-resistant TB and PMDT expansion

plan. Operational guidelines on PPM or PMDT need to include the PPM drug-resistant TB component to guide the implementation. The implementation of planned activities should be in a phased manner. Finally, the surveillance of drug-resistant TB, monitoring and evaluation needs to be implemented by NTPs and all the PPM drug-resistant TB providers.

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CHAPTER 18

Models for delivering MDR-TB treatment and care

18.1 Introduction

A major question that the national tuberculosis control programme (NTP) manager faces when establishing or scaling up programmatic management of drug-resistant TB (PMDT) is "where should the patient receive treatment – in a hospital (inpatient) or in an ambulatory care setup (outpatient); and if hospitalization is needed then for how long?" The answer to these questions has major implications on the costs, speed of access to, and patient's acceptability of PMDT services.

WHO 2011 recommendation *(1)*:

> **Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization (conditional recommendation/ very low quality evidence).**

This recommendation is based on a systematic review and cost-effectiveness analysis comparing PMDT using mainly inpatient with outpatient models of care *(1)*. It was found that the overall cost-effectiveness of care for a patient receiving treatment for multidrug-resistant TB (MDR-TB) could be improved with an ambulatory model. A recent systematic review conducted after the production of the WHO 2011 Guidelines, indicates that, despite the limitations in the data available, there is no significant difference in treatment outcomes between inpatient and outpatient models of care *(2)*.

Most programmes would require a combination of models to serve the needs of all patients. Relying exclusively on an inpatient model of care may slow down or even make it impossible to achieve universal access to PMDT, while relying solely on an ambulatory model will ignore the very sick that need hospitalization.

Furthermore, the ambulatory model of care can either be clinic-based (patient travels to the clinic daily for directly observed therapy (DOT)) or community-based (a health care worker travels to the house daily for DOT, or meets the patient at a mutually agreed point). The community-based model is also referred to as a home-based model of care.

This chapter describes the variables to be considered by the NTP when deciding on the model of care to preferentially use in PMDT, and presents the three most commonly used models of care: (i) inpatient at a district hospital; (ii) outpatient at a peripheral health care unit; and (iii) outpatient at the household level or equivalent with support of community members. The preference of patients (and family) on where they would like to receive treatment should be taken into consideration.

18.2 Hospital-based model of MDR-TB treatment and care

Under this model patients stay in hospital only to receive treatment until the end of the intensive phase or until they convert to smear negative/culture negative status. Box 18.1 lists the minimum conditions to be met wherever this model is preferably used.

The implementation of this model of care requires proper infection control measures in place (see Chapter 14) to reduce at a minimum the risk of nosocomial transmission to staff and other patients. In many low-resource areas, infection control measures are poor or even absent; hence, **working in a hospital or being hospitalized in these settings can be a significant risk factor for MDR-TB infection**. Health care workers are not ethically obliged to care for patients if infection control conditions are not appropriate *(3)*. Furthermore, hospitals should also provide or enable access to all social support services needed by patients, including adequate food, a proper heating system in cool areas and fans or cooling systems in hot climates.

In some settings, the hospital-based model of care is being enforced in all MDR-TB patients, that is, compulsory isolation while sputum smear/culture remains positive. Compulsory isolation should be considered only and exclusively when all measures, and not only the measures easy to implement, to ensure adherence to treatment have been systematically exhausted (see Chapter 23).

Very good communication and coordination needs to be in place between the hospital(s) and outpatient care providers. This should include notification to appropriate outpatient teams several days ahead of planned discharge of the patient from the hospital, sending all clinical information about the patient, including all prescribed drugs needed for the first 2–4 weeks of treatment as an outpatient. A proper assessment of the risks for a patient's non-adherence and a plan to mitigate those risks with proper social support should be discussed and agreed with the peripheral outpatient unit, well ahead of the patient's discharge from hospital.

BOX 18.1 BASIC CONDITIONS MET BY AN OPTIMUM HOSPITAL-BASED MODEL OF MDR-TB CARE

- Hospital bed-occupancy is not made at the expense of non-TB patients in need of hospital-based medical care.
- Basic infrastructure is fully compliant with international standards for respiratory infection control.
- Respiratory isolation rooms are available for all patients who remain smear positive/culture positive.
- All staff are trained and adhere to administrative protocols for TB infection control.
- Sufficient staff are available to guarantee DOT for all patients.
- Open and safe space is available for patients to socialize and conduct occupational therapy activities.
- Friendly administrative procedures are in place to facilitate regular access of relatives visiting patients.
- Protocols are in place for effective communication and coordination with laboratories providing services during treatment, and with peripheral units receiving patients after discharge from hospital.
- Social support to patients covers out-of-pocket and indirect costs, which may include transport to and from the hospital of closer relatives or family caregivers.

18.3 Clinic-based model of MDR-TB treatment and care

Under this model patients receive the full course of treatment on ambulatory basis at an outpatient health care facility, irrespective of the sputum smear/culture status. Box 18.2 lists the minimum conditions to be met wherever this model is preferably used.

The clinic-based model of care requires staff at the clinic to be properly trained, especially on the early detection and proper management of adverse drug reactions, and in the management of social support services. This model of care requires the patient to travel from home and receive the medicines under DOT at the clinic. Long daily travel times can be a reason for defaulting treatment. When the patient receives clinic-based treatment, rapid access to DOT should be ensured to allow a quick departure from the facility. This practice will not only reduce the exposure to potential sources of TB and other infections but also enable patients to reduce the costs associated with reduced time at the workplace or household. Some NTPs arrange temporary accommodation at hostels to lessen the financial hardship for patients who have to relocate to the nearest clinic offering MDR-TB care, until a more convenient alternative for the patient is found or established. Through social protection mechanisms NTPs often provide a monthly stipend to lessen the financial hardship for these patients.

BOX 18.2. BASIC CONDITIONS MET BY AN OPTIMUM CLINIC-BASED MODEL OF MDR-TB CARE

- Patient has no medical indication for receiving long-term care in the hospital and is not too sick to travel every day to the clinic to receive treatment under DOT.
- Basic infrastructure is fully compliant with international standards for respiratory infection control.
- All staff are trained and adhere to administrative protocols for TB infection control.
- Patient and relatives at the household are informed and educated on TB infection control practices.
- Sufficient staff are available to guarantee DOT for all attending patients.
- DOT services are available at least six days a week, with an extended timetable to allow the delivery of treatment twice a day when needed.
- Protocols are in place for effective communication and coordination with laboratories providing services for monitoring response to treatment and detection of adverse drug reactions.
- Ready availability of medical services by a practitioner and of medicines for management of adverse drug reactions.
- Social support to patients covers out-of-pocket and indirect costs, especially transport to and from the clinic.

18.4 Community-based model of MDR-TB treatment and care

Under this model patients receive full course of treatment under direct observation on ambulatory basis, irrespective of their sputum smear/culture status, at a venue in the community, such as a patients' or relatives' household, the workplace, or even a nearby park. The venue is agreed between the patient and the DOT provider. The backbone of community based MDR-TB care is often a community MDR-TB supporter, who may come from the same neighborhood where the patient lives. Community MDR-TB supporters must respect and preserve patient confidentiality at all times. They also can play an important role in educating the community on TB and help reduce stigma around the disease (also see Chapter 12). Box 18.3 lists the minimum conditions to be met wherever this model is preferably used.

The organization of community-based care can be extremely challenging and even unrealistic in some settings whereby social tradition or law requires that the delivery of some health care services like injections or pills has to be done by a formal health care worker and under all circumstances. Therefore, organizing a clinic-based model of care may be more suitable and appropriate in countries without a tradition of community engagement in primary health care.

Community-based MDR-TB providers need to be properly trained and supervised by qualified health care workers. A community-based MDR-TB provider can even be a family member. However, the nature of the family relations should be properly evaluated to ensure that the patient would have a reliable and fully supportive care provider as a poor family relationship may interfere with the ability to monitor treatment.

BOX 18.3. BASIC CONDITIONS MET BY AN OPTIMUM COMMUNITY-BASED MODEL OF MDR-TB CARE

- Public health legal framework allowing community members to deliver some health care functions.
- Patient has no medical indication for receiving long-term care in hospital.
- Ideally, patient's household infrastructure is fully compliant with basic standards for respiratory infection control.
- All community MDR-TB supporters are trained and adhere to protocols for TB infection control.
- Sufficient number of community MDR-TB supporters are available to guarantee DOT to all patients at least six days a week, and with an extended timetable to allow the delivery of treatment twice a day when needed.
- A team consisting of a general practitioner, a nurse, a pharmacist and a social worker is in place and fully engaged in supervising, monitoring and supporting community-based supporters.
- Protocols are in place for effective communication and coordination with laboratories providing services for monitoring response to treatment and detection of adverse drug reactions; and with a practitioner for effective management of adverse drug reactions in a timely fashion.
- All community-based MDR-TB supporters are trained in patient confidentiality issues and in methods to decrease stigma.
- All community-based MDR-TB supporters are fully covered for all out-of-pocket costs associated with their work, and also receive a fair compensation for the services being provided to the patients (note: compensation is above and beyond reimbursement of out-of-pocket costs of doing the job and needs to be planned for in the budget of all PMDT programmes that use community-based MDR-TB supporters).

Drug-resistant TB care providers should live near the patient to allow twice-daily DOT visits for treatment observation. Although some programmes only do once-a-day dosing, twice daily dose is optimal to lessen the adverse effects of some drugs (see Chapter 5). The community-based team will still require a range of expertise and support; they should be able to respond to urgent home visits when needed. The team should consist of doctors, a drug-resistant TB community nurse supervisor, social workers and the DOT providers at a minimum. The complexity of planning and managing community-based MDR-TB care should not be underestimated, but it is beyond the scope of this document. Excellent resources that present all critical elements to be considered in the planning and management of community-based MDR-TB are however available in the public domain *(4)*.

18.5 Deciding which model is best for a particular situation

The debate about the model of care can be misleading, if made on the premise that only one model serves the needs of all patients in a setting. Some patients may need hospital-based care for medical reasons, either while receiving treatment or while on end-of-life care. Yet, in some settings and circumstances, relying exclusively on an inpatient model of care may slow down or even make it impossible to achieve universal access to PMDT due to high costs; create long patient waiting lists due to the lack of bed capacity; reduce the epidemiological impact of PMDT on the morbidity and mortality caused by MDR-TB; and contribute to prolonging the suffering of affected people. In some settings, task shifting to alleviate human resource shortages and to encourage greater and more meaningful community engagement may be crucial elements in accelerating the scale-up of services to universal access. Under field conditions, all these models may coexist depending on the needs of the patients, the capacity in place, and the resources available in the health care system.

When comparing the options for treatment delivery models, there are a number of variables to consider that are listed in Box 18.4. A framework to address ethical issues needs to be in place (refer to Chapter 23). While outpatient care is often socially more acceptable to patients and costs are much lower for the health system, the consequent implementation of DOT is more challenging requiring access to a primary health care network, strong social support and community-based care. Community-based care may reduce cost to the health system and can be more cost-effective than hospital care *(1,5)*, but in many ways it is more challenging to implement.

In some settings, the community-based model of care can be the only way to achieve universal access to PMDT, at least in the near- or mid-term future. Whichever model of care is chosen to provide treatment for drug-resistant TB, care should be delivered by a multidisciplinary team of providers, including physicians, nurses, social workers and community health workers or volunteers. The roles and responsibilities of each of these groups of providers will vary depending on the needs and resources available in specific settings.

Adherence to MDR-TB therapy is challenging in all three models and therefore, social support measures to enable adherence should be pursued whichever model is used (see Chapter 12 for more information on social support and adherence to treatment).

Hospitals play a very important role in the management of MDR-TB for several reasons. The management of complications in common TB comorbidities, such as HIV or diabetes; surgical treatment of selected MDR-TB patients; management of severe adverse drug reactions to second-line anti-TB drugs; pulmonary complications in patients with advanced TB disease; medical support during palliative and end-of-life care; and the initial care of patients who are homeless, have difficult family situations, or live in remote areas where MDR-TB care is not yet available. The exclusive reliance on a hospital-based model of care can become a barrier to start MDR treatment, especially when there is a lack of sufficient hospital beds. An outpatient system needs to be developed to support patients upon discharge during the continuation phase even in settings that mainly rely on a hospital-based model. Thus, capacity to provide

BOX 18.4 FACTORS TO CONSIDER WHEN SELECTING THE MODEL OF CARE FOR THE MAJORITY OF MDR-TB PATIENTS DURING THE INTENSIVE PHASE OF TREATMENT

- Local laws and ethical standards
- Geographical access to points of M/XDR-TB care
- Quality of infection control measures practiced in the hospital or clinic
- Capacity to educate, and not only to train, patients and family on hygiene and infection control measures at the household level
- Training requirements for the different models
- Hospital-bed capacity (a fair match between number of patients needed to treat and beds)
- Cost of hospitalization
- Funding to support the health care workforce delivery of DOT
- Availability of private sector and public hospitals with M/XDR-TB management according to national guidelines.
- Attitudes of caregivers, patients and their families to the different options of care
- Capacity to supervise drug-resistant TB supporters.
- Social support networks that facilitate a patient-centred approach to DOT
- Attitudes of caregivers to the different options of care.
- Patient-related factors
- Patients' needs and preferred options for treatment
- Comorbidities
- Costs of a specific model of care.

ambulatory MDR-TB has to be built into whatever model of care is selected for delivering the intensive phase of treatment.

The risk of MDR-TB transmission, in the absence of proper infection control measures, occurs in all models of care whenever the patient remains sputum smear/culture positive. However, the absence of proper TB infection control is particularly serious in the hospital-based model as the impact on transmission could be higher.

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CHAPTER 19

Community engagement to support universal access to diagnosis, care and treatment of drug-resistant TB

19.1 Introduction

One third of people estimated to have TB are either not reached for diagnosis and treatment by the current health systems or are not being reported. In 2012, only one third of the reported TB patients estimated to have multidrug-resistant TB (MDR-TB) were detected. Even in patients who are identified, TB or MDR-TB is often diagnosed and treated late. In order to reach the unreached and to find TB patients early in the course of their illness, a wider range of stakeholders already involved in community-based activities needs to be engaged. These include the nongovernmental organizations and other civil society organizations that are active in community-based development, particularly in primary health care, human immunodeficiency virus (HIV) infection and maternal and child health, but have not yet included TB in their priorities and activities *(1)*.

Nongovernmental organizations and other civil society organizations are non-profit-making organizations that operate independently from the state and from the private for-profit sector. They include a broad spectrum of entities, such as international, national and local nongovernmental organizations, community-based organizations (CBOs), faith-based organizations (FBOs), patient-based organizations and professional associations. CBOs are membership-based non-profit-making organizations that are usually self-organized in specific local areas (such as a village) to increase solidarity and mutual support to address specific issues. These include HIV support groups, women's groups, parent–teacher associations and micro-credit village associations. CBO membership consists entirely of the community members themselves, so these organizations can be considered to represent the community most directly. Nongovernmental organizations and other civil society organizations engage in activities that range from community mobilization, service delivery and technical assistance to research and advocacy *(1)*.

The strengths of nongovernmental organizations and other civil society organizations active in health care and other development interventions at the community level include their reach and spread and their ability to engage marginalized or remote groups. These organizations have a comparative advantage because of their understanding of the local context. Greater collaboration between nongovernmental organizations and other civil society organizations and local and national governments could greatly enhance development outcomes *(2)*. A more decentralized approach that formally recognizes the critical role of nongovernmental organizations and other civil society organizations as partners addressing gaps through support to community-based actions will expand drug-resistant TB prevention, diagnosis, treatment and care activities. The actions described in WHO's ENGAGE-TB operational guidance to integrate community-based activities into the work of nongovernmental organizations and other civil society organizations are also summarized in this Chapter *(3)*.

19.2 Community-based TB activities

Community–based TB activities cover a wide range of activities contributing to prevention, diagnosis, improved treatment adherence and care that positively influence the outcomes of drug-susceptible, drug-resistant and HIV-associated TB. The activities also include community mobilization to promote effective communication and participation among community members to generate demand for TB prevention, diagnosis, treatment and care services. While diagnostic tests for TB continue to be performed in clinical settings, for lack of simpler diagnostic methods, community-based TB activities are conducted outside the premises of formal health facilities (e.g. hospitals, health centres and clinics) in community-based structures (e.g. schools, places of worship, congregate settings) and homes. Such community-based TB activities could and should be integrated with other community-based activities supporting primary health care services, including those for HIV infection, maternal and child health and noncommunicable diseases (NCDs) to improve synergy and impact. Community-based TB activities utilize community structures and mechanisms through which community members, CBOs and other groups interact, coordinate and deliver their responses to the challenges and needs affecting their communities *(4)*.

19.3 Community health workers and community volunteers

Community health workers and community volunteers carry out community based TB activities, depending on national and local contexts. Community health workers are people with some formal education who are given training to contribute to community based health services, including TB prevention as well as patient care and support. Their profile, roles and responsibilities vary greatly among countries, and their time is often compensated by incentives in kind or in cash. Community volunteers are community members who have been systematically sensitized about TB prevention and care, either through a short, specific training scheme or through repeated, regular contact sessions with professional health workers. Community health workers and community volunteers may be supported by nongovernmental organizations and other civil society organizations or by government departments. In either case, they engage primarily within the homes and community structures rather than at health facilities. They usually play an important role in linking community-based activities with facility-based services. For example, community health workers and community volunteers

BOX 19.1 EXAMPLES OF COMMUNITY-BASED TB ACTIVITIES

- Awareness-raising, behaviour change communication and community mobilization.
- Reducing stigma and discrimination.
- Screening and testing for TB and TB-related morbidity (e.g. HIV counselling and testing; diabetes screening) including through home visits.
- Facilitating access to diagnostic services (e.g. sputum or specimen collection and transport).
- Initiation and provision of TB prevention measures (e.g. isoniazid preventive therapy, TB infection control).
- Referral of community members for diagnosis of TB and related diseases.
- Treatment initiation, provision and observation for TB and comorbidities.
- Treatment adherence support through peer support and education and individual follow-up.
- Social and livelihood support (e.g. food supplementation, income-generation activities).
- Home-based palliative care for TB and related diseases.
- Community-led local advocacy activities.

could refer persons with suspected TB to health facilities or collect and transport their sputum to laboratories. They could help in managing the delivery of TB drugs from the health facilities to persons with TB. They could work with the staff at facilities to identify and follow-up those who might otherwise suspend or terminate their treatment prematurely. They could convey the latest information on TB and TB services to communities and provide feedback from communities to facilities and so serve as strong vehicles for community-based communication and advocacy.

19.4 Integrating drug-resistant TB into community-based work

Nongovernmental organizations and other civil society organizations could integrate drug-resistant TB into their community-based work in many ways, without trained medical staff. It is particularly important for them to do so when they are working with high-risk populations (such as people living with HIV and the very poor), people living in congested environments (urban slums and prisons), drug users, sex workers and migrant workers.

The following are examples of drug-resistant TB activities that can be integrated.

- Assisting early case finding: Encouraging people who present with symptoms of TB such as chronic cough, weight loss, night sweats and fever to contact a health worker or visit a health facility. Sputum examination is the mainstay of TB investigation in many settings. In community meetings (e.g. women's groups, health clubs, farmers' groups), the main symptoms of TB could be explained. People with symptoms could be helped to have their sputum examined by transporting either the person or the sputum sample to the nearest health facility.

- Assisting contact investigation: Engaging members of the community to assist health care workers in contact tracing can be especially useful in difficult settings where geographical barriers prevent proper identification and follow up of contacts.
- Providing treatment support: Ensuring patients being treated for drug-resistant TB are given support to take their drugs and finish their treatment. Family members and community-based volunteers and workers can be trained as treatment supporters by nongovernmental organizations and other civil society organizations. Patients can also be provided with nutritional and psychosocial support, if needed.
- Preventing the transmission of drug-resistant TB: Encouraging simple behaviour change such as covering the mouth and nose when coughing and sneezing to limit the spread of infected sputum particles and thus reducing the risk to others of being infected. nongovernmental organizations and other civil society organizations could spread this message using various social communication media.
- HIV programmes and projects: Encouraging every person living with HIV to be screened for TB and, depending on the result, helping them receive TB prevention treatment (isoniazid preventive therapy) or further examination for TB disease.
- Maternal and child health programmes and projects: Encouraging all pregnant women to test for HIV and to be screened for TB symptoms at the nearest facility. Children under five years are particularly vulnerable to TB infection if an adult in the home has TB. Health workers should be made aware of this and keep watch for any symptoms and signs of TB in households with young children.
- Education programmes and projects: Incorporating messages of TB prevention and care into curricula and classroom learning, that contribute to de-stigmatizing the disease, preventing discrimination and promoting early case detection and adherence to treatment. Schoolchildren should be able to recognize TB symptoms and the importance of sputum examination so that they can encourage those at home who may have TB to get tested.
- Agriculture and income-generation programmes and projects: Raising awareness about TB symptoms and signs among organized groups (such as farmers' groups and savings and credit groups). Members with symptoms of TB could be encouraged to get their sputum examined. Those being treated for drug-resistant TB could be supported to complete their course of treatment. Nutritional and psychosocial support will improve the outcome of TB treatment.

19.5 Creating an enabling environment for community engagement

A mutually enabling legal and policy environment based on the principles of equity, equality and mutual respect will increase the engagement of nongovernmental organizations and other civil society organizations in TB activities, particularly those who are newly engaged in TB prevention and care. A facilitated registration process of nongovernmental organizations and other civil society organizations in accordance with local norms and needs and ensuring greater integration of processes and requirements between different government departments could be key areas for the government to support the operations of nongovernmental organizations and other civil society organizations. Reducing the complexity of transactions and increasing the speed of facilitation are key factors that improve the operating environment for nongovernmental organizations and other civil society organizations. NTPs or their equivalents have the responsibility of creating enabling national or local legal, policy and administrative

environments to support the effective engagement of nongovernmental organizations and other civil society organizations in TB activities. This should be done in close consultation with the relevant government and legislative structures (e.g. parliament, ministry of justice or other regulatory bodies) depending on the local context and aligned with the national health strategy, if necessary.

Nongovernmental organizations and other civil society organizations should also stimulate and support the development of an enabling legal and policy environment through constructive dialogue and engagement with the NTPs or relevant legislative structures, with the participation of the segments of society they represent. This can be best done on a sustained, continuing basis if nongovernmental organizations and othercivil society organizations form an umbrella nongovernmental organizationcoordinating body (NCB) to represent their best interests and to allow systematic sharing and dissemination of lessons learnt by individual organizations. NTPs should support the formation of such nongovernmental organization coalitions and make time to meet with them in order to understand their needs, constraints and the lessons learnt.

The NCB should also include representatives of patients and affected communities including women and young people or other target groups or beneficiaries of the nongovernmental organizations. The NCB should meet regularly and have mechanisms for sharing information and for discussing issues of common interest related to community-based TB activities and the relations with NTPs or its equivalents at all levels. Nominated representatives of the NCB should meet regularly (preferably quarterly) with the NTP or its equivalents to improve contributions to national TB strategies and plans, discuss challenges and opportunities and secure support. If needed, a bilateral or multilateral organization could help to initiate and facilitate the linkage and partnership between the NCB and the NTP and host its meetings. NCB representatives should ensure that all NCB members are fully involved in discussions and negotiations and have opportunities to provide input and receive feedback regularly. The NTP, with inputs from the NCB and other stakeholders, should prepare a national policy to facilitate effective engagement of nongovernmental organizations and other civil society organizations in TB prevention, diagnosis, treatment, patient care and support, and in research activities aligned with the national health strategy. In countries with decentralized political authority, the policy could be prepared at appropriate administrative levels (e.g. provincial or state authorities). Nongovernmental organizationsand other civil society organizations must always be involved in policy preparation as partners or even as initiators and leaders of the process.

Existing structures can also be used for the functions of the NCB, if they are acceptable to the nongovernmental organizations and other civil society organizations concerned, particularly in satisfying their desire for independence from both the government and the private for-profit sector. In some countries, national stop TB partnerships already exist. A national stop TB partnership is a voluntary alliance between organizations drawn from the public, civil society and private sectors who commit to work collaboratively towards TB prevention, care and control, in which all partners contribute from their core competences, share risks and responsibilities and benefit by achieving their own, each others' and the overall goal. Depending on the local context and the need of the nongovernmental organizations and other civil society organizations, linkages can be sought with effective and vibrant national stop TB partnerships, especially as previously unengaged NGOs and other CSOs take up TB prevention and care activities.

At the community level, nongovernmental organizations should support the growth and development of CBOs that include TB prevention, care and support in their mission. Existing CBOs, such as HIV support groups, could be approached to integrate TB into their work. It will be important for nongovernmental organizations and other civil society organizations to create mechanisms to interact regularly with these CBOs, listen and respond to their concerns and promote their continuing growth and empowerment.

19.6 Monitoring and evaluation of community engagement

Regular monitoring and evaluation will help in assessing the quality, effectiveness, coverage and delivery of community-based TB activities and the engagement of nongovernmental organizations and other civil society organizations. It promotes a learning culture and serves as a foundation to ensure continuous improvement of programme implementation. NTPs or their equivalents should ensure that there is a single national monitoring and evaluation system that recognizes the contribution and engagement of nongovernmental organizations and other civil society organizations.

Quarterly reviews of progress would help to uncover issues in implementation and enable midstream correction to plans and budgets and to the overall strategy. The NTP should help to smooth any operational difficulties that nongovernmental organizations and other civil society organizations may face and cannot independently resolve. Quarterly meetings to discuss the review findings could be held at subnational or local levels so that there is cross-fertilization of learning between nongovernmental organizations and other civil society organizations and with the NTP. Annual meetings at the national level should be organized by the NCB and a broad spectrum of implementing nongovernmental organizations and other civil society organizations invited to share their findings and report progress. The resulting national report issued by the NTP should be shared widely with all stakeholders within the government, nongovernmental organizations and other civil society organizations, patients and community members, donors and the general public.

Evaluation of the results of initial implementation of the action plan is important to guide replication and scaling-up of activities. Evaluation should be an ongoing process and include evaluation of both the activities (process evaluation) and achievement of the objectives (impact evaluation) of the action plan. Qualitative methods and periodic surveys could be used to provide an understanding of how well nongovernmental organizations and other civil society organizations are supported and how they have engaged in community based TB activities.

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CHAPTER 20

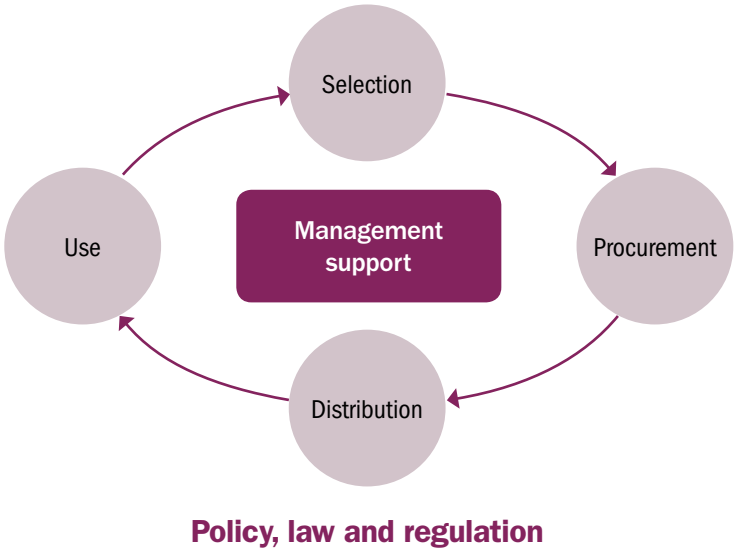
Managing medicines for drug-resistant TB

20.1 Introduction

Second-line medicines to treat drug-resistant TB must be managed appropriately in order to ensure that the correct medicines are selected, procured in the right quantities, distributed to treatment centres in a timely manner, handled and stored to maintain quality and availability of sufficient stocks, and used rationally by the health worker and patient alike.

Figure 20.1 represents the main drug management functions (also referred to as the pharmaceutical management cycle). TB programmes can organize their drug management activities in line with these functions.

Figure 20.1 Pharmaceutical management cycle



Source: Center for Pharmaceutical Management. 2011. Center for Pharmaceutical Management: Technical Frameworks, Approaches, and Results. Arlington, Virginia: Management Sciences for Health.

These functions need continuous management support and legal frameworks from responsible institutions, such as the country's national drug regulatory authority and national TB control programme (NTP) *(1,2)*. These national bodies should also facilitate the drug registration process and importation of quality-assured anti-TB medicines. Box 20.1 provides further descriptions of the key functions of the drug management cycle.

BOX 20.1 SHORT DESCRIPTION OF KEY FUNCTIONS OF THE DRUG MANAGEMENT CYCLE

Selection: Careful selection of anti-TB medicines results in a high quality of care for patients, rational use of medicines and cost-effective use of health resources. Anti-TB medicines are selected based on disease prevalence, efficacy and safety evidence, drug resistance patterns, and shall include the selection of medicines from quality-assured sources (WHO Prequalification of Medicines Programme (PQP), Stringent Drug Regulatory Authority (SRA), Expert Review Panel (ERP)).

Quantification: Sometimes called 'forecasting' quantification is a process used to estimate the amount of medicines and commodities needed by the national TB control programme for a period of time. Quantification is a key planning step to prepare and justify budgets for procurement.

Procurement is timely acquisition of quality-assured anti-TB medicines and commodities at the best possible cost.

Distribution is the process by which medicines are received at the port of entry, cleared through customs, transported from the central warehouse to storage and health facilities, stored and maintained at warehouses and treatment centres.

Rational use refers to proper use of medicines to improve patient safety by providing comprehensive information on the use, dosage, adverse effects, contradictions, warnings and guidance on selecting the right medicines for TB patients.

20.2 Selection of anti-TB drugs for programmatic management of drug-resistant TB

The selection process for multidrug-resistant TB (MDR-TB) medicines differs considerably from the selection of first-line treatment because:

- a number of different regimens and medicines may be prescribed at the start of, and within the treatment period, due to the drug resistance patterns, availability and affordability;
- treatment periods are long (up to 24 months or more);
- medicines are more toxic to patients, which frequently results in changes made to the original regimen prescribed;
- only a limited supply of quality assured MDR-TB medicines (according international standards or WHO prequalification programme) is available; and
- medicines are much more expensive (up to 100 times more than drug-susceptible TB).

A number of factors must be considered when selecting second-line drugs, including the efficacy of the drugs, the treatment strategy, possible adverse effects and the cost of treatment. For these reasons MDR-TB medicine selection is based on the development of national treatment guidelines in line with WHO-recommended standards for TB control and on the evidence underlying the development of treatment guidelines. The selection of medicines should be based on the process described in Chapter 5. Most of the second-line drugs are also included in the *17th WHO Model List of Essential Medicines* meaning that these basic drugs, when used in accordance with appropriate therapeutic guidelines, cost-effectively meet the needs of a large proportion of drug-resistant TB patients.

The NTP's empiric standardized or individualized treatment regimens are designed based on history of anti-TB drug use, laboratory capacity and resistance patterns in TB patients in their country. Empiric standardized regimens are easier to manage in terms of quantification and ordering processes. Individualized regimens require a more advanced information system and additional updated data to monitor drug consumption for each second-line anti-TB drug. The choice of whether to use a standardized or individualized strategy should not be based on ease of procurement but what will result in the ability of the programme to cure the majority of the patients (see Chapter 5).

20.3 Quantification and procurement

Quantification. In order to procure appropriate quantities of these medicines, TB managers need to know how many patients are currently under different treatment regimens and how many patients are expected to be enrolled for each treatment regimen during the next planned procurement period.

Annex 9 describes how to forecast and place drug orders.

Procurement. Effective management of procurement ensures the availability of selected drugs of assured standards of quality (see Box 20.2), in the right quantities, at the right time and at affordable prices *(3)*.

BOX 20.2 QUALITY ASSURANCE FOR SECOND-LINE ANTI-TB MEDICINES

Same quality requirement for all medicines:

- Compliance to WHO good manufacturing practices for manufacturing site.
- Product conformity with internationally recognized quality standards (active pharmaceutical ingredients (API) quality, stability, specifications, etc.).
- Bio-equivalence studies for rifampicin-containing products and second-line drugs.
- Dissolution profiles acceptable only for the following drugs: ethambutol (E), isoniazid (H), pyrazinamide (Z), levofloxacin/ofloxacin.

However, for some of the second-line anti-TB drugs, the market is currently so small that it is difficult to find suppliers willing to spend the funds to prequalify their products according to the international quality assurance policies, or even to register these medicines in several countries. Section 20.5 on the Global Drug Facility (GDF) shows the requirements for approved suppliers, the medicines they produce and an overview of the procurement process.

After forecasting has been performed, the programmes are ready to place orders for a defined period. In some cases the TB programme may wish to order less than a full year's supply or to split second-line anti-TB drugs shipments on a six-month basis because of short expiry dates of drug-resistant TB drugs, lack of funding, or change in treatment regimen rendering the need for only some medicines. Box 20.3 outlines some of the key considerations when assessing the quantification aspects of a drug procurement system.

Order periods are normally six to 12 month cycles and based on government budget cycles.

BOX 20.3 QUANTIFICATION (SOMETIMES CALLED FORECASTING): AN INTEGRAL PART OF PROCUREMENT

A. Accurate demand forecasting for second-line drugs, i.e. correct quantification of drug requirements for a specific period of time is one of the elements that guarantees an uninterrupted drug supply. The main approaches for demand forecasting are based on incidence and drug resistance patterns.

- In this method, the treatment regimen (standardized, individualized or empirical) and the number of patients to be treated with each regimen are taken into account. Several other key factors must also be considered, including the existing stock, lead time for delivery, safety stock needed and the shelf lives of each drug. In order to reduce the risks of stock-out it is recommended to stock sufficiently to cover the needs for a period equivalent to 2–3 times the delay in delivering a drug request.

20.4 Drug distribution, storage and ordering

Distribution is the process by which medicines are received at the port of entry, cleared through customs, transported to the central warehouse and distributed to health centres. During this process, second-line anti-TB drugs can be stored at different warehouses and treatment

centres in varying conditions that may affect the quality of the drugs. At every step, this process requires rigorous recording and inventory management according to known best practices. Drug-resistant TB programmes need to consider and include the lead-time of distribution in the second-line anti-TB drug management timeframe. It is important to process the port and custom clearance days before the actual delivery, including clarification on customs fees to be paid with adequate interfaces, since these could take up some time and hamper the whole distribution process.

Drug distribution. Procedures vary depending on the health system structure *(4)*. If centralized, vehicles will make regular medicine deliveries to treatment centres or district warehouses. If peripherally controlled, each district warehouse and treatment centre will need to retrieve their own medicines, using their own vehicles. This is important because fuel and other maintenance costs would be borne by the responsible unit, which must be planned for and budgeted in advance *(2,4,7)*. Box 20.4 provides a list of activities that are important for good drug storage practices.

BOX 20.4 ACTIVITIES IMPORTANT FOR GOOD DRUG STORAGE PRACTICES

Storage procedures are very important as they impinge on quality and availability of medicines. The following activities are very important in good storage practices.

- Inspect medicines for quality when they are received for the following: broken or damaged tablets or vials, correct package labelling (medicines name and strength), and missing quantities in the delivered packages.
- Record exact quantities received on bin cards/register and note any discrepancies found during inspection.
- Secure the area where medicines are stored to avoid theft and misuse (only authorized persons may enter; areas should otherwise be locked).
- Organize medicines on shelves or in cabinets in order by generic name or therapeutic category.
- Review expiry dates of medicines on shelves and in storage areas every month – MDR-TB medicines have short expiry dates.
- Use bin cards or registers for each medicine received and stored in the warehouse or treatment centre.
- Record quantities received, transferred to another facility and dispensed to patients on bin cards/register each day.
- Store PASER® granules (PAS) in a refrigerator to maintain the cold chain (PASER® is stable for up to 8 weeks at 40 °C and 75% humidity, and therefore can be distributed to the treatment facilities on a monthly basis in most environments with no cold chain).
- Isolate expired medicines from medicines still good for patient use – discard the expired medicines by returning to the supplying warehouse or incineration with proper documentation.
- Return medicines to the district TB coordinator when: no more drug-resistant TB patients are being treated at the TB centre, medicines reach their expiry dates (shelf lives), and medicines are damaged and not useable for patients.

Ordering medicines can occur in two ways – *push* and *pull* depending on whether the order is placed by the treatment centre (pull) or whether the order quantities are decided by the TB coordinator (push) at the district or national level. When placing orders, a standardized form should be used so that medicines, strengths and dosage forms are correct for the treatment regimens established by the TB programme. Order forms may be completed manually or using a computer and printer. Box 20.5 outlines how to calculate drugs based on procurement needs *(6)*.

BOX 20.5 REQUIRED INFORMATION TO MAKE A GOOD ORDER

- Number of patients expected to enrol during the next order period, number of patients currently on each treatment regimen, list of medicines and dosages for each treatment regimen, quantities of existing stocks and amount of buffer stock to include in the forecast, estimated lead time (time between placing the order and when the second-line anti-TB drugs are received in the country).
- Unit prices should be added to the medicine calculations and compared with the annual budget. Where needs exceed the budget, other sources of funding must be obtained so that all MDR-TB patients will be treated and drug resistance will not spread.
- A simple spreadsheet can be used once the required data are known. For more information on the elements to include in a spreadsheet for forecasting purposes, please see a simple step-by-step process presented in Annex 9. Annex 9 also presents a non-exhaustive list of several existing tools made available to help develop appropriate forecasts of drug-resistant TB medicines.
- New information systems offering dedicated functions for electronic recording and reporting and drug management including forecasting tools were recently introduced *(6,7)*.

Order = [Needs for a specific period – (stock plus pipeline)]. So the quantities to order are the quantities to cover the needs for a specific period, minus the quantities in stock and minus the quantities already ordered and currently in the delivery pipeline. This holds as long as the drugs in the pipeline arrive before the specific period. Also see Annex 9 for tips on drug ordering.

20.5 Rational medicine use and adherence

Rational medicine use

In the specific case of drug-resistant TB treatment, the best way to implement a rational use of drugs is to follow the treatment recommendations as described in Chapter 5. This will ensure the maximum benefit to the patients and to the health programme at the same time. This has to be complemented with full adherence to a properly prescribed treatment (see Chapter 10). From a drug management perspective the health worker should check that the patient knows at least the following about their treatment:

- Name of their TB medicines
- Number of tablets in one dose

- Number of doses to take per day
- When to return to the TB centre for more medicines
- Need to report to the health care provider any adverse reactions that are encountered while taking second-line anti-TB drugs.

A structured pharmacovigilance system in the programme is encouraged to ensure patients' safety and proper management of any side-effects (see Chapter 11) *(8)*. If adverse reactions are encountered, these should be recorded at least in the TB register and the health worker should seek guidance from a drug-resistant TB specialist or a reference centre on how to proceed with treatment for the patient. Ancillary medicines are essential to improve adherence to treatment and they must be available at the health centres to manage adverse reactions. Although many ancillary medicines for adverse reactions may be available since they are used for other health problems (e.g. pain, nausea, etc.), there are cases where they are not, and it is a good practice to allocate funds for their procurement and distribution along with anti-TB medicines.

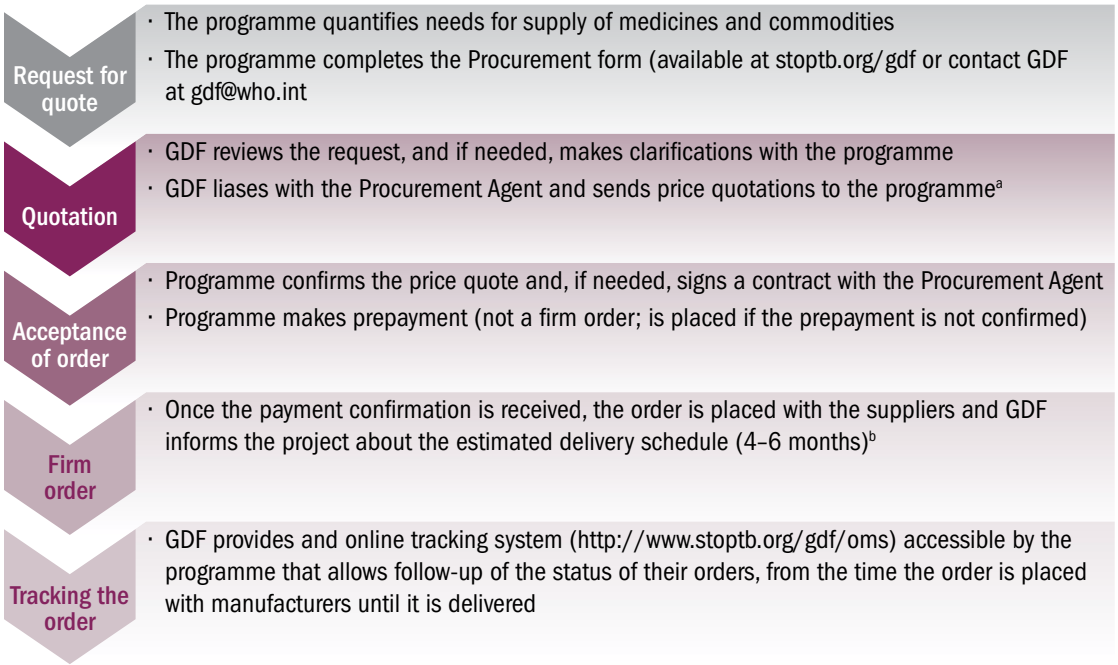
20.6 Global Drug Facility

NTPs have had to face several obstacles in the area of drug procurement, including the inconsistent availability and high cost of second-line drugs, and the lack of local capacity to apply a stringent quality assessment on drug manufacturers and their products.

The GDF, which is housed at the WHO, procures medicines to treat MDR-TB. Medicines include those in the *WHO Model Essential Medicines* List for MDR-TB, those included in WHO treatment guidelines for management of drug-resistant TB, and other medicines used for other types of infection and for XDR-TB. GDF procurement procedures (see Figure 20.2) include setting up supply agreements only with eligible medicine manufacturers who have been prequalified/authorized/recommended for procurement by the following organizations *(3,9)*.

- World Health Organization Pre-qualification of Medicines Programme (WHO-PQP).
- Stringent National Regulatory Authority (SRA) – those authorities that are a member, observer or associate of the International Committee on Harmonisation (www.ich.org).
- Expert Review Panel (ERP) – a group of regulatory experts convened by WHO's Department of Essential Medicines and Health Products who conducts quality risk assessments of finished pharmaceutical products for which there are less than three WHO-PQP or SRA authorized sources; the ERP recommends procurement of these medicines for a limited period of time.

Figure 20.2 GDF procurement procedure



Notes:

[a] The proforma invoice price includes a small margin to cover costs of procurement and quality control of the medicines prior to shipment, insurance and shipping.

[b] Medicines for treating drug-resistant TB usually have short expiry dates, only 24 months from date of manufacture in most cases – for that reason, the TB programme should order sufficient medicines to cover those patients currently on treatment and those expected to be enrolled for a one year period once the medicines are delivered to the country; as mentioned above the TB programme may decide to make a partial order.

In 2001, the Global Fund and WHO signed an agreement that GDF would provide drug-resistant TB medicines to countries using Global Fund grants. The agreement is still in effect.

20.7 Registration, importation and market control of MDR-TB medicines

All drugs used in a regimen for drug-resistant TB should meet the WHO recommended standards for safety, efficacy and quality.

Specific points for drug-resistant TB include:

- fast track registration or at least authorization for import and use of all drug-resistant TB drugs prequalified by WHO;
- authorization to use drug-resistant TB drugs in the framework of the NTP drug-resistant TB treatment programmes;
- legal framework to use potential new drugs for compassionate use.

GDF (through its Procurement Agent) works with manufacturers to transfer all relevant documentation to national drug regulatory authorities as per official requirements, to facilitate

the registration process when requested by the recipient country. The registration process is established at the time procurement begins.

Although reserving medicines for drug-resistant TB is difficult for countries since some of the medicines are used for other infections as well (e.g. fluoroquinolones), some countries have taken regulatory measures to ban key second-line anti-TB drugs from the private sector and reserved these medicines exclusively for drug-resistant TB within a public network of capacitated treatment centres. These regulatory actions are likely to contribute to maintaining lower levels of resistance to these medicines and to create a rational framework to protect medicines efficacy in the context of the imminent introduction of new classes of medicines to treat TB/drug-resistant TB.

BOX 20.6 UNDERSTANDING KEY REGULATORY ASPECTS IN CONTROLLING THE SECOND-LINE ANTI-TB DRUGS MARKET FOR MDR-TB AND ENSURING THE QUALITY OF MEDICINES USED BY TB PROGRAMMES IN-COUNTRY

The following quality assurance components of a drug supply system, when rationally implemented and based on WHO international standards, ensure that each drug used by a patient is safe, efficacious and of appropriate quality.

- Documentation analysis and drug registration process
- Inspection of local/imported product samples, manufacturing sites and market places
- Product testing at National Regulation Authorities laboratories for post-marketing surveillance
- Adequate and functional reporting mechanisms within the health system

Regular data analysis and evaluation of information produced allows countries to have adequate decision-making mechanisms to enforce their legal framework.

Most countries require medicines to be registered before importation. In some cases the government will waive this requirement on humanitarian grounds until such time when the country's drug regulatory authority can register the medicines.

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CHAPTER 21

Ethics in programmatic management of MDR-TB

21.1 Introduction

Prevention, diagnosis, care and treatment of TB, including drug-resistant TB, raise important ethical and human rights issues that must be addressed (see Box 21.1) *(1,2)*. For example, TB particularly affects poor and vulnerable populations, and therefore social justice and equity must be at the heart of the response. TB can be a lethal infectious disease that, in the absence of proper treatment and care of patients, and control of the epidemic, raises questions on how to ensure balance of individual responsibilities, rights and liberties of those affected by the disease with the protection of those who are at risk of infection. In 2010, the WHO published a guidance document entitled *Guidance on ethics of TB prevention, care and control (3)*. TB and drug-resistant TB human resource development plans of a country should include the basic elements of WHO guidance on ethics and human rights, adapted to the national policies and law (see Box 21.2). This chapter presents the key ethical guidance points developed in the WHO guidance *(3)*; and a checklist for TB control managers to identify early-on ethical issues that require action to prevent or remediate inappropriate practices (see Box 21.1).

BOX 21.1 FREQUENT ETHICAL DILEMMAS IN TB CARE

- Do patients have the right to refuse treatment?
- Is it ever legitimate to isolate contagious patients against their will?
- When governments do not fulfill their obligations to provide quality-assured drugs, would it be ethically preferable to give drugs of unknown quality than to for go treatment entirely?
- Do health care workers have an obligation to provide care, even when it involves significant health risks to themselves?
- Should a patient's TB status ever be disclosed to third parties against his or her will?
- Should financial incentives be offered to increase adherence to treatment?
- Should patients be diagnosed in the absence of adequate treatment?
- What are the obligations towards patients who cannot be cured and have no treatment alternatives?
- Should the patient receive a drug likely to be effective drug when it is not always possible to predict if the drug will do more good than harm?
- Should the patient receive a potentially effective drug that is not registered for MDR-TB treatment?

21.2 Key ethical principles in response to the TB and drug-resistant TB epidemic

21.2.1 Governments have a responsibility to provide free and universal TB services of high quality

Governments have an ethical responsibility to provide free and universal access to TB diagnostic and treatment services. This obligation is grounded in their duty to respect, protect and fulfill human rights and, more specifically, to fulfill the human right to health. Not only does TB treatment significantly improve the health condition of individuals, it also benefits the broader community by stopping the spread of a highly infectious disease. This duty of free and universal access extends to all multidrug-resistant TB (MDR-TB) services. Patients need to be fully informed and counselled about their treatment options. Individuals have a right to know what is being done to their bodies; therefore patients undergoing TB testing and treatment should receive comprehensive information about the risks, benefits and alternatives available to them. National TB control programmes have an ethical obligation to provide quality assured anti-TB drugs, as substandard drugs can both harm individual patients and contribute to the development, spread and amplification of drug-resistant strains. As with any other significant medical intervention, the voluntary and informed decision of the patient is necessary to start TB treatment.

21.2.2 Access to diagnosis should not necessarily be limited by the absence of treatment

In TB testing, there is normally no need to request a patient's specific consent with the diagnostic procedure based on sputum testing. However, capacity building for rapid diagnostic tests for rifampicin resistance, for example, may advance more rapidly than the development of capacity for treatment. This may create situations in which consent should be sought or the choice to opt out of the test may be offered to patient. Thus, when patients are offered rapid rifampicin-resistant tests in the absence of treatment, they should be informed of the risks and benefits of testing (i.e. life planning, need of strengthening of infection control measures) and specifically asked if they are willing to consent under these circumstances. Consent does not necessarily need to be in writing; what is important is that the patient be given relevant information and an opportunity to decide, and the decision documented *(4)*.

Drug resistance surveys (DRSs) provide valuable estimations on the magnitude of the problem, plan a response, and guide decisions on how best to treat MDR-TB patients, and it is therefore considered to be justified under some conditions, even if treatment is not immediately available *(4)*. Countries undergoing DRSs should link any cases identified with drug-resistant TB to proper treatment. If no treatment is available, then obtaining informed consent, as part of the DRS, is required, and establishment of proper TB infection control practices should be pursued.

21.2.3 Health care workers have obligations to provide care, but also a right to adequate protection

Health care workers have an ethical obligation to care for their patients, even if doing so involves some degree of risk *(5)*. However, they should not be expected to assume risks that result from inadequate conditions to provide care: governments and health care institutions must provide the necessary goods and services to allow for a safe working environment. Also, health care workers who are at heightened risk of contracting TB themselves, such as those who are living with HIV, may be exempted from their duty to care.

21.2.4 Involuntary isolation is rarely justified and should be a very last resort

TB treatment should be provided on a voluntary basis *(2)*. If a patient refuses treatment, this is likely due to insufficient counselling or lack of treatment support. In extremely rare cases, where all efforts to engage a patient to adhere to treatment have failed, the rights of other members of the community might justify the isolation of the contagious patient involuntarily. However, involuntary isolation should always be used as a very last resort, and only when all measures are exhausted. It is essential that the manner in which it is decided and implemented complies with applicable ethical and human rights principles. Furthermore, isolation should be least restrictive and intrusive with adequate infection control and reasonable social support measures in place.

21.2.5 Health care providers have an obligation to support patients' ability to complete therapy

There are several ethically sound strategies to support patients' ability to adhere to treatment, including directly observed therapy with a patient-centred approach *(6)*. Financial incentives can be useful, but should be managed carefully and priority should be given to enablers that help the patient in tackling barriers to adhere to treatment. It is crucial for patients to be engaged as partners in the treatment process, respecting their autonomy and privacy. If the majority of patients have problems with adherence, this suggests the system has failed in providing a person-centred approach. Nonconsensual treatment, that is, physically forcing patients to take medicines over their objection, results in humiliating, degrading or cruel treatment, and is strongly discouraged on ethical and human rights grounds. Use of all reasonable and ethical means to persuade (including the option of nonvoluntary isolation) and to enable patient's adherence to treatment in order to protect public health are usually sufficient, and should always be tried first whenever a patient refuses treatment *(2)*.

21.2.6 TB programmes and practitioners have a duty not to abandon their patients

As long as MDR-TB remains a life-threatening condition there is a fundamental ethical obligation to provide palliative care to all MDR-TB patients. The alleviation of suffering should not be limited to the delivery of treatment with second-line anti-TB drugs. When all available curative treatments fail, patients should continue receiving the care needed, including end-of-life care, and never be abandoned. Also, it is unacceptable to deny treatment based on predictions about non-adherence by particular patients *(4)*.

BOX 21.2 BASIC TB ETHICS AND HUMAN RIGHTS INFORMATION AND SKILLS THAT HEALTH CARE WORKERS MUST POSSESS

- Be knowledgeable about all the ethical and human rights dimensions in TB, and principles as described in the WHO *Guidance on ethics of TB prevention, care and control.*
- Be able to recognize ethical and human rights pitfalls in national, regional or local TB control programmes.
- Be able to address issues and resolve them by implementing sound measures based on the WHO recommended framework.
- Be knowledgeable and competent to provide information and seek informed consent in patients prescribed with drugs that have a low or uncertain safety profile but are considered the last therapeutic option.
- Advocate for the importance of addressing ethics, human rights, equity and social dimensions in TB programmes.

21.2.7 Research on TB is necessary and should be conducted in an ethical manner

There is a need for further research on TB prevention, diagnosis, treatment and care. It is crucial that research be guided by the ethical principles articulated in the international guidelines for biomedical research involving human subjects (such as the CIOMS and Declaration of Helsinki) *(7)*. In general, research should always ensure the dignity of the research subjects, and results should lead to a benefit for the affected.

21.2.8 Ethical integrity in a national TB control programme

The answer to ethical dilemmas in the management of TB comes from debates that have to take place at the setting where the dilemma occurs and with the proper engagement of the actors involved in the issue. The WHO *Guidance on ethics of TB prevention, care and control (3)* provides broad advice based on international standards of the ethics of public health practice. Patients and affected communities want to be confident that health care providers deliver services according to the international ethics standards in public health. Box 21.3 is an example of a checklist that NTPs and, especially, MDR-TB programmes can use to identify ethical and human right issues in their health delivery services.

BOX 21.3 CHECKLIST TO IDENTIFY ETHICAL AND HUMAN RIGHT ISSUES IN TB PROGRAMMES

- Does the TB programme have any specific policies to improve access to TB diagnosis, treatment and support for vulnerable sub-populations?
- Are there any laws, policies or practices that lead to the exclusion of certain sub-populations from TB diagnosis, treatment and support?
- Do the TB programme guidelines contain a protocol for the management of patients where all treatment treatments options have failed?
- Do the NTP guidelines exclude the possibility of treating patients against their will?
- Have there been patients who were treated against their will in the past few years?
- Does the NTP ensure that informed consent is obtained in patients before receiving bedaquiline and other drugs in which balance of harms and benefits is uncertain?
- In settings where no MDR-TB treatment is available, are patients asked for their informed consent prior to diagnosis?
- Is informed consent sought in MDR-TB patients before treatment with drugs of uncertain safety and efficacy profile?
- Does the country have laws, regulations or policies establishing procedures and conditions of involuntary isolation?
- Have there been patients isolated against their will in the past few years?
- Are there plans to conduct training courses on ethics of TB for health care workers?

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CHAPTER 22

Use of drugs under development and preapproval by national drug regulatory authorities

22.1 Introduction

By 2014, several new compounds for the treatment of multidrug-resistant TB (MDR-TB) were at different stages of development. The US Food and Drug Administration (FDA) gave conditional approval to bedaquiline in 2012 *(1)*, and the European Medicines Agency and the Japanese drug regulatory authority approved delamanid in 2014. Dossiers of these compounds are under review by other national drug regulatory agencies, with the expectation of approval in the very near future *(2)*.

MDR-TB is a life-threatening diseases for which the currently approved drugs are not always effective. In some cases, TB drugs under development, used in combination with approved drugs, could potentially be more effective than the treatment regimens that can be designed with approved drugs. Mechanisms have been established in some countries to ensure that patients in need do benefit as early as possible from drugs that are at the last stages of development. *Compassionate Use* (CU) and *Expanded Access* (EA) are used in this chapter to refer to the two more common mechanisms, acknowledging that these names correspond to the framework set up in the US drug regulatory environment, probably one of the most developed in this area; but that other names are used in other countries for very similar mechanisms. CU developed to a large extent in response to the activism demanding more effective ways to address diseases such as cancer and HIV/AIDS *(3)*.

This chapter presents guidance to countries to implement mechanisms such as CU and EA programmes. The chapter also discusses the regulatory framework, the indications for CU and the specific mechanisms (request, medical committee, patient protection), the programmatic

requirements, the use of companion drugs in regimen(s) and the needed monitoring and data collection.

22.2 General considerations and definitions

In the context of the development of anti-TB drugs, several members of the stop TB community belonging to the EA Working Group of Research Excellence to Stop TB Resistance (RESIST-TB) (http://www.resisttb.org/) and the Critical Path to TB Drug Regimens (http://cptrinitiative.org) have proposed the following definitions *(3)*:

CU refers to programmes "for which a physician requests a drug for a specific individual patient. The physician usually applies directly to the manufacturer. The manufacturer provides the drug to the physician for use for that specific patient, and the patient's condition must meet criteria established by the manufacturer, usually based on the absence of any other treatment with any likelihood of success. The manufacturer provides guidelines on the use of the drug, but does not monitor its use or outcomes. In general, the country of residence is required to have regulations in place permitting such 'compassionate use' of an unapproved drug. The physician is responsible for following local regulations, such as importation or the need for Institutional Review Board (IRB) approval" *(3)*.

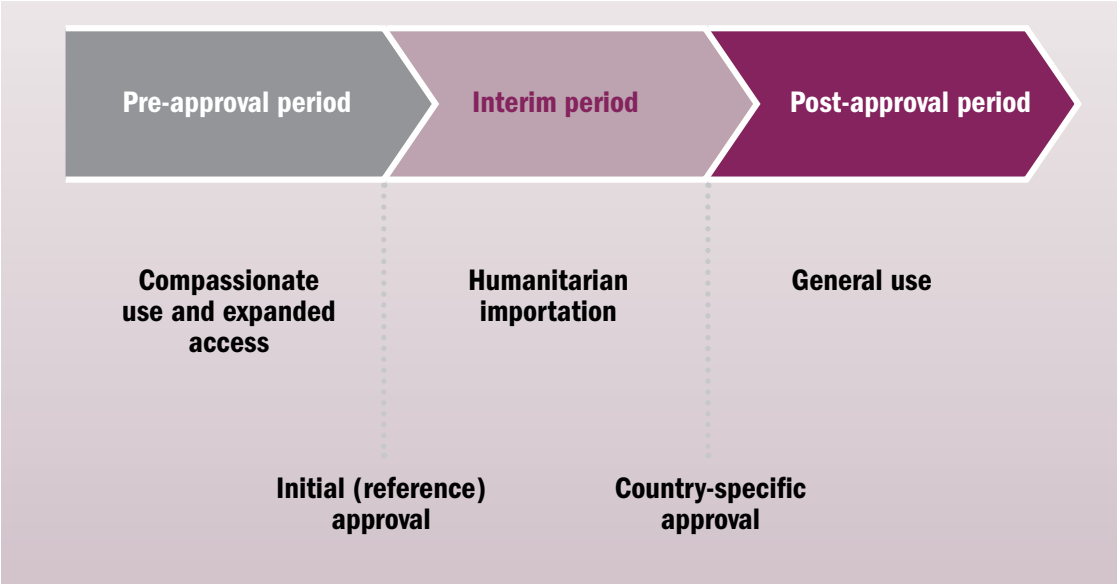
EA refers to programmes "that focus on enrolling groups of patients; in this way they are a type of clinical trial. In an EA programme, the manufacturer sets up a trial into which patients can be enrolled if they meet specific criteria. Rather than evaluating individual patients case by case on the basis of need, a target population for enrolment is defined and only those patients who meet the enrolment criteria can participate. There is more emphasis on patient follow-up than in the CU mechanism, and data collection on safety and follow-up/treatment outcome is requisite. The drug is used on an open-label basis, and its use is required to follow program guidelines. In this situation, the program is established in specific countries, where it is registered as a clinical trial. Access is thus limited to the countries where the trial is taking place." *(3)*.

WHO supports the implementation of CU/EA programmes for new drugs in countries, especially those with high MDR-TB burden *(4)*. National health authorities of these countries are encouraged to develop or update the necessary framework to facilitate rapid access to the potential benefit of these programmes and to ensure that adequate precautions are implemented to protect patients from undue risks while at the same time preserve the efficacy of the drugs as much as possible. The expected increase in the number of notified XDR-TB cases in whom limited treatment options are available and the relatively long time it takes to national drug regulatory authorities to review and approve a new drug, makes it even more appropriate for countries to develop a legal framework for CU.

The place of CU and EA programmes in the management of MDR-TB has to be reviewed in the context of clinical trials for drug development. The three stages of the path followed for the approval of a new drug is presented in Figure 22.1. The preapproval period starts from the moment the drug manufacturer shows it to be effective and submits an application to a drug regulatory authority until the initial reference approval is given. The interim period

corresponds to the country specific approval process, which varies among countries. The post-approval period corresponds to the full marketing of a country approved drug.

Figure 22.1 New drug approval pathway



Country specific regulations have resulted in different definitions of CU and EA to underpin programmes that, broadly speaking, aim for the same goal: enabling access to patients most in need of a drug shown to be effective but still in the preapproval period, while at the same time protecting the public health interest.

22.3 Supporting patients to benefit from CU and EA programmes: Steps for NTPs to set up programmes to enable access to drugs in the preapproval period

Table 22.1 lists the essential steps that national TB control programmes (NTPs) should consider, at the minimum, for setting up programmes to enable access to drugs in the preapproval period, which may correspond to a clinical trial Phase IIb.

TABLE 22.1 **Essential steps for introducing preapproval drugs in programmes managing MDR-TB**

- Ensure that the capacity to apply basic international standards for patient treatment and care are in place
- Identify the existing national regulatory mechanisms for use of drugs in the preapproval period
- Determine the criteria for a patient to be eligible to access drugs in the preapproval period
- Define and apply the ethical standards that will protect patients, ensure equity and promote human rights
- Monitor the implementation of the programme.

1. Ensure that the capacity to apply basic international standards for patient treatment and care are in place

The benefit for patients accessing CU/EA and the preservation of the efficacy of pre-approval drugs is determined, to a large extent, by the conditions under which the treatment is delivered. Thus, creation of programmes to enable access to drugs in the preapproval period should only be considered if adequate clinical, biological and bacteriological monitoring capacity is in place, including mechanisms for collecting and reporting patient data through specific case report forms. It is of the utmost importance that the programme diligently reports adverse events, following the standards set for pharmacovigilance of anti-TB drugs *(5)*.

Patient adherence to treatment is critical to reduce the risk of amplification of resistance. All patients should be provided with the social support measures needed to adhere to treatment at no cost to the patient. Access to experts in the clinical management of MDR-TB is crucial to make the most rational use of the resources available. There should be a guarantee of uninterrupted supply of the companion agents.

2. Identify the existing national regulatory mechanisms for use of drugs in the preapproval period

The regulations for use of drugs in the preapproval period vary among countries. The national regulation may consist of a well developed framework for CU; a set of special rules to import drugs not yet nationally approved; or a collection of interim ad hoc procedures set up by the health ministry while a more comprehensive framework is being developed. The NTP should identify the existing national regulation and develop the programme accordingly.

Most existent regulations are based on similar modus operandi:

- The practitioner (usually a physician):
  - is responsible for initiating a request to the regulatory agency on behalf of a single patient or a group of patients. The request must include: a description of the conditions and circumstances necessitating treatment, a discussion of why existing therapies are unsatisfactory (including relevant clinical and laboratory data) and why the probable risk of adverse outcome by using the preapproval drug is no greater than the probable risk from the disease; and
  - must agree to provide the regulatory agency with a report on the results of use of the drug, including any adverse reactions.
- The sponsor[12]:
  - is willing to provide the product and has the final word on whether the drug will be supplied and under which conditions;
  - is responsible for providing information, requested by relevant regulatory agencies, on pharmaceutical quality or requirements such as good manufacturing practices (GMP) certificate for the manufacturing site, certificate of analysis, chemical and microbial parameters, stability data, batch number and expiry date; and

[12] An individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial.

  - is also responsible for providing all drug information to requesting practitioners and/or patients.
- Requests for such access are considered by the medical committee of the regulatory agency on a case-by-case basis, taking into consideration the nature of the medical condition, the availability of marketed alternatives and the information provided in support of the request regarding the use, safety and efficacy of the drug.
- The authorization of the regulatory agency to use an experimental drug outside a clinical trial does not constitute an opinion or statement that the drug is safe and efficacious.

3. Determine the criteria for a patient to be eligible to access drugs in the preapproval period

In the case of MDR-TB, access to anti-TB drugs in the preapproval period should be considered for patients with a deteriorating clinical condition due to MDR-TB and/or severe immune depression; when available treatments have failed; or when authorized drugs with bactericidal activity are insufficient for designing an effective regimen, according to WHO treatment guidelines. The preapproval drug should never be used in monotherapy, that is, it should always be used in conjunction with other drugs with probable efficacy in the specific patient in order to reduce the risk of emerging resistance to the preapproval drug. A local or national expert MDR-TB committee, accredited as needed by the national regulatory agency, should be the body in charge of defining and applying the patient selection criteria.

4. Define and apply ethical standards that will protect patients, ensure equity and promote human rights

There are several ethical issues to consider in CU/EA programmes. The patient must be well-informed about the drug, its intended actions and potential side-effects and its possible impact on other conditions or treatments. It is imperative that the patient is informed of effective treatment alternatives, if any, of palliative care services available, and that he or she understands that there is no guarantee of benefit from the preapproval drug. The preapproval drug should be provided free of charge to the patient. Patients must consent in writing to be treated under a CU/EA programme. The inclusion of a patient in any of these programmes should not be made in replacement of, but in addition to palliative care and end-of-life care services, whenever needed.

It is recommended that a local ethics review committee approves the proposed use of the drug. Controlled clinical trials are the only means of obtaining reliable and interpretable efficacy and safety data for a medicinal product; under no circumstance should a CU programme be used for the purpose of obtaining efficacy and safety data.

As the manufacturer may have insufficient supply capacity to meet the demand, the NTP should ensure fairness in the selection process of patients to benefit from the limited coverage the programme may have. The participation of civil society and patient organizations should be actively involved in the monitoring of the CU/EA programmes as it contributes to ensure that the best interests of patients, and not only those of public health, are protected.

5. Monitor the implementation of the programme

The monitoring of case-holding activities, extent of adherence to programme protocols, application of standards of care, and recording and reporting of treatment outcomes, should not differ from the programmatic management of drug-resistant TB monitoring evaluation standards. Access to preapproval drugs is not a guarantee of a cure rate higher than in patients that otherwise would not have had the opportunity to be treated with these drugs. Regular and in-depth monitoring of the programme is fundamental to identify the areas in need of adjustments in order to increase coverage, improve the care being delivered and increase impact.

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PART 3

Anti-TB drug information sheets

Adapted from Tuberculosis Drug Information Guide. 2nd Edition. California: Curry International Tuberculosis Center and California Department of Public Health; 2012, except where otherwise referenced.

Common presentations of the drugs are described; actual preparations may vary depending on the manufacturer.

Amikacin (Am)

DRUG CLASS: AMINOGLYCOSIDE

Activity against TB, mechanism of action, and metabolism	**Bactericidal:** Inhibits protein synthesis. Cross-resistance with kanamycin is considered complete and some data suggesting cross-resistance with capreomycin can occur. Primarily excreted unchanged through the kidney by glomerular filtration.
Dose	**Adults:** 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 gram). 15 mg/kg/dose, 3 times per week can be used after culture conversion is documented after initial period of daily administration. **>59 years of age:** 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. Alternatively, 15 mg/kg/dose 3 times per week. **Children:** 15–30 mg/kg/day (max 1 gram) 5–7 days per week. 15–30 mg/kg/day (max 1 gram) 3 days per week after initial period daily.
Preparation and administration	**Given intravenous (IV) or intramuscular (IM).** Not absorbed orally. For IV solution, mix with D5W or other solutions (in at least 100 ml of fluid for adults or 5 mg/ml for children). IM absorption can be delayed if same site is used consistently. For IV administration, infuse over 30–60 minutes for adults; 1–2 hours for children; IM absorption is complete within 4 hours.
Storage	Solution is stable at room temperature (15–25 °C); diluted solution is stable at room temperature for at least 3 weeks or in the refrigerator for at least 60 days.
CSF penetration	Variable penetration; appears to penetrate inflammed meninges better.
Special circumstances	**Use in pregnancy/breastfeeding:** Generally avoided during pregnancy due to congenital deafness seen with streptomycin and kanamycin. Can be used while breastfeeding. **Use in renal disease:** Use with caution. Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. 12–15 mg/kg/dose after dialysis 2–3 times weekly (not daily). The drug is variably cleared by haemodialysis. **Use in hepatic disease:** Drug concentrations not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution in patients with severe liver disease as it may progress rapidly to hepatorenal syndrome.

Adverse reactions	**Common:** Local pain with intramuscular injections. Proteinuria. **Occasional:** Nephrotoxicity, ototoxicity (hearing loss), vestibular toxicity (vertigo, ataxia, dizziness). All increases with advanced age and prolonged use. Electrolyte abnormalities, including hypokalaemia, hypocalcaemia, and hypomagnesaemia. **Rare:** Neuropathy, rash.
Contraindications	**Pregnancy** — relative contraindication (congenital deafness). Hypersensitivity to aminoglycosides. Caution with renal, hepatic, vestibular or auditory impairment.
Drug interactions	Co-administration of loop diuretics (furosemide) and aminoglycoside antibiotics carries an increased risk of ototoxicity.
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly audiology exam; follow monthly electrolytes, magnesium and calcium. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough concentrations at baseline if there is any question about renal function. Some experts monitor aminoglycoside concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.
Patient instructions and alerting symptoms	**Instruct patients to inform their health care provider right away if any of the following occurs:** • Problems with hearing, dizziness or balance • Rash or swelling of your face • Trouble breathing • Decreased urination • Swelling, pain or redness at your IV site • Muscle twitching or weakness.

Amoxicillin/Clavulanate (Amx/Clv)

DRUG CLASS: PENICILLIN/BETA-LACTAM INHIBITOR

Activity against TB, mechanism of action, and metabolism	Conflicting and limited reports, but possible early bactericidal activity. Clavulanate is a beta-lactam inhibitor. Amoxicillin component is renally excreted and clavulanate is cleared by the liver.
Dose[1]	**Expressed in amoxicillin component** **Adult (and child >30 kg):** 80 mg/kg/day in 2 divided doses **Child under 30 kg:** 80 mg/kg/day in 2 divided doses Maximum dose: 3000 mg daily
Preparation and administration	An oral drug with different preparations: • 875 mg amoxicillin/125 mg clavulanic acid tablet (ratio 7:1) • 400 mg amoxicillin/57 mg clavulanic acid/5 ml, powder for oral suspension (ratio 7:1) • 500 mg amoxicillin/62.5 mg clavulanic acid tablet (ratio 8:1) • 500 mg amoxicillin/62.5 mg clavulanic acid/5 ml, powder for oral suspension (ratio 8:1).
Storage	Tablets are stable at room temperature (15–25 °C); reconstituted suspension should be stored in the refrigerator and discarded after 7 days.
Oral absorption	Good oral absorption, best tolerated and well absorbed when taken at the start of a standard meal.
CSF penetration	Approximately 5% of the plasma concentration reaches the CSF.
Special circumstances	**Use in pregnancy/breastfeeding:** Probably safe in pregnancy (no known risk); can be used while breastfeeding. **Use in renal disease:** Amoxicillin is renally excreted and the dose should be adjusted for renal failure. For creatinine clearance 10–30 ml/min dose 1000 mg as amoxicillin twice daily; for creatinine clearance <10 ml/min dose 1000 mg as amoxicillin once daily. It is cleared by dialysis, so should be dosed after dialysis – single dose every 24 hours and after each dialysis session. **Use in hepatic disease:** Clavulanate is cleared by the liver, so care should be used when using in patients with liver failure.
Adverse reactions	**Common:** Diarrhoea and abdominal discomfort are most common. Nausea and vomiting. **Uncommon:** Hypersensitivity and rash. Rare side-effects have been reported in other organ systems.
Contraindications	Penicillin allergy; use with caution with cephalosporin allergies.
Monitoring	No specific monitoring is required.
Patient instructions and alerting symptoms	Take at beginning of a meal **Instruct patients to inform their health care provider right away if any of the following occurs:** • Rash or swelling • Trouble breathing • Severe diarrhoea.

[1] Tuberculosis: Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries. Médecins Sans Frontières and Partners In Health; 2013 (http://refbooks.msf.org/msf_docs/en/tuberculosis/tuberculosis_en.pdf, accessed 24 March 2014).

Bedaquiline[2] (Bdq)*

DRUG CLASS: DIARYLQUINOLINE

Activity against TB, mechanism of action, and metabolism	**Bactericidal:** Inhibits ATP synthesis; novel method of action; The drug has a 5.5-month half-life. CYP3A4 is the major CYP isoenzyme involved in the metabolism of bedaquiline. The metabolism leads to the formation of N-monodesmethyl metabolite (M2). M2 is not thought to contribute significantly to clinical efficacy given its lower average exposure (23–31%) in humans and lower antimycobacterial activity (4- to 6-fold lower) compared to the parent compound. M2 concentrations appeared to correlate with QT prolongation. Bedaquiline is mainly eliminated in faeces. The renal clearance of unchanged drug is insignificant.
Dose	**Adults:** 400 mg once daily for 2 weeks, followed by 200 mg, 3 times per week for 22 weeks with food. **Children:** Not yet determined. If a dose is missed during the first 2 weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule. From week 3 onwards, if a 200 mg dose is missed, patients should take the missed dose as soon as possible, and then resume the 3 times a week regimen.
Preparation and administration	100 mg tablets.
Storage	Store tablet at room temperature (15–25 °C).
Oral absorption	Better absorption is obtained if taken with food.
CSF penetration	No data are available regarding CNS penetration.
Special circumstances	**Use in pregnancy/breastfeeding:** Not recommended during pregnancy or breastfeeding due to limited data. Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus. **Use in renal disease:** No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution). **Use in hepatic disease:** No dosage adjustment is required in patients with mild to moderate hepatic impairment. Dosing and toxicity not well established in severe hepatic impairment, use with caution and only when the benefits outweigh the risks.

[2] Highlights of drug prescribing information for Sirturo (bedaquiline). Titusville, NJ 08560: Janssen Therapeutics, Division of Janssen Products. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf, accessed 24 March 2014).

* see Annex 4.1 for additional information

Adverse reactions	**Common:** Gastrointestinal distress (nausea, vomiting, abdominal pain, loss of appetite), joint pain (arthralgia), headache. (Note: haemoptysis and chest pain were also more frequently reported in the group receiving bedaquiline than in the placebo treatment group). **Less common:** QT prolongation, hyperuricaemia, phospholipidosis (the accumulation of phospholipids in the body's tissues), elevated aminotransferases. Possibly an increased risk of pancreatitis. **WARNINGS:** A significant imbalance in fatalities was noted in Trial C208 Stage 2, with a higher number of deaths in the bedaquiline group (10 vs 2 in the placebo group; RR=5.1; p=0.017).[3] There was no sudden death reported in the study. There was no discernible pattern for cause of deaths and the reason for the imbalance in deaths is not clear.
Contraindications/ Caution	**Do not use or discontinue bedaquiline** • Clinically significant ventricular arrhythmia. • A QTcF interval of >500 ms (confirmed by repeat ECG). • Severe liver disease. • Abnormal electrolytes. **Use with caution in the following situations (with more frequent ECG monitoring and evaluation of risk versus benefit):** • Use with other QT prolonging drugs (see drug interactions) • A history of torsade de pointes • A history of congenital long QT syndrome • A history of hypothyroidism and bradyarrhythmias • A history of uncompensated heart failure • Serum calcium, magnesium or potassium levels below the lower limits of normal.
Drug interactions	Bedaquiline is metabolized by CYP3A4. Rifampicin (a CYP3A4 inducer) reduces bedaquiline in blood by half. Efavirenz based on a single dose study appears to reduce the amount of bedaquiline though inducing CYP3A4. CYP3A4 inhibitors (e.g. azole anti-fungal drugs, some macrolides, protease inhibitors, and many others) can raise the level of bedaquiline but can be considered for use if the benefits outweigh the risk. Avoid use with other drugs that prolong the QT interval as additive QT prolongation may occur (e.g. clofazimine, fluoroquinolones, delamanid, azole anti-fungal drugs, and many others); any syncopal event (fainting) should prompt an immediate medical evaluation and ECG.
Monitoring	An ECG should be obtained before initiation of treatment, and at least 2, 4, 8, 12 and 24 weeks after starting treatment. More frequently if heart conditions, hypothyroidism or electrolyte disturbances are present. Liver function tests should be done monthly.

[3] Anti-Infective Drugs Advisory Committee Meeting Briefing Document: TMC207 (bedaquiline), treatment of patients with MDR-TB. NDA 204–384, Janssen Pharmaceutical companies of Johnson & Johnson, 28 November 2012.

Patient instructions and alerting symptoms	The patient should be informed that bedaquiline is a new anti-TB drug and there could be unknown risks and side-effects. The following serious side-effects can occur with bedaquiline: death, heart rhythm abnormalities, and/or hepatitis. This medicine should be taken with food. Avoid alcohol. The patient should be informed that in one clinical trial, more deaths were seen in people who were treated with bedaquiline compared to people who did not receive. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Abdominal pain • Yellowing of your skin or eyes • Palpitations • Chest pain • Fainting and near fainting events.

Capreomycin (Cm)

DRUG CLASS: CYCLIC POLYPEPTIDE

Activity against TB, mechanism of action, and metabolism	**Bactericidal:** has strong anti-TB activity; inhibits protein synthesis. Some data suggest cross-resistance with amikacin and kanamycin.
Dose	**Adults:** 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 g, but a large, muscular person could receive more and should have the concentrations monitored). 15 mg/kg/dose, 2–3 times per week after an initial period of daily administration (some experts use up to 25 mg/kg/dose for intermittent therapy; monitor concentrations). **>59 years of age:** 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after the initial period. Alternatively, 15 mg/kg/dose, 3 times per week. **Children:** 15–30 mg/kg/day (max 1 g), 5–7 days per week. 15-30 mg/kg/day (max 1 g), 2–3 days per week after initial period daily. **Renal failure/dialysis:** 12–15 mg/kg/dose, 2–3 times weekly (not daily). **Markedly obese individuals** should have an adjusted dose due to decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations. **For dosing, use adjusted weight as follows:** Ideal body weight + 40% of excess weight Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft. Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft. *Serum concentrations should be followed closely when possible.*
Route of administration	IV or IM.
Preparation	Capreomycin is available in vials of 1 gram for either IM or IV administration. The contents of the vial should be reconstituted with 2 ml or more of normal saline or sterile water.
Storage	Package insert indicates that reconstituted capreomycin can be stored in the refrigerator up to 24 hours prior to use. Other data suggest that it may be held for 14 days in the refrigerator or 2 days at room temperature (15–25 °C).
Oral absorption	There is no significant oral absorption. Intramuscular absorption may be delayed if the same site is used consistently.
CSF penetration	There is a paucity of data regarding capreomycin's penetration of the meninges.

Special circumstances	**Use in pregnancy/breastfeeding:** Generally avoided during pregnancy due to congenital deafness seen with streptomycin and kanamycin. There are case reports of its safe use in pregnancy (unaffected newborns). Can be used while breastfeeding. **Use in renal disease:** Use with caution. Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See section above for dosage under renal disease or dialysis. **Use in hepatic disease:** Drug concentrations are not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution – some patients with severe liver disease may progress rapidly to hepatorenal syndrome.
Adverse reactions	Similar to the aminoglycosides. Nephrotoxicity: 20–25% including proteinuria, reduced creatinine clearance, and depletion of potassium and magnesium. Ototoxicity (hearing loss): Occurs more often among the elderly or those with pre-existing renal impairment and vestibular toxicity. Local pain with intramuscular injections. Electrolyte abnormalities, including hypokalaemia, hypocalcaemia and hypomagnesaemia.
Contraindications	**Hypersensitivity to capreomycin.** Some experts would not use capreomycin if vestibular side-effects resulted from aminoglycoside use. **Generally avoided during pregnancy** due to congenital deafness seen with aminoglycosides and mechanism of ototoxicity may be similar with capreomycin. There are case reports of its safe use during pregnancy (unaffected newborns).
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any other concerns; document baseline and monthly audiology exam; follow monthly electrolytes, magnesium and calcium. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough concentrations at baseline if there is any question about renal function. Some experts monitor capreomycin concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.

Patient instructions and alerting symptoms	**Instruct patients to inform their health care provider right away if any of the following occurs:** • Rash • Fever or chills • Bleeding or bruising • Problems with hearing, dizziness or balance • Bleeding or a lump where the shot is given • Decreased urination • Trouble breathing • Muscle weakness.

Clarithromycin (Clr)

DRUG CLASS: MACROLIDE

Activity against TB, mechanism of action, and metabolism	Much more active against nontuberculous mycobacteria, especially *Mycobacterium* avium-complex (MAC), but some isolates of TB are susceptible in vitro. Does not have proven value for the treatment of TB in humans, and in vitro data are not particularly encouraging (*M. tuberculosis* is intrinsically resistant to macrolides, a characteristic associated with expression of the *erm*(37) gene).[4] Inhibits protein synthesis by binding to the 50S ribosomal subunit. The drug is cleared both hepatically and renally. Because of high intracellular concentrations, tissue levels are higher than in the serum.
Dose	**Adults:** 500 mg twice daily or 1 g daily of extended release formulation. **Children:** 7.5 mg/kg q 12 hours up to 500 mg. **Renal failure/dialysis:** The drug is cleared both hepatically and renally. In severe renal impairment, the interval doses should be increased, i.e. 500 mg/day.
Preparation	Oral tablets of 250 and 500 mg. Also available in extended release tablets for once daily use. Oral suspension 125 mg/5 ml and 250 mg/5 ml.
Storage	Store tablets and unmixed granules for suspension at room temperature (15–25 °C) in a well-sealed container and protect from light. The mixed suspension should not be refrigerated and can be stored for 14 days.
Oral absorption	The drug is rapidly absorbed after oral administration and is about 50% bioavailable. It can be given without regard to food. Food slightly delays the peak serum level but also slightly increases the peak concentration achieved.
CSF penetration	There is no information available about CNS penetration.

[4] Andini N, Nash KA. Intrinsic macrolide resistance of the *Mycobacterium tuberculosis* complex is inducible. Antimicrobial Agents and Chemotherapy 2006;50(7):2560–2562.

Special circumstances	**Pregnancy/breastfeeding:** Pregnancy category C and generally should not be used during pregnancy unless no other alternative is available. It is not known if the drug is excreted in human breast milk. **Use in renal disease:** In severe renal impairment, the interval between doses should be increased, i.e. 500 mg daily. **Use in hepatic disease:** No adjustment is necessary.
Adverse reactions	**Common:** Diarrhoea, nausea, abnormal taste, dyspepsia, abdominal pain /discomfort, headache. **Rare** allergic skin reactions, liver toxicity, QT prolongation, *Clostridium difficile* colitis, hearing loss.
Contraindications	**Patients with known hypersensitivity to macrolide antibiotics. Should not be given with the any of the following drugs:** bedaquiline, cisapride, pimozide, astemizole, terfenadine, and ergotamine or dihydroergotamine.
Monitoring	No routine laboratory monitoring is indicated.
Patient instructions and alerting symptoms	This medication may be taken with or without food. Be sure to tell your health care provider what other medications you are taking. Do not take cisapride, pimozide, astemizole, terfenadine, and ergotamine or dihydroergotamine when taking clarithromycin. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Severe diarrhoea. • Rash.

Clofazimine (Cfz)

DRUG CLASS: IMINOPHENAZINE

Activity against TB, mechanism of action, and metabolism	In vitro activity against *M. tuberculosis* without much in vivo data. Generally reserved for cases with few other options. Tissue half-life estimated to be around 70 days.
Dose	**Adults:** 100–200 mg daily (oral) has been used. A regimen of 200 mg daily for 2 months, followed by 100 mg daily has been used. **Children:** Limited data, but doses of 1 mg/kg/day have been given.
Preparation and administration.	50 and 100 mg capsules. Oral, not available parenterally. Improved tolerance and absorption with food.
Storage	Room temperature (15–25 °C).
Oral absorption	70% absorption after an oral dose.
CSF penetration	Limited data are available regarding CNS penetration.
Special circumstances	**Use in pregnancy/breastfeeding:** Not recommended due to limited data (some reports of normal outcomes, some reports of neonatal deaths). Avoided with breastfeeding due to pigmentation of the infant. **Use in renal disease:** No dosage adjustment required. **Use in hepatic disease:** Partially metabolized by the liver; use caution and/or adjust the dose for severe hepatic insufficiency.
Adverse reactions	**Common:** Orange/red discoloration of skin, conjunctiva, cornea and body fluids. Dry skin, pruritus, rash, ichthyosis, xerosis. Gastrointestinal intolerance. Photosensitivity. **Less common:** retinopathy, severe abdominal symptoms, bleeding and bowel obstruction; QT prolongation.
Contraindications	Allergy to clofazimine.
Drug interactions	Using with drugs that prolong the QT interval may cause additive QT prolongation (e.g. bedaquiline, fluoroquinolones, delamanid, azole anti-fungal drugs, and many others); further research is needed to understand potential interactions with antiretrovirals.
Monitoring	Symptomatic monitoring.
Patient instructions and alerting symptoms	Take with food to avoid stomach upset and improve absorption. This medicine may discolor your skin and body secretions are orange, red or brownish-black. This should go away after stopping the medicine, but may take a long time. Avoid the sun and use strong sunscreens. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Bloody or black stools or diarrhoea • Yellowing of skin or eyes • Severe nausea, vomiting, abdominal pain, cramps or burning • Depression or thoughts of hurting oneself.

Cycloserine (Cs) [and Terizidone (Trd)]

DRUG CLASS: ANALOG OF D-ALANINE.

Activity against TB, mechanism of action, and metabolism	**Bacteriostatic:** inhibits cell wall synthesis.
Dose	**Adults:** 10–15 mg/kg/day usually (max. 1000 mg/day); Usually 500–750 mg/day given in two divided doses or once a day if tolerated. Some patients may require only alternate day 250 mg and 500 mg dosing to avoid toxicity. **Children:** 10–20 mg/kg/day divided every 12 hours (daily maximum 1 g). **Pyridoxine (vitamin B6):** Although supporting data are not extensive, MDR-TB experts recommend that all patients should receive vitamin B6 while taking cycloserine. Adults need 100 mg or more (or 50 mg per 250 mg of cycloserine) and children should receive a dose proportionate to their weight (1–2 mg/kg/day, with a usual range of 10–50 mg/day). **Renal failure/dialysis:** 250 mg once daily or 500 mg, 3 times per week; monitor drug concentrations to keep peak concentrations <35 mcg/ml.
Route of administration	Oral; not available parenterally.
Preparation	250 mg capsule.
Storage	Room temperature (15–25 °C) in airtight containers.
Oral absorption	Modestly decreased by food (best to take on an empty stomach); not significantly affected by antacids or orange juice.
CSF penetration	Concentrations approach those in serum.
Special circumstances	**Use in pregnancy/breastfeeding:** Not well studied, but no teratogenicity documented. Use if there are not better choices. Can be used while breastfeeding (dose the infant with vitamin B6 if breastfed). **Use in renal disease:** Cycloserine is cleared by the kidney and requires dose adjustment for renal failure (see above). Use with caution. **Use in hepatic disease:** Not associated with hepatotoxicity.
Adverse reactions	CNS toxicity, including inability to concentrate and lethargy. More serious CNS side effects, including seizure, depression, psychosis and suicidal ideation, *usually* occur at peak concentrations >35 mcg/ml, but may be seen in the normal therapeutic range. Other side-effects include peripheral neuropathy and skin changes. Skin problems include lichenoid eruptions and Stevens-Johnson syndrome.
Contraindications	Relative contraindications include seizure disorder, psychotic disease or alcohol abuse.

Monitoring	Peak concentrations should be obtained within the first 1–2 weeks of therapy and monitored serially during therapy. The peak concentration should be kept below 35 mcg/ml. Baseline and monthly monitoring for depression using a tool such as the Beck Depression Index should be done.
Patient instructions and alerting symptoms	If food is taken, avoid a large fatty meal. Avoid alcohol. You must also take a high-dose vitamin B6 supplement while on this drug. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Seizures • Shakiness or trouble talking • Depression or thoughts of hurting yourself • Anxiety, confusion or loss of memory • Personality changes, such as aggressive behavior • Rash or hives • Headache.

Delamanid (Dlm)[5]

DRUG CLASS: NITRODIHYDRO-IMIDAZO-OXAZOLE.

Activity against TB, mechanism of action, and metabolism	Inhibition of the synthesis of the mycobacterial cell wall components, methoxy-mycolic and keto-mycolic acid. Delamanid is a pro-drug that must be reduced by the deazaflavin-dependent nitroreductase to its des-nitro metabolite to be active. The complete metabolic profile of delamanid in man has not yet been fully elucidated. Therefore the potential for drug-drug interactions of clinical significance to occur with delamanid and the possible consequences, including the total effect on the QTc interval, cannot be predicted with confidence. Plasma albumin and CYP3A regulate the formation and metabolism of DM-6705 respectively. The identified metabolites of delamanid do not show anti-mycobacterial activity. Concentrations of the identified metabolites progressively increase to steady state after 6 to 10 weeks. QTc prolongation is very closely correlated with the major delamanid metabolite DM-6705. Delamanid disappears from plasma with a t1/2 of 30-38 hours. Delamanid is not excreted in urine.
Dose	**Adults:** 100 mg twice daily for 24 weeks. It is recommended to administer with water and to be taken with, or just after a meal. **Children:** Not yet determined (pediatric trials are ongoing)[6].

[5] Highlights of drug prescribing information for delamanid are taken from the European Medicines Agency web site: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002552/WC500166232.pdf, accessed 23 March, 2014, accessed 15 August, 2014. See Annex 4.2 for additional information.

[6] https://clinicaltrials.gov/ct2/show/NCT01859923?term=delamanid&rank=1; https://clinicaltrials.gov/ct2/show/NCT01856634?term=delamanid&rank=4

Preparation and administration.	50 mg film-coated tablets.
Storage	Store tablet at room temperature and in original package.
Oral absorption	Absorption is increased with a standard meal.
CSF penetration	No data are available regarding CNS penetration.
Special circumstances	**Use in pregnancy/breastfeeding:** There are very limited data from the use of delamanid in pregnant women. Studies in animals have shown reproductive toxicity. Available pharmacokinetic data in animals have shown excretion of delamanid and/or its metabolites in milk. **Use in renal disease:** No dosage adjustment is required in patients with mild to moderate renal impairment Dosing not established in severe renal impairment, use with caution and only when the benefits outweigh the risks. **Use in hepatic disease:** No dosage adjustment is required in patients with mild to moderate hepatic impairment. Dosing and toxicity not well established in severe hepatic impairment, use with caution and only when the benefits outweigh the risks.
Adverse reactions	**Common:** The most frequently observed adverse drug reactions in patients treated with delamanid (i.e. incidence > 10%) are nausea (38.3%), vomiting (33%), and dizziness (30.2%). **Less common:** QT prolongation.
Contraindications/ caution	**Do not use or discontinue delamanid** • Clinically significant ventricular arrhythmia. • A QTcF interval of > 500 ms (confirmed by repeat ECG). • Severe liver disease. • Serum Albumin less than 2.8. • Abnormal electrolytes. **Use with caution in the following situations (with more frequent ECG monitoring and evaluation of risk versus benefit):** • Use with other QT prolonging drugs (see drug interactions). • A history of torsade de pointes. • A history of congenital long QT syndrome. • A history of hypothyroidism and bradyarrhythmias. • A history of uncompensated heart failure. • Serum calcium, magnesium, or potassium levels below the lower limits of normal. **Use with caution in patients sensitive to lactose.**

Drug Interactions	Avoid concomitant administration of strong CYP3A inducers (e.g. rifampicin, carbamazepine). No clinically relevant reduction in delamanid exposure was observed with weak inducers. If co-administration of delamanid with any strong inhibitor of CYP3A (e.g. ritonavir, ketokonazole) is necessary, consider more very frequent monitoring of ECGs, throughout the delamanid treatment. Delamanid does not affect plasma exposure of coadministered anti-TB drugs, Rifater (isoniazid/rifampicin/pyrazinamide) + ethambutol in a clinically relevant manner (25% increase in ethambutol). Delamanid does not affect plasma exposure of ARV drugs tenofovir, Kaletra (lopinavir/ritonavir), or efavirenz. Antiretroviral drugs, tenofovir, efavirenz, and Kaletra (lopinovir/ritonavir), do not affect delamanid exposure in a clinically relevant manner (24% increase). Avoid using with other drugs that prolong the QT interval as additive QT prolongation may occur (e.g. clofazimine, fluoroquinolones, bedaquiline, azole anti-fungal drugs, ondansetron, and several others).
Monitoring	An ECG should be obtained before initiation of treatment, and at least 2, 4, 8, 12, and 24 weeks after starting treatment with delamanid. Monitoring ECGs should be done monthly if taking other QT prolonging drugs (i.e moxifloxacin, clofazimine, etc).
Patient instructions and alerting symptoms	The patient should be informed that delamanid is a new anti-TB drug and there could be unknown risks and side-effects. One serious side-effect associated with delamanid is it can change the electrical conduction of the heart, which could put a patient at risk for arrhythmias. This medicine should be taken with food. Avoid alcohol. **Instruct patient to inform health care provider right away if any of the following occurs:** • Palpitations • Chest pain • Fainting and near fainting events

Ethambutol (Emb)

DRUG CLASS: UNSPECIFIED

Activity against TB, mechanism of action, and metabolism	**Bacteriostatic:** inhibitor of cell wall synthesis; bactericidal only at the high end of the dosing range. At doses used over long periods of time, ethambutol protects against further development of resistance.
Dose	**Adults:** 15–25 mg/kg/day. Higher doses should be used only during the initial months of therapy. For prolonged therapy, the dose should be closer to 15 mg/kg/day to avoid toxicity. **Children:** 15–25 mg/kg/day; doses closer to 15 mg/kg/day should be used if the drug is used for more than 2 months. **Renal failure/dialysis:** 15–25 mg/kg/dose, 3 times weekly (not daily). **Obesity:** For obese patients, base dosing on adjusted weight as follows: Ideal body weight + 40% of excess weight Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft
Route of administration	Oral; not available parenterally in the US.
Preparation	100 mg tablets; scored 400 mg tablets; coated 100 mg tablets; coated, scored 400 mg tablets.
Storage	Room temperature (15–25 °C).
Pharmacokinetics	**Peak oral absorption** occurs 2–4 hours after the dose. Draw a peak serum concentration 2–3 hours after the dose; a second sample 6 hours post-dose could be obtained if there is concern about late absorption and in order to estimate the serum half-life. **Peak concentrations** of 2–6 mcg/ml are expected with daily dosing. Intermittent doses of 50 mg/kg can be expected to produce peaks of 4–12 mcg/ml.
Oral absorption	80% bioavailability independent of food.
CSF penetration	Ethambutol penetrates meninges poorly.
Special circumstances	**Use in pregnancy/breastfeeding:** Safe in pregnancy; can be used while breastfeeding. **Use in renal disease:** Use with caution – cleared by the kidneys; dose adjustment required for renal failure. Increased risk of toxicity with renal failure. If needed for use in the regimen, consider therapeutic drug monitoring. **Use in hepatic disease:** Safe in liver disease.
Adverse reactions	Retrobulbar neuritis (dose-related – exacerbated during renal failure).
Contraindications	**Pre-existing optic neuritis; visual changes on ethambutol.**

Monitoring	Patients should be counselled to report any changes in vision. Baseline and monthly visual acuity and colour discrimination monitoring should be performed (particular attention should be given to individuals on higher doses or with renal impairment).
Patient instructions and alerting symptoms	Can be taken with food or on an empty stomach. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Any problems with your eyes: vision changes, blurring, colour blindness, trouble seeing or eye pain • Swelling of face • Rash, hives or trouble breathing • Numbness, pain or tingling in hands or feet • Joint pain • Fever or chills • Nausea, vomiting, poor appetite or abdominal pain • Headache or dizziness.

Ethionamide (Eto)/Protionamide (Pto)

DRUG CLASS: CARBOTHIONAMIDES GROUP, DERIVATIVES OF ISONICOTINIC ACID

Activity against TB, mechanism of action, and metabolism	**Weakly bactericidal:** blocks mycolic acid synthesis.
Dose	**Adults:** 15–20 mg/kg/day frequently divided (max dose 1 gram per day); usually 500–750 mg per day in 2 divided doses or a single daily dose. **Children:** 15–20 mg/kg/day usually divided into 2–3 doses (max dose 1 gram per day). A single daily dose can sometimes be given at bedtime or with the main meal. Many individuals require gradual ramping up of the dose and treatment for gastrointestinal upset. **Pyridoxine (vitamin B6):** Although there is little supporting data, most MDR-TB experts recommend that all patients should receive vitamin B6 while taking ethionamide. Suggested dose for adults is 100 mg and children should receive a dose proportionate to their weight (1–2 mg/kg/day, with a usual range of 10–50 mg/day). **Renal failure/dialysis:** No change.
Route of administration	Oral; not available parenterally.
Preparation	Coated 250 mg tablet.
Storage	Store at room temperature (15–25 °C).
Oral absorption	Erratic absorption, possibly due to gastrointestinal disturbances associated with the medication.
CSF penetration	Concentrations approach those in the serum; one paediatric study evaluating drug concentrations in the CSF suggests that ethionamide should be dosed on the high end of the range for patients with meningitis.
Special circumstances	**Use in pregnancy/breastfeeding:** Generally avoided during pregnancy due to reports of teratogenicity; little data about use during breastfeeding – an estimated 20% of the infant therapeutic dose will be passed on to the baby in the breast milk (dose the infant with vitamin B6 if breastfed). **Use in renal disease:** No precautions are required for renal impairment. **Use in hepatic disease:** Can cause hepatotoxicity similar to that of isoniazid – use with caution in liver disease.

Adverse reactions	Gastrointestinal upset and anorexia: sometimes intolerable (symptoms are moderated by food or taking at bedtime). Premedication with an antiemetic like ondansetron is often helpful. Low dose Ativan 0.5 mg has also been used successfully. Metallic taste. Hepatotoxicity. Endocrine effects: Gynaecomastia, hair loss, acne, impotence, menstrual irregularity, and reversible hypothyroidism – treat with thyroid replacement. Neurotoxicity (patients taking ethionamide should take high doses of vitamin B6). Side effects may be exaggerated in patients also taking cycloserine.
Contraindications	**Sensitivity to ethionamide.**
Monitoring	Monitor thyroid stimulating hormone for evidence of hypothyroidism requiring replacement; therapeutic drug monitoring required if malabsorption is suspected. Monitor liver function tests.
Patient instructions and alerting symptoms	Take this medicine with food. You must also take a high-dose vitamin B6 supplement while on this drug. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Any problems with your eyes: eye pain, blurred vision, colour blindness or trouble seeing • Numbness, tingling or pain in your hands or feet • Unusual bruising or bleeding • Personality changes such as depression, confusion or aggression • Yellowing of your skin or eyes • Dark-colored urine • Nausea and vomiting • Dizziness • Swollen breasts (in men).

Gatifloxacin (Gfx)

DRUG CLASS: FLUOROQUINOLONE

Activity against TB, mechanism of action, and metabolism	**Bactericidal:** acts by inhibiting the A subunit of DNA gyrase (topoisomerase), which is essential in the reproduction of and metabolism bacterial DNA.
Dose	400 mg/day
Route of administration	Oral.
Preparation	Tablets, 200 or 400 mg.
Storage	Room temperature (15–25 °C), airtight containers protected from light.
Oral absorption	Readily absorbed from the gastrointestinal tract with an absolute bioavailability of 96%. Gatifloxacin in an anion and taking with divalent cations will result in bonding and not being absorbed. Administrate two hours before or four hours after ingestion of milk-based products, antacids or other medications containing divalent cations (iron, magnesium, calcium, zinc, vitamins, didanosine, sucralfate).
CSF penetration	Widely distributed in body fluids including CSF.
Special circumstances	**Pregnancy/breastfeeding:** safety class C. Fluoroquinolones are not recommended during breastfeeding due to the potential for arthropathy. Animal data demonstrated arthropathy in immature animals, with erosions in joint cartilage. **Renal disease:** doses of gatifloxacin should be reduced in patients with renal impairment. When creatinine clearance is less than 30 ml/min, the recommended dosing is 400 mg, 3 times per week.
Adverse reactions	Generally well tolerated. Occasional: gastrointestinal intolerance; Rare CNS-headache; malaise; insomnia; restlessness; dizziness; allergic reactions; diarrhoea; photosensitivity; increased liver function tests; tendon rupture (increased incidence seen in older men with concurrent use of corticosteroids). Severe dysglycaemia, hypoglycaemia and hyperglycaemia, and diabetes have been reported (many countries have removed the drug form their national formularies for this reason).
Contraindications	**Pregnancy** **Intolerance of fluoroquinolones** **Diabetes.** Gatifloxacin can worsen diabetes and glycaemic control.
Monitoring	Glucose monitoring every 1–2 weeks.

Patient instructions and alerting symptoms	**Instruct patients to inform their health care provider right away if any of the following occurs:** • Rashes, hives, bruising or blistering, trouble breathing • Pain, swelling or tearing of a tendon or muscle or joint pain. • Diarrhoea • Yellow skin or eyes • Anxiety, confusion or dizziness (signs of hypoglycaemia or hyperglycaemia) • Increased thirst or frequent urination (sign of hyperglycaemia)

Imipenem (Imp)/Cilastatin (Cln)

DRUG CLASS: BETA-LACTAM – CARBAPENEM (IT IS RELATED TO THE PENICILLIN/ CEPHALOSPORIN FAMILY OF ANTIBIOTICS BUT IS CLASSIFIED AS BELONGING TO THE CARBAPENEM CLASS).

Activity against TB, mechanism of action, and metabolism	In vitro activity – very limited clinical experience. Given that imipenem is rapidly degraded by renal proximal tubule dipeptidases, it is used in combination with the dipeptidase inhibitor, cilastatin. (Conversely, meropenem a similar drug as imipenem is stable to renal dipeptidases and requires no cilastatin). Cilastatin is partially metabolized renally.
Dose	**Adults:** 1000 mg IV every 12 hours. (Dosed on the imipenem component). Should be given with clavulanate (available as amoxicillin/clavulanate) 125 mg every 8–12 hours. **Children:** Meropenem preferred. See *Meropenem*, drug sheet for dosing.
Route of administration	IV or IM (total recommended IM dose is not more than 1.5 gram/ day and therefore not very practical for treatment of drug-resistant TB). No oral absorption.
Preparation	Lypholized powder 1:1 ratio of imipenem and cilastatin. Vials available as 250 mg, 500 mg, 750 mg, or 1 gram and contain equal amounts of both drugs. (i.e. a “500 mg vial” contains 500 mg of imipenem and 500 mg cilastatin).
Storage	Powder should be kept at room temperature (15–25 °C); suspended product should be kept no more than 4 hours at room temperature or no more than 24 hours refrigerated.
CSF penetration	Good CSF penetration, but children with meningitis treated with imipenem had high rates of seizures (meropenem preferred for meningitis and for children).
Special circumstances	**Use in pregnancy/breastfeeding:** Little information is known regarding use in pregnancy; unknown safety during breastfeeding. **Use in renal disease:** Adjustment in dose based on severity of renal failure – for example, 750 mg every 12 hours for creatinine clearance 20–40 ml/min, 500 mg every 12 hours for creatinine clearance <20 ml/min. Dose after dialysis. **Use in hepatic disease:** Elevated liver function tests have been noted in up to 6% of patients, but no definite liver damage has been documented.
Adverse reactions	**Common:** Diarrhoea, nausea, or vomiting. **Less common:** Seizure (noted with CNS infection), palpitations, pseudomembranous colitis.
Contraindications	Carbapenem intolerance; meningitis (use meropenem rather than imipenem).
Monitoring	Symptomatic monitoring.

Patient instructions and alerting symptoms	Make sure your health care provider knows if you are also taking ganciclovir or have allergy to penicillins or cephalosporins. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Fast or irregular heartbeat • Seizures • Severe diarrhoea (watery or bloody) • Skin rash, hives, or itching • Swelling of the face, throat or lips • Wheezing or trouble breathing.

Isoniazid (Inh)

DRUG CLASS: ISONICOTINIC ACID HYDRAZIDE

Activity against TB, mechanism of action, and metabolism	**Bactericidal:** Especially for rapidly dividing cells. Affects mycolic acid (cell wall) synthesis. Inclusion of isoniazid in the regimen of patients with strain W MDR-TB was also associated with improved outcomes.
Dose	**Adults:** 4–6 mg/kg/day (oral or IV); usual adult dose 300 mg daily; high dose isoniazid (up to 600 mg daily, see Annex 2 for weight-based dosing) used for patients with low-level isoniazid resistance or documented isoniazid resistance other than due to the Kat G gene mutation. **Children:** see Annex 3 for weight-based dosing in children; – Patient <30 kg: 7 to 15 mg/kg once daily – Patient ≥30 kg: 4 to 6 mg/kg once daily – Maximum dose: 300 mg daily **Renal failure/dialysis:** 300 mg once daily or 900 mg thrice weekly. **Pyridoxine (vitamin B6)** should be used when high-dose isoniazid is administered and in patients with diabetes, uraemia, HIV infection, seizure disorders, alcohol abuse, malnutrition or peripheral neuropathy. Additionally, pregnant and postpartum women and exclusively breastfed infants should receive vitamin B6 while taking isoniazid. (Normal dose of pyridoxine when used prophylactically for prevention of neuropathy in patients taking isoniazid is 10–25 mg/day.)
Route of administration	Oral, IV or IM.
Preparation	50 mg, 100 mg or 300 mg scored or unscored tablets; 50 mg/5 ml oral suspension in sorbitol; solution for injection is 100 mg/ml. When given IV, dilute in 25 ml normal saline and infuse as a slow bolus over 5 minutes. Since compatibility information is not available, do not infuse "piggyback" with other drugs through a shared IV line.
Storage	Suspension must be kept at room temperature (15–25 °C).
Oral absorption	Well absorbed orally or intramuscularly; best absorbed on an empty stomach; up to 50% reduction in peak concentration with a fatty meal.
CSF penetration	Concentration equivalent to plasma in inflammed meninges. 20% of concentrations in plasma in noninflammed meninges.

Special circumstances	**Use in pregnancy/breastfeeding:** Safe during pregnancy; safe during breastfeeding (both baby and mother should receive pyridoxine supplementation). Up to 20% of the infant therapeutic dose will be passed on to the baby in the breast milk. **Use in renal disease:** No dose adjustment for renal failure, but pyridoxine supplementation should be used. **Use in hepatic disease:** May exacerbate liver failure. Use with caution. **Drug Interactions:** Isoniazid is a CYP3A4 inhibitor. Isoniazid may increase the concentrations of certain cytochrome P450 enzyme substrates, including phenytoin and carbamazepine.
Adverse reactions	Hepatitis (age-related). Peripheral neuropathy. Hypersensitivity reactions. Other reactions, including optic neuritis, arthralgias, CNS changes, drug-induced lupus, diarrhoea, and cramping with liquid product.
Contraindications	**Patients with high-level isoniazid resistance** who have failed an isoniazid-containing regimen should not receive isoniazid. History of allergic reaction to isoniazid.
Drug Interactions	Monitor concentrations of phenytoin or carbamazepine in patients receiving those drugs (increases phenytoin concentrations and risk of hepatotoxicity with carbamazepine), especially when undergoing isoniazid monotherapy. Rifampin tends to lower concentrations of these drugs and balance the effect of isoniazid.
Monitoring	**Clinical monitoring of all patients on isoniazid is essential.** Routine laboratory monitoring is not recommended for patients receiving isoniazid monotherapy for latent TB infection. For patients receiving multiple TB drugs or other hepatotoxic drugs, or with underlying liver disease (including viral hepatitis), baseline liver function testing is recommended. Follow-up liver function testing is determined by baseline concerns and symptoms of hepatotoxicity.
Alerting symptoms	**Instruct patients to inform their health care provider right away if any of the following occurs:** • Loss of appetite for a few days that does not go away • Tiredness, weakness • Moderate stomach pain, nausea or vomiting • Numbness, pain or tingling of your fingers or toes • Blurred vision, eye pain • Yellow skin or eyes or dark-colored urine.

Kanamycin (Km)

DRUG CLASS: AMINOGLYCOSIDE

Activity against TB, mechanism of action, and metabolism	**Bactericidal:** has strong anti-TB activity. Cross-resistance with amikacin and some data suggesting cross-resistance with capreomycin; inhibits protein synthesis.
Dose	**Adults:** 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 gram, but a large, well-built person could receive more and should have concentrations monitored). **>59 years of age:** 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. Alternatively, 15 mg/kg/dose, 3 times per week. **Children:** 15–30 mg/kg/day (max 1 gram) 5–7 days per week. **Renal failure/dialysis:** 12–15 mg/kg/dose, 3 times weekly. **Markedly obese individuals** should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations. **For dosing, use adjusted weight as follows:** Ideal body weight + 40% of excess weight Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft *If possible, concentrations should be followed closely.*
Route of administration	IV or IM; not absorbed orally.
Preparation	250 mg/ml in vials of 500 mg or 1 gram; 1 gram in 3 ml vial; or 75 mg/vial for infants. Can be mixed with D5W or normal saline for intravenous infusion. Adult IV doses should be mixed in at least 100 ml of fluid, and paediatric IV doses should be mixed to a concentration of at least 5 mg/ml. For intravenous administration, infuse over 60 minutes for adults; 1–2 hours for children.
Storage	The product supplied by the Global Drug Facility does not need storage in in the refrigerator.
Oral absorption	Not absorbed orally; 40–80% of the dose is absorbed intramuscularly.
CSF penetration	Minimal and variable CSF penetration – slightly better with inflammed meninges.

Special circumstances	**Use in pregnancy/breastfeeding:** Generally avoided in pregnancy due to documented congenital deafness. Can be used while breastfeeding. **Use in renal disease:** Use with caution. Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See section above for dosage under renal disease or dialysis. The drug is variably cleared by haemodialysis. **Use in hepatic disease:** Drug concentrations are not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution because patients with severe liver disease may progress rapidly to hepatorenal syndrome. **Diuretic use:** Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity.
Adverse reactions	Nephrotoxicity: Appears to be more nephrotoxic than streptomycin. Ototoxicity (hearing loss) and vestibular toxicity: Increases with advanced age and prolonged use; appears to occur slightly more commonly with kanamycin than with streptomycin and about the same frequency as amikacin. Kanamycin seems to have slightly less vestibular toxicity.
Contraindications	**Pregnancy** (congenital deafness seen with streptomycin and kanamycin use in pregnancy); **hypersensitivity to aminoglycosides;** caution with renal, vestibular or auditory impairment; patients with intestinal obstructions.
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment is present); document creatinine clearance if there is baseline renal impairment or any other concern; document baseline and monthly audiology exam. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough concentrations at baseline if there is any question about renal function. Some experts monitor aminoglycoside concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.
Alerting Symptoms	Instruct patients to inform their health care provider right away if any of the following occurs: • Problems with hearing, dizziness or balance • Rash or swelling of your face • Trouble breathing • Decreased urination • Watery or bloody diarrhoea • Swelling, pain, or redness at your IV site • Muscle twitching or weakness.

Levofloxacin (Lfx)

DRUG CLASS: FLUOROQUINOLONE (FQN)

Activity against TB, mechanism of action, and metabolism	**Bactericidal:** has strong anti-TB activity. Cross-resistance with other fluoroquinolones but may not be complete. Data suggests greater activity than ciprofloxacin or ofloxacin. Inhibits DNA gyrase.
Dose	**Adults:** For treatment of TB disease 10–15 mg/kg once daily. (also see Annex 2 Weight-based dosing for adults): **Children:** 5 years and under: 15–20 mg/kg split into two doses (morning and evening). Over 5 years: 10–15 mg/kg once daily (also see Annex 3 Weight-based dosing for children). **Renal failure/dialysis:** 750–1000 mg/dose, 3 times weekly (not daily) for creatinine clearance <30 ml/min.
Route of administration	Oral or intravenous.
Preparation	Coated tablets (250 mg, 500 mg, 750 mg); solution for injection 25 mg/ml; 250 mg in 50 ml container; 500 mg in 100 ml container; 750 mg in 150 ml container. Oral suspension is 25 mg/ml.
Storage	Oral forms, undiluted solution, and pre-mixed solutions are stored at room temperature (15–25 °C). Once diluted, the solution can be kept at room temperature for 3 days, in the refrigerator for 2 weeks, or frozen for 6 months.
Oral absorption	Excellent oral absorption. Levofloxacin in an anion and taking with divalent cations will result in bonding and not being absorbed: administrate two hours before or four hours after ingestion of milk-based products, antacids, or other medications containing divalent cations (iron, magnesium, calcium, zinc, vitamins, didanosine, sucralfate).
CSF penetration	Concentrations are 65% of that in the serum.
Special circumstances	**Use in pregnancy/breastfeeding:** Fluoroquinolones are generally avoided during pregnancy and breastfeeding due to possibility of arthropathy. However, there are a few case reports of fluoroquinolones being used safely during pregnancy. **Use in renal disease:** Dosage adjustment is recommended if creatinine clearance is <50 ml/min. The drug is not cleared by haemodialysis; supplemental doses after dialysis are not necessary. **Use in hepatic disease:** Drug concentrations are not affected by hepatic disease. Presumed to be safe in severe liver disease.
Adverse reactions	Nausea and bloating. Headache, dizziness, insomnia or tremulousness. **Rare** tendon rupture, arthralgias (can usually be treated symptomatically). QTc prolongation, hypoglycaemia.

Contraindications	Fluoroquinolone intolerance, prolonged QTc, pregnancy (relative contraindication).
Monitoring	Side effect monitoring, but no specific laboratory monitoring required.
Patient instructions and alerting symptoms	You can take levofloxacin with food. Drink plenty of beverages. Do not take milk-based products, antacids (especially aluminum-containing), mineral supplements such as iron or magnesium, or multivitamins within 2 hours of this medication or within 4 hours after. This medicine may cause sun sensitivity; use sunscreens. Do not undertake new strenuous activities. Instruct patients to inform their health care provider right away if any of the following occurs: • Pain, swelling or tearing of a tendon (such as the back of your ankle, elbow, etc.), or muscle or joint pain • Rashes, hives, bruising or blistering, trouble breathing or tightness in your chest • Diarrhoea • Yellow skin or eyes • Anxiety, confusion or dizziness.

Linezolid (Lzd)

DRUG CLASS: OXAZOLIDINONES

Activity against TB, mechanism of action, and metabolism	Has in vitro bactericidal activity – increasing clinical experience[7]; inhibits protein synthesis.
Dose	**Adults:** 600 mg, once daily. (Reduce to 400–300 mg/day if serious adverse effects develop). **Children:** 10 mg/kg three times daily in children up to 11 years of age and 10 mg/kg (maximum dose 600 mg) twice daily in older children.[8] 10 mg/kg/dose every 12 hours. **Vitamin B6:** All patients should receive vitamin B6 while receiving linezolid.
Preparation	Coated tablets: 400 and 600 mg; intravenous solution: 2 mg/ml: 100, 200 or 300 mg bags. Intravenous doses are administered over 30–120 minutes. Oral powder for suspension: 100 mg/5 ml, 240 ml bottle.
Storage	Store tablet at room temperature (15–25 °C). Reconstituted oral suspension may be stored at room temperature for 21 days. Parenteral preparation should be stored at room temperature (protect from light and do not freeze).
Oral absorption	Nearly complete oral absorption.
CSF penetration	CSF concentrations are about 1/3 of those in serum in animal models, and linezolid has been used to treat meningitis in humans.
Special circumstances	**Use in pregnancy/breastfeeding:** Not recommended during pregnancy or breastfeeding due to limited data. **Use in renal disease:** No dose adjustment is recommended, but metabolites may accumulate. **Use in hepatic disease:** Rarely associated with increased transaminases.
Adverse reactions	Myelosuppression (decreased level of platelets, decreased level of white blood cells, and/or anaemia). Diarrhoea and nausea. Optic and peripheral neuropathy may be irreversible and linezolid should stopped if these develop; weigh against the risk of permanent blindness or disabling permanent neuropathy. Lactic acidosis – patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving linezolid should receive immediate medical evaluation, including a lactic acid blood test.

[7] Sotgiu G et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. European Respiratory Journal 2012; 40(6):1430-42.

[8] Zyvox: linezolid injection, linezolid tablets, linezolid for oral suspension package insert. Kalamazoo, MI: Pharmacia & Upjohn Company; 2002.

Contraindications	**Hypersensitivity to oxazolidinones.** **Symptoms of neuropathy** (pain, numbness, tingling or weakness in the extremities).
Drug Interactions	Avoid use with patients taking serotonergic agents, such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (e.g. fluoxetine, paroxetine), lithium, tricyclic antidepressants, etc. as it may cause serious CNS reactions such as serotonin syndrome.
Monitoring	Monitor for peripheral neuropathy and optic neuritis (visual eye tests every two months or if symptoms develop, clinical examination for peripheral neuropathy monthly or if symptoms develop). Monitor a complete blood count weekly during the initial period, then monthly, and then as needed based on symptoms; there is little clinical experience with prolonged use.
Patient instructions and alerting symptoms	This medicine may be taken with or without food. Take it with food if it irritates the stomach. Avoid food and drinks that contain tyramine: aged cheeses, dried meats, sauerkraut, soy sauce, tap beers and red wines. Make sure your doctor knows if you are taking medicines for colds, congestion or depression. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Pain, numbness, tingling or weakness in the extremities • Black, tarry stools or severe diarrhoea • Unusual bleeding or bruising • Unusual tiredness or weakness • Headache, nausea or vomiting.

Meropenem (Mpm)

DRUG CLASS: BETA-LACTAM – CARBAPENEM (IT IS RELATED TO THE PENICILLIN/ CEPHALOSPORIN FAMILY OF ANTIBIOTICS BUT IS CLASSIFIED AS BELONGING TO THE CARBAPENEM CLASS).

Activity against TB, mechanism of action, and metabolism	In vitro activity – very limited clinical experience (meropenem is stable to renal dipeptidases and requires no cilastatin).
Dose	**Adults:** No oral absorption. Recent case–controlled study used 1000 mg IV every 8 hours.[9] Must be given with clavulanate (available as amoxicillin/clavulanate), 125 mg every 8–12 hours. **Children:** Not established for TB however for other bacterial infections in children: 20 mg/kg/dose and 40 mg/kg/dose for meningitis or particularly severe infections. Given IV every 8 hours up to 2 g per dose. Renal failure/dialysis: Adjustment required – 750 mg every 12 hours for creatinine clearance of 20–40 ml/min; 500 mg every 12 hours for creatinine clearance <20 ml/min.
Route of administration	IV only; No oral absorption.
Preparation	Crystalline powder. Product is available in 500 mg, or 1 g vials.
Storage	Powder should be kept at room temperature (15–25 °C); suspended product should be kept no more than 4 hours at room temperature or no more than 24 hours refrigerated.
CSF penetration	Adequate CSF penetration.
Special circumstances	**Use during pregnancy/breastfeeding:** There is little information regarding use during pregnancy; unknown safety during breastfeeding. **Use in renal disease:** Dose adjustment required (see above); dose after dialysis. **Use in hepatic disease:** Liver disease does not alter the pharmacodynamics of meropenem. Adjustment in dose and interval are based on severity of renal failure and body weight – e.g. 750 mg every 12 hours for creatinine clearance of 20–40 ml/min, 500 mg every 12 hours for creatinine clearance <20 ml/min.
Adverse reactions	Diarrhoea, nausea or vomiting. Seizure (noted with CNS infection), but rare compared to imipenem. Rarely elevated LFTs, haematologic toxicity, hypersensitivity
Contraindications	Carbapenem intolerance.
Monitoring	Symptomatic monitoring.

[9] De Lorenzo S et al. Efficacy and safety of meropenem/clavulanate added to linezolid containing regimens in the treatment of MDR-/XDR-TB. European Respiratory Journal 2013;41(6):1386-1392.

Patient instructions and alerting symptoms	Make sure your doctor knows if you are also taking valproic acid or have allergy to penicillins or cephalosporins. Instruct patients to inform their health care provider right away if any of the following occurs: • Severe diarrhoea (watery or bloody) • Skin rash, hives or itching • Swelling in the face, throat or lips • Wheezing or trouble breathing.

Moxifloxacin (Mfx)

DRUG CLASS: FLUOROQUINOLONE

Activity against TB, mechanism of action, and metabolism	**Bactericidal:** inhibits DNA gyrase; cross-resistance with other fluoroquinolones, but may be more active based on in vitro data.
Dose	**Adults:** 400 mg daily (oral or IV). **Children:** No established dose. **Renal failure/dialysis:** No dose adjustment required.
Route of administration	Oral or IV.
Preparation	Tablets (400 mg); aqueous solution (400 mg/250 ml) for IV injection.
Storage	Store oral and IV products at room temperature (15–25 °C). Do not refrigerate.
Oral absorption	Good oral absorption (90% bioavailable). Moxfloxacin is an anion and taking with divalent cations will result in bonding and not being absorbed: Administrate 2 hours before or 4 hours after ingestion of milk-based products, antacids, or other medications containing divalent cations (iron, magnesium, calcium, zinc, vitamins, didanosine, sucralfate).
CSF penetration	Good penetration in animal model studies.
Special circumstances	**Use during pregnancy/breastfeeding:** Fluoroquinolones are generally avoided during pregnancy and breastfeeding due to observation of arthropathy in animal models. However, there are a few case reports of fluoroquinolones being used safely during pregnancy. **Use in renal disease:** Excretion unchanged during renal failure; no data on effect of dialysis. **Use in hepatic disease:** Rarely associated with hepatotoxicity; use with caution. No dose adjustment required for mild or moderate liver disease.
Adverse reactions	Nausea and diarrhea. Headache and dizziness. Rare tendon rupture; arthralgias. Rare hepatotoxicity. QTc prolongation, hypo/hyperglycaemia.
Contraindications	Fluoroquinolone intolerance, prolonged QTc.
Monitoring	Symptomatic monitoring.

Patient instructions and alerting symptoms	Moxifloxacin can be taken with food, but do not take milk-based products, antacids (especially aluminum-coating), vitamin supplements, or sucralfate within 2 hours of this medication or 4 hours after. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Pain, swelling or tearing of a tendon (such as the back of your ankle, elbow), or muscle or joint pain • Rashes, hives, bruising or blistering, trouble breathing, or tightness in the chest • Diarrhoea • Yellow skin or eyes • Anxiety, confusion or dizziness.

Para-aminosalicyclic acid (PAS)

DRUG CLASS: SALICYLIC ACID – ANTI-FOLATE

Activity against TB, mechanism of action, and metabolism	**Bacteriostatic.**
Dose	**Adults:** 8–12 g per day divided 2–3 times per day **Children:** 200–300 mg/kg/day divided 2–4 times per day **Renal failure/dialysis:** No change
Route of administration	Oral; should be given sprinkled on or stirred into yogurt or similar food. Not available parenterally in the US
Preparation	4 g per packet
Storage	Packets should be kept in the refrigerator or freezer
Oral absorption	Incomplete absorption – sometimes requires increased doses to achieve therapeutic concentrations
CSF penetration	Poorly penetrates the meninges (somewhat better with inflammation)
Special circumstances	**Use during pregnancy/breastfeeding:** Not studied, but no teratogenicity known. There is little data regarding use during breastfeeding. In one patient, the milk concentration was 1 mcg/ml compared to a serum concentration of 70 mcg/ml **Use in renal disease:** Inactive metabolite is cleared by the kidneys. The package insert says to avoid with severe renal failure. Other authorities believe it can be used with caution (toxicity of metabolite not known) **Use in hepatic disease:** Use with caution; 0.5% incidence of hepatotoxicity
Adverse reactions	Gastrointestinal distress (less with the PASER® formulation than with older preparations) Rare hepatotoxicity and coagulopathy Reversible hypothyroidism (increased risk with concomitant use of ethionamide); treat with thyroid replacement
Contraindications	Pregnancy (relative).
Monitoring	Monitor TSH, electrolytes, blood counts and liver function tests.

Patient instructions and alerting symptoms	New presentation of PASER® does not need storage in refrigerator or freezer. Sprinkle granules over apple-sauce or yogurt or swirl in acidic juices (tomato, grape, grapefruit, cranberry, apple or orange). Do not chew the granules. Take with food if desired. Do not use the packet if it is puffed up or if the granules are discoloured. Gastrointestinal discomfort and diarrhoea usually improve over time. The shells of the granules may be seen in the stool, which is normal. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Skin rash, severe itching or hives • Severe abdominal pain, nausea or vomiting • Unusual tiredness or loss of appetite • Black stools or bleeding.

Pyrazinamide (Pza)

DRUG CLASS: SYNTHETIC DERIVATIVE OF NICOTINAMIDE.

Activity against TB, mechanism of action, and metabolism	**Bactericidal** for semi-dormant *M. tuberculosis*. Mechanism unclear.
Dose	**Adults:** 25 mg/kg/day (max dose 2 g). Intermittent dosing at twice or thrice weekly up to 50 mg/kg can be given. **Children:** 30–40 mg/kg/dose. Renal failure/dialysis: 25 mg/kg/dose, 3 times per week (not daily). **Obesity:** Use adjusted weight as follows: Ideal body weight + 40% of excess weight Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft
Route of administration	Oral; not available parenterally.
Preparation	500 mg scored or unscored tablet.
Storage	Store the tablets at room temperature (15–25 °C).
Oral absorption	Well absorbed from the gastrointestinal tract.
CSF penetration	Concentrations equivalent to serum.
Special circumstances	**Use during pregnancy/breastfeeding:** In the United States, pyrazinamide is avoided during pregnancy for drug-susceptible disease due to lack of data regarding teratogenicity, but should be used for drug-resistant TB when the isolate is sensitive to pyrazinamide (no known teratogenicity). Can be used while breastfeeding. **Use in renal disease:** Cleared by the kidneys; dose 3 times a week and after dialysis. **Use in hepatic disease:** Use with caution; pyrazinamide is associated with hepatotoxicity in about 1% of patients. It can be quite severe and worsen treatment progress.
Adverse reactions	Gout (hyperuricaemia) and arthralgias. Hepatotoxicity. Rash. Photosensitivity. Gastrointestinal upset.
Contraindications	Allergy to pyrazinamide; severe gout.
Monitoring	Monitor transaminases and uric acid.

Patient instructions and alerting symptoms	May be taken with or without food; this medicine may cause a rash after sun exposure, so limit sun exposure. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Skin rash, severe itching or hives • Pain or swelling in the joints • Yellowing of the skin or eyes or dark urine • Nausea or vomiting • Unusual tiredness or loss of appetite.

Rifabutin (Rfb)

DRUG CLASS: RIFAMYCIN

Activity against TB, mechanism of action, and metabolism	**Bactericidal:** same mechanism of activity as rifampin (inhibits RNA polymerase). Less than 20% of rifampin-resistant strains are susceptible to rifabutin.
Dose	**Adults:** 5 mg/kg/dose (max dose 300 mg, though doses up to 450 mg are sometimes used). Dose adjustments sometimes required when dosing with interacting drugs. **Children:** The paediatric dose is not established, but doses of 5–10 mg/kg/day have been used (higher doses have been recommended for children <1 year of age). Caution is advised when used in very young children in whom visual changes might not be obvious. **Renal failure/dialysis:** No dose adjustment in mild renal insufficiency. For creatinine clearance of <30 ml/minute, the usual dose may be used, but monitor drug concentrations to avoid toxicity. **Concomitant medications:** Dosage adjustment may be required, particularly with antiretroviral therapy is being given. See Tables 15 a-e in http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf
Route of administration	Oral; not available parenterally.
Preparation	150 mg capsule.
Storage	Capsules should be kept at room temperature (15–25 °C).
Oral absorption	Well absorbed from the gastrointestinal tract.
CSF penetration	Penetrates inflammed meninges.
Special circumstances	**Use during pregnancy/breastfeeding:** Insufficient data about use during pregnancy. Unknown effects from breastfeeding. **Use in renal disease:** Used without dose adjustment in mild renal insufficiency. For creatinine clearance <30 ml/minute, the usual dose may be used, but monitor drug concentrations to avoid toxicity. **Use in hepatic disease:** Use with caution and additional monitoring in liver disease. Dose adjustments are necessary for drug interactions, especially HIV drugs.

Adverse reactions	Leukopenia (dose dependent); thrombocytopenia. Rashes and skin discolouration (bronzing or pseudojaundice). Anterior uveitis and other eye toxicities. Hepatotoxicity similar to that of rifampin. Drug interactions with many other drugs—but only 40% of that is seen with rifampin. Rifabutin concentrations may be affected by other drugs. Arthralgias.
Contraindications	Rifamycin hypersensitivity. Data are lacking on cross-sensitivity to rifabutin in patients with hypersensitivity. If used, use with caution, with careful monitoring of patient for development of hypersensitivity. Should not be used for patients with MDR-TB.
Monitoring	Increased liver function monitoring; monitor drug concentrations of interacting medications; blood counts and vision screening.
Patient instructions and alerting symptoms	May be taken with or without food; if it irritates the stomach, try taking it with food. It is normal for urine, tears and other secretions to turn a brownish-orange color when taking this medicine. Sometimes the skin becomes discoloured. Soft contact lenses may become discoloured while on this medicine. Make sure your doctor knows all the medicines you take, as there are many drugs that interfere with this one. Avoid the use of oral hormone-based birth control methods because rifabutin may decrease their effectiveness. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Any eye pain, change in vision or sensitivity to light • Fever, chills or sore throat • Pain or swelling in the joints • Yellowing of the skin or eyes or dark urine • Nausea or vomiting • Unusual tiredness or loss of appetite.

Rifampin (Rif)

DRUG CLASS: RIFAMYCIN

Activity against TB, mechanism of action, and metabolism	**Bactericidal:** inhibits protein synthesis; cross-resistance with other rifamycins.
Dose	**Adults:** 10 mg/kg/dose up to 600 mg (oral or IV). **Children:** 10-20 mg/kg/dose up to 600 mg (oral or IV). **Renal failure/dialysis:** No adjustment required. **Concomitant medications:** Dosage adjustment may be required for concurrent medications, including warfarin. After stopping rifampin, warfarin dosage may require downward adjustment to prevent toxicity. Concurrent treatment with most antiretroviral drugs is not recommended, as antiretroviral drug concentrations are substantially reduced. Rifampin plasma concentrations are not affected by most other drugs (based on current data).
Route of administration	Oral or IV.
Preparation	150 and 300 mg capsules; lyophilized powder for injection: 600 mg/vial; contents of capsules can be mixed with liquid or semi-soft vehicles. Extemporaneously prepared oral solutions have unproven homogeneity and shelf life. Immediate administration of the dose after mixing capsular contents in a vehicle is ideal.
Storage	Capsules and powder should be kept at room temperature (15–25 °C); powder suspended in saline is stable for 24 hours; powder suspended in dextrose solutions is stable for 4 hours.
Oral absorption	Usually absorption is rapid but may be delayed or decreased by high-fat meals.
CSF penetration	Rifampin CSF penetration is variable and typically achieves only 10–20% of serum concentrations in CSF (may be better in the face of inflammed meninges), but this may still be an important contribution to the regimen. Some authors recommend increased doses of rifampin in patients with TB meningitis.
Special circumstances	**Use during pregnancy/breastfeeding:** Recommended for use during pregnancy; can be used while breastfeeding. **Use in renal disease:** Can be used without dose adjustment. **Use in hepatic disease:** Use with caution as it can be associated with hepatotoxicity.

Adverse reactions	**Many drug interactions.** Orange staining of body fluids Rash and pruritus Gastrointestinal upsets, flu-like syndrome (usually only with intermittent administration). Hepatotoxicity. Haematologic abnormalities (thrombocytopenia, haemolytic anaemia).
Contraindications	**Rifamycin allergy;** due to drug interactions, may be contraindicated with concurrent use of certain drugs.
Monitoring	Liver function monitoring if appropriate (if given with other hepatotoxic medications or if there are symptoms of hepatotoxicity); monitor drug concentrations of interacting medications.
Patient instructions and alerting symptoms	Best taken without food; if it irritates the stomach, try taking it with a small amount of food. It is normal for urine, tears and other secretions to turn an orange color when taking this medicine. Soft contact lenses may become discolored while on this medicine. Make sure your doctor knows all the medicines you take because many drugs can interfere with this one. Avoid the use of oral hormone-based birth control methods because rifampin may decrease their effectiveness. Instruct patients to inform their health care provider right away if any of the following occurs: • Unusual tiredness or loss of appetite • Severe abdominal upset • Fever or chills

Rifapentine (Rpt)

DRUG CLASS: RIFAMYCIN

Activity against TB	**Bactericidal:** same mechanism of action as rifampin, inhibits RNA polymerase. 100% cross-resistant with rifampin.
Dose Tuberculosis Disease	**Adults:** 600 mg once weekly during the continuation phase of treatment. (Not recommended in the US for the initial treatment phase.) Higher daily doses are being studied. **Children:** (12 years and older), 600 mg once weekly if ≥45 kg. 450 mg once weekly if <45 kg.
Dose for LTBI	**Adults:** 900 mg once weekly for 12 doses given with isoniazid 900 mg. **Children:** (12 years and older), once weekly dose for 12 weeks based on weight (10.0–14.0 kg = 300 mg; 14.1–25.0 kg = 450 mg; 25.1–32.0 kg = 600 mg; 32.1–49.9 kg = 760 mg; ≥50 kg = 900 mg) given with isoniazid 15 mg/kg weekly. **Renal failure/dialysis:** No adjustment required. Only 17% of ingested dose is excreted renally. **Concomitant medications:** Dosage adjustment may be required for concurrent medications. Concurrent treatment with most antiretroviral drugs is not recommended, as antiretroviral drug concentrations are substantially reduced, as with rifampin. However, rifapentine plasma concentrations are not affected by most other drugs (based on current data).
Route of administration	Oral
Preparation	150 mg tablets.
Storage	Tablets should be stored at room temperature (15–25 °C).
Pharmacokinetics	**Time to peak concentration** after an oral dose is 5–6 hours. **Peak concentrations** after a 600 mg dose are expected to be 8–30 mcg/ml. The half-life is approximately 13 hours.
Oral absorption	Oral bioavailability is 70%. Peak concentration and area under the curve (AUC) are increased if given with a meal.
CSF penetration	No information available
Special circumstances	**Use during pregnancy:** Pregnancy category C. Use only if potential benefit outweighs possible risk. **Use in renal disease:** Insufficient data, but likely to be safe since only minimally excreted by the kidneys. **Use in hepatic disease:** Pharmacokinetics are very similar to normal volunteers in persons with mild to severe liver impairment. **Dose adjustments:** Not necessary to adjust rifapentine dosage due to drug interactions but may be needed for concurrent drugs, as for rifampin.

Adverse reactions	Many drug interactions. Red–orange staining of body fluids Rash and pruritis Hypersensitivity reaction Hepatoxicity Haematologic abnormalities.
Contraindications	History of hypersensitivity to any of the rifamycins (i.e. rifampin or rifabutin)
Monitoring	Liver function monitoring if appropriate (if given with other hepatotoxic medications or if there are symptoms of hepatotoxicity); monitor drug concentrations of interacting medications.
Patient instructions and alerting symptoms	Rifapentine may cause reddish coloration of your urine, sweat, sputum, tears, and breast milk – be aware that your contact lenses or dentures may be permanently stained. The reliability of oral or other systemic hormonal contraceptives may be affected; consider using alternative contraceptive measures. If you are prone to nausea, vomiting, or gastrointestinal upsets, taking rifapentine with food may be useful. **Instruct patients to inform their health care provider right away if any of the following occurs:** • Fever • Loss of appetite • Malaise • Nausea and vomiting • Darkened urine • Yellowish discolouration of the skin and eyes • Pain or swelling of the joints.

Streptomycin (S)

DRUG CLASS: AMINOGLYCOSIDE

Activity against TB, mechanism of action, and metabolism	**Bactericidal:** inhibits protein synthesis; no significant cross-resistance with other aminoglycosides.
Dose	**Adults:** 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 g) **>59 years of age:** 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after the initial period. Alternatively, 15 mg/kg/dose, 3 times per week. **Children:** 20–40 mg/kg/day (max 1 gram), 5–7 days per week. **Renal failure/dialysis:** 12–15 mg/kg/dose, 2–3 times weekly (not daily). **Markedly obese individuals** should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations. **For dosing, use adjusted weight as follows:** Ideal body weight + 40% of excess weight. Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft *If possible concentrations should be followed closely.*
Route of administration	IV or IM (has been used intrathecally and intraperitoneally). Not absorbed orally.
Preparation	1 gram vial for injection.
Storage	Store in the refrigerator.
Oral absorption	There is no significant oral absorption. Intramuscular absorption might be delayed if the same site is used consistently.
CSF penetration	Variable penetration; appears to penetrate inflammed meninges better.
Special circumstances	**Use during pregnancy/breastfeeding:** Avoided during pregnancy due to documented cases of congenital deafness. Can be used while breastfeeding. **Use in renal disease:** Use with caution. Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See section above for dosage under renal disease or dialysis. The drug is variably cleared by haemodialysis. **Use in hepatic disease:** Drug concentrations are not affected by hepatic disease (expect a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution as patients with severe liver disease may progress rapidly to hepatorenal syndrome. **Diuretic use:** Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity.

Adverse reactions	Nephrotoxicity: Less nephrotoxic than amikacin. Ototoxicity (hearing loss): Increased with advanced age and prolonged use. Vestibular toxicity. Local pain with IM injections. Electrolyte abnormalities, including hypokalaemia, hypocalcaemia, and hypomagnesaemia.
Contraindications	**Pregnancy** (congenital deafness seen with streptomycin and kanamycin use during pregnancy); **Hypersensitivity to aminoglycosides:** caution with renal, vestibular or auditory impairment.
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly audiology exam. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough concentrations at baseline if there is any question about renal function. Some experts monitor aminoglycoside concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.
Patient instructions and alerting symptoms	**Instruct patients to inform their health care provider right away if any of the following occurs:** • Problems with hearing, dizziness or balance • Rash or swelling of your face • Trouble breathing • Decreased urination • Watery or bloody diarrhoea • Swelling, pain or redness at your IV site • Muscle twitching or weakness.

PART 4

Forms for drug-resistant TB programmes

TB Control Programme

Second-line TB treatment card

Form 01

Second-line Registration Number:_____

Date of second-line treatment registration:_____

Treatment Centre:_____

Patient Name:_____

Address & Telephone:_____

District:_____

Sex (circle one): M F

Age: DOB:_____

Initial weight (kg):_____

Height (cm):_____

Site (circle one or both): Pulmonary Extrapulmonary

If extrapulmonary, specify site:_____

Registration Group	Choose one only
New	
Relapse	
After loss to follow-up	
After failure of first treatment with first-line drugs	
After failure of retreatment regimen with first-line drugs	
Other (previously treated without known outcome)	

Transfer in (from another second-line treatment programme) If yes name of center:_____	Yes
_____	No

HIV INFORMATION
HIV Testing done (circle one): Y / N / Unknown
Date of Test:_____Result:_____
Started on ART (circle one): Y / N Date:_____
Started on CPT (circle one): Y / N Date:_____

Previous Tuberculosis Treatment Episodes

District TB Register No. (i.e. BMU register number)	**Start Date** (if unknown put year)	**Regimen** (write regimen in drug abbreviations)	**Outcome**

Previous use of second-line drugs for more than one month?

Yes / No / Unknown

If Yes, indicate in Table above

Drug Abbreviations

First-line drugs	second-line drugs		
H=isoniazid	Am=amikacin		Bdq=bedaquiline
R=rifampicin	Km=Kanamycin	Pto=Prothionamide	Clr=clarithromycin
R=ethambutol	cm=capreomycin	Cs=cycloserine	Cfz=clofazimine
S=streptomycin	lfx=levofloxacin	"Pas=p-amino-salycilic acid"	Dlm=delamanid
Z=Pyrazinamide	Mfx=Moxifloxacin		Ipm=imipenem
	Ofx=ofloxacin	Amx/cCv=amox-icillin/ clavulanate	Lzd=linezolid
	Gfx=gatifloxacin		Mpm=meropenem

Transfer In (from another second-line treatment programme)

If yes name of centre:_____

Meetings of review panel (medical commission, selection committee, consilium)

Meetings of the review panel: dates and decisions		
Date	Decision	Next Date

TB Control Programme

Form 01

Second-line TB treatment card

Month of Treatment	Sputum Microscopy		
	Date*	Sample Number	Result
Prior**			
0			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			

Month of Treatment	Culture		
	Date*	Sample Number	Result
Prior**			
0			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			

Drug Susceptibility Testing (DST) Results§					
	Date specimen (e.g. sputum) collected				
Drug					
H					
R					
E					
S					
Am					
Km					
Cm					
FQ					
Other					
Other					
Other					

Notation method for DST:
R=resistant
S=susceptible
C=contaminated
Unk=Unknown

§ indicate near result if initial resistance was detected on line-probe assay or Xpert MTB/RIF

Notes:
*All dates in both tables are the dates the sputum was collected from the patient
**The date the sputum was collected that led to the patient being registered with MDT-TB (if performed)

Notation Method for Recording Smears:	
No AFB	0
1–9 AFB per 100 HPF	Scanty (and report number of AFB)
10–99 AFB per 100 HPF	+
1–10 AFB per HPF	++
>10 AFB per HPF	+++

Notation Method for Recording Cultures (solid media):	
No growth reported	0
Fewer than 10 colonies	Report number of colonies (1-9)
10–100 colonies	+
More than 100 colonies	++
Innumerable or confluent growth	+++
Non-tuberculous mycobacteria	NTM
Contaminated	contaminated

Notation method for Xpert MTB/RIF results	
T	= MTB detected, rifampicin resistance not detected
RR	= MTB detected, rifampicin resistance detected
TI	= MTB detected, rifampicin resistance indeterminate
N	= MTB not detected
I	= invalid / no result / error

TB Control Programme

Form 01

Second-line TB treatment card

Patient Name:_____

Second-line Treatment Regimen (Date treatment started and dosage (mg), change of dosage and cessation of drugs):																
Date	H	R	E	S	Z	Amk	Km	Cm	FQ	Pto/Eto	CS	PAS	Other	Other	Other	Comments

Administration of Drugs (one line per month). NAME OF DRUG:																																
Month	**Day**																															**Wt (kg), Lab, X-ray**
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	

Mark in the boxes:
√ = Directory Observed
N = Not Supervised
Ø = Drugs Not Taken
Split cell diagonally to record two administrations in one day


if split doses are used mark the upper left half for the Morning dose and the lower right for the Evening dose

TB Control Programme

Form 01

Second-line TB treatment card

Patient Name:_____

Administration of Drugs (one line per month). NAME OF DRUG:																																
Month	**Day**																															**Wt (kg), Lab, X-ray**
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	

Mark in the boxes: √ = Directory Observed
N = Not Supervised
Ø = Drugs Not Taken
Split cell diagonally to record two administrations in one day

Comments:_____

Final outcome (circle one)	**Date**
Cured	
Completed	
Treatment failed	
Died	
Lost to follow-up	
Not evaluated	

TB Control Programme

Form 02

Second-line TB treatment register

Unique Second-line TB Treatment Register No.	Date Entered in Second-line TB treatment register	Name	Sex (M/F)	Age/ Date of Birth D/M/Y	Address	BMU TB Register No ____ Date entered in BMU TB Register	Site of Disease (P/EP/Both)	Registration Group*	Second-line Drugs received previously (Y/N/Unk)	Date Sample taken for DST	Result of Drug Susceptibility Testing (DST)** R=resistant; S=susceptible; C=contaminated; – = Testing not done (FQ=fluoroquinolone)										
											H	R	E	S	Amk/ Km	Cm	FQ ___	Other __	Other __	Other __	Other __
1				/ /																	
2				/ /																	
3				/ /																	
4				/ /																	
5				/ /																	
6				/ /																	
7				/ /																	

* 1=New; 2=Relapse; 3=After Loss to follow-up; 4=After failure of first treatment with first-line drugs; 5=After failure of retreatment with first-line drugs; 6=Transfer in (from another Second-line TB treatment centre)

** Enter DST result that led to the patient being registered for second-line treatment. If DST is pending, complete when the results become available

Drug Abbreviations

First-line Drugs	Second-line Drugs		
H=Isoniazid	Amk=Amikacin	Eto=Ethionamide	Bdq=Bedaquiline
R=Rifampicin	Km=Kanamycin	Pto=Prothionamide	Clr=Clarithromycin
E=Ethambutol	Cm=Capreomycin	Cs=Cycloserine	Cfz=Clofazimine
S=Streptomycin	Lfx=Levofloxacin	"PAS=p-amino-salycilic acid"	Ipm=Imipenem
Z=Pyrazinamide	Mfx=Moxifloxacin		Lzd=Linezolid
	Ofx=Ofloxacin	Amx/Clv=Amoxi-cillin/ clavulanate	T=Thiacetazone
	Gfx=Gatifloxacin		

TB Control Programme

Form 02

Second-line TB treatment register

Reasons for Registering on Second-line TB Treatment (tick)		Smear (S), Culture (C) or Xpert MTB/RIF (X) Results (if more than one smear or culture or Xpert test done in a month, enter in the most recent positive result. Xpert MTB/RIF only for Month 0. *Dates are for the sample collection*)													Smear (S) and Culture (C) Results during Treatment (if more than one smear or culture done in a month, enter in the most recent positive result) CONTINUED																			
		Second-line TB Treatment		Start of treatment Month 0			Month 1		Month 2		Month 3		Month 4		Month 5		Month 6		Month 7		Month 8		Month 9		Month 10		Month 11		Month 12		Month 13		Month 14	
RR-TB / MDR-TB confirmed	Presumptive RR-TB / MDR-TB (as per national policy)	Regimen (in drug initials) Date started (D/M/Y)		S	C	X	C	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C
				(D/M/Y)			(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)	
		Date:		/ /			/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /	
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Notation Method for Recording Smears (for non-centrifuged specimens)	
No AFB	0
1–9 AFB per 100 HPF	Scanty (and report number of AFB)
10–99 AFB per 100 HPF	+
1–10 AFB per HPF	++
>10 AFB per HPF	+++

Notation Method for Recording Cultures:	
No growth reported	0
Fewer than 10 colonies	Report # of colonies
10–100 colonies	+
>100 colonies	++
Innumerable or confluent growth	+++

HPF=high power field

Notation method for Xpert MTB/RIF results	
T	= MTB detected, rifampicin resistance not detected
RR	= MTB detected, rifampicin resistance detected
TI	= MTB detected, rifampicin resistance indeterminate
N	= MTB not detected
I	= invalid / no result / error

TB Control Programme

Form 02

Second-line TB treatment register

Smear (S) and Culture (C) Results during Treatment (if more than one smear or culture done in a month, enter in the most recent positive result) CONTINUED																																					
Month 15		Month 16		Month 17		Month 18		Month 19		Month 20		Month 21		Month 22		Month 23		Month 24		Month 25		Month 26		Month 27		Month 28		Month 29		Month 30		Month 31		Month 32		Month 33	
S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C
(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)		(D/M/Y)	
/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /	
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TB Control Programme

Form 02

Second-line TB treatment register

Smear (S) and Culture (C) Results during Treatment (if more than one smear or culture done in a month, enter in the most recent positive result) CONTINUED						Final outcome (Cured, Completed, Treatment failed, Died, Loss to follow-up, Not evaluated)	TB/HIV Activities					Comments
Month 34		Month 35		Month 36		Date Outcome Assigned	HIV Testing			Antiretroviral (Y/N)	Cotrimoxazole Prevention Therapy (Y/N)	
S	C	S	C	S	C		Testing Done (Y/N/ Unknown)	Date of Test	Result			
(D/M/Y)		(D/M/Y)		(D/M/Y)								
/ /		/ /		/ /		/ /						
/ /		/ /		/ /		/ /						
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/ /		/ /		/ /		/ /						

TB Control Programme Form 03

Request for examination of biological specimen for TB

Treatment Unit: _____ Date of request: _____

Patient Name: _____

Age (years): _____ Date of Birth: _____ Sex (mark one): ❑ M ❑ F

Patient Address: _____

_____ Patient Telephone: _____

Reason for examination (mark one):	Diagnostic	Presumptive RR-TB/ MDR-TB:	❑ Y ❑ N
	Follow-up	If follow-up, month of treatment:	
Specimen type:	Sputum	Other (specify):	_____
		HIV infection	❑ Y ❑ N ❑ Unknown

Patient previously treated for TB (mark one):	❑ Yes ❑ No ❑ Unknown
If information available specify if	
New	After failure of 1st treatment with 1st-line drugs
Relapse	After failure of retreatment regimen with 1st-line drugs
After Loss to follow-up	Other

Test requested:	Microscopy	Xpert MTB/RIF	Culture	Drug susceptibility	Line probe assay

Name, signature and telephone of requestor: _____

RESULTS (to be completed in the laboratory)

Microscopy results

Date sample collected (to be filled by requestor)	Specimen type	Laboratory serial number/s	Visual appearance (blood-stained, mucopurulent or saliva)	Result (check one)				
				Negative (0 AFB/ 100HPF)	1–9/100HPF (scanty; report number of AFB)	+ 10–99 AFB/100HPF	++ 1–10 AFB/HPF	+++ >10 AFB/ HPF

Examined by (Name & signature): _____ Date of result: _____

Xpert MTB/RIF test result (to be completed in the laboratory)

Date collected (to be filled by requestor)

M. tuberculosis			Rifampicin resistance		
Detected	Not detected	No result / Invalid / Error	Detected	Not detected	Indeterminate result

Examined by (Name & signature): _____ Date of result: _____

Culture results (to be completed in the laboratory)

Date sample collected (to be filled by requestor)	Media used (liquid or solid)	Laboratory serial number/s	Result (check one)						
			Negative (0 colonies)	1–9 <10 colonies	+ 10–100 colonies	++ >100 colonies	+++ Innumerable / confluent growth	NTM[1]	Contaminated

Examined by (Name & signature): _____ Date of result: _____

Drug-susceptibility test (DST) and line-probe assay (LPA) results (to be completed in the laboratory)

Date sample collected (to be filled by requestor)	Media used (liquid or solid media; direct or indirect LPA)	DST laboratory serial number/s	H	R	E	S	Am	Km	Cm	FQ ____	Other ____	Other ____	Other ____	Other ____

R: Resistant; S: Susceptible; C: Contaminated; - Not done

Examined by (Name & signature): _____ Date of result: _____

1 Non-tuberculous mycobacteria

Laboratory register for culture, Xpert MTB/RIF and drug susceptibility testing (DST)

Form 04

Laboratory Serial Number	Date Specimen Received	Patient Name	Sex (M/F)	Age (yrs) Date of birth	Patient Address	Treatment unit	BMU TB register no.	HIV infection (Y/N/Unk)	Patient previously treated for TB (Y/N/Unk)*	Date Specimen Collected	Date Specimen Inoculated

* may be adapted as per Request Form if more details on prior treatment are available

Form 04

Laboratory register for culture, Xpert MTB/RIF and drug susceptibility testing (DST)

Type of Examination			Result of Confirmatory Test of M. tuberculosis (Positive or Negative)	Culture Sent for DST (Yes or No)	Name of Person Reporting Culture or Xpert MTB/RIF Results	Signature	Date Results Reported	Comments
Diagnosis[1]		Follow-up[2]						
Culture[3]	Xpert[4]							
Date	Date	Month						

1. New patients or patients starting a re-treatment regimen; mark with a tick according to test used

2. Patient on TB treatment; indicate months of treatment at which follow-up examination is performed

3. Culture result (solid media) reported as follows:

No growth reported	0
<10 colonies	Report number of colonies
10–100 colonies	+
>100 colonies	++
Innumerable or confluent growth	+++

4. Xpert MTB/RIF results reported as follows:

T	= MTB detected, rifampicin resistance not detected
RR	= MTB detected, rifampicin resistance detected
TI	= MTB detected, rifampicin resistance indeterminate
N	= MTB not detected
I	= invalid / no result / error

Laboratory register for culture, Xpert MTB/RIF and drug susceptibility testing (DST)

Form 04

Results of drug susceptibility testing (DST)[5]												Name of Person Reporting DST Results	Signature	Date Results Reported	Comments
H	R	E	S	Amk	Km	Cm	FQ	Other	Other	Other	Other				

5. Report results as S = susceptible, R = resistant, C = contaminated, — = Testing not done H = isoniazid; R = rifampicin; E = ethambutol; S = streptomycin; Z = pyrazinamide Am = amikacin; Km = kanamycin; Cm = capreomycin; FQ = fluoroquinolone; Lfx = levofloxacin; Mfx = moxifloxacin; Ofx = Ofloxacin; Gfx = gatifloxacin; Eto = ethionamide; Pto = prothionamide; Cs = cycloserine; PAS = p-aminosalicylic acid; Amx/Clv = amoxicillin/clavulanate; Bdq = bedaquiline; Clr = clarithromycin; Cfz = clofazimine; Dlm = Delamanid; Ipm = imipenem; Lzd = linezolid; Mpm = meropenem; T = thioacetazone

Form 05

Six-monthly report on detection of TB cases with rifampicin resistance (RR-TB) and multidrug resistance (MDR-TB)

Name of Area:_____Name of Area Coordinator:_____

Patients assessed during the six-month period:_____of_____Date of Report: _____
months year

Risk category	Number of TB cases						
(list as many as exist in the national policy)	Total	With results for susceptibility to rifampicin only	Resistant to rifampicin (RR) only*	With results for susceptibility to both isoniazid and rifampicin	Resistant to both isoniazid and rifampicin (MDR)	With MDR and tested for a fluoroquinolone and a 2nd line injectable	With XDR
Treatment failure after initial treatment with first-line drugs							
Contact of a confirmed MDR-TB case							
Other risk categories as per national policy (specify)...							
.....							
Total							

* from among cases tested for rifampicin +/- isoniazid (i.e. may include mono-resistant R cases)

NUMBER OF RR-TB AND MDR-TB CASES WITH INFORMATION ON INTERVAL	INTERVAL BETWEEN PRESUMPTION OF RR-/MDR-TB AND DST RESULTS (IN DAYS)		
	MEAN	MINIMUM	MAXIMUM

Form 06

Six-monthly report on enrolment of TB cases with rifampicin resistance (RR-TB) and multidrug resistance (MDR-TB) on second-line TB treatment

Name of Area:_____Name of Area Coordinator:_____

Patients assessed during the six-month period:_____of_____Date of Report: _____
months year

TB patient type	Identified during assessment period	Enrolled on second-line treatment during period of assessment
All patients eligible for treatment*		
<15 years		
Female		
Confirmed RR-TB or MDR-TB		
Confirmed RR/MDR, HIV+ on ART		
Confirmed RR/MDR, HIV+ not on ART		
Confirmed XDR-TB		

* presumptive or confirmed RR-TB or MDR-TB

NUMBER OF RR-TB & MDR-TB CASES WITH INFORMATION ON INTERVAL	INTERVAL BETWEEN DST RESULTS AND START OF TREATMENT (IN DAYS)		
	MEAN	MINIMUM	MAXIMUM

Form 07

Quarterly report on interim results of TB cases with rifampicin resistance (RR-TB) and multidrug resistance (MDR-TB) on second-line TB treatment

Name of Area:_____Name of Area Coordinator:_____

Patients assessed during the six-month period:_____of_____Date of Report: _____
months year

NUMBER OF CONFIRMED RR-TB AND MDR-TB CASES STARTED ON SECOND-LINE TREATMENT	CULTURE NEGATIVE AT SIX MONTHS	DIED BY SIX MONTHS	LOST TO FOLLOW-UP BY SIX MONTHS

Number of cases started on second-line treatment found not to have RR or MDR ☐

Number of cases started on XDR-TB treatment found not to have XDR ☐

Form 08

Annual report of final outcomes of TB cases with rifampicin resistance (RR-TB), multidrug resistance (MDR-TB) and extensive drug resistance (XDR-TB) on second-line TB treatment

Year of Treatment Start:_____

TB patient type	Number of TB cases						
	Started on treatment	Cured	Treatment Completed	Treatment Failed	Died	Lost to follow-up	Not evaluated
All confirmed rifampicin resistant (RR-TB) and MDR-TB cases							
All confirmed XDR-TB cases*							
All confirmed rifampicin resistant (RR-TB) and MDR-TB cases infected with HIV*							

* see Chapter 2 (Sect 2.5 and Box 2.5) for the conditions under which these separate strata are indicated

ANNEX 1

Suggestions for further reading and available training materials and tools

The references presented in this annex aim to provide additional sources of information on the most topical areas of programmatic management of drug-resistant TB (PMDT). These references do not necessarily reflect current WHO policies, and its contents are not necessarily endorsed by WHO.

Background

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2. Resolution WHA67.1. Global strategy and targets for tuberculosis prevention, care and control after 2015. In: Sixty-seventh Word Health Assembly, 19–24 May 2014. Geneva: World Health Organization; 2014 (http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R1-en.pdf, accessed 28 October 2014).
3. Resolution WHA62.15. Prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. In: Sixty-second Word Health Assembly, 18–22 May 2009. Geneva: World Health Organization; 2009 (http://apps.who.int/gb /ebwha/pdf_files/WHA62-REC1 /WHA62_REC1-en.pdf, accessed 27 March 2014).
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Prevention and drug-resistant TB diagnosis, treatment and care

Monitoring, detection, enrolment and treatment outcomes

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3. Electronic recording and reporting for tuberculosis care and control. Geneva: World Health Organization; 2012 (WHO/HTM/TB/2011.22).

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5. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infectious Diseases 2009;9(3):153–161.

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3. Policy framework for implementing new tuberculosis diagnostics. Geneva: World Health Organization; 2010 (http://www.who.int/tb/laboratory/whopolicyframework_rev_june2011.pdf, accessed 24 March 2014).
4. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. Policy statement. Geneva: World Health Organization; 2011 (WHO/HTM/TB/2011.4).
5. Commercial serodiagnostic tests for diagnosis of tuberculosis. Policy statement. Geneva: World Health Organization; 2011 (WHO/HTM/TB/2011.5).
6. Xpert MTB/RIF implementation manual. Technical and operational 'how-to': practical considerations. Geneva: World Health Organization;2014. (WHO/HTM/TB2014.1).
7. Guidelines for surveillance of drug resistance in tuberculosis. Geneva: World Health Organization; 2009 (WHO/HTM/TB/2009.422).
8. Policy guidance on drug-susceptibility testing (DST) of second-line antituberculosis drugs. Geneva: World Health Organization; 2008 (WHO/HTM/TB/2008.392).
9. Guidelines for drug susceptibility testing for second-line anti-tuberculosis drugs for DOTS-Plus. Geneva: World Health Organization; 2001 (WHO/CDS/TB/2001.288).
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Treatment

1. Treatment of tuberculosis: guidelines. 4th edition. Geneva: World Health Organization; 2009 (WHO/HTM/TB/2009.420).
2. PIH guide to the medical management of multidrug-resistant tuberculosis. 2nd edition. Boston: Partners In Health. USAID TB CARE II; 2014.

3. Tuberculosis: Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries. Médecins Sans Frontières and Partners In Health; 2013.
4. Caminero JA. Guidelines for clinical and operational management of drug-resistant tuberculosis. Paris: International Union Against Tuberculosis and Lung Disease; 2013.

HIV and MDR-TB

1. WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. Geneva: World Health Organization; 2012 (WHO/HTM/TB/2012.1).
2. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2013.
3. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization; 2011 (WHO/HTM/TB/2011.11).
4. WHO policy on TB infection control in health-care facilities, congregate settings and households. Geneva: World Health Organization; 2009 (WHO/HTM/TB/2009.419).
5. Policy guidelines for collaborative TB and HIV services for injecting and other drug users – an integrated approach. Geneva: World Health Organization; 2008 (WHO/HTM/TB/2008.404).
6. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents – Recommendations for HIV-prevalent and resource-constrained settings. Geneva: World Health Organization; 2007 (WHO/HTM/TB/2007.379 & WHO/HIV/2007.1).
7. A guide to monitoring and evaluation for collaborative TB/HIV activities. Geneva: World Health Organization; 2009 (WHO/HTM/TB/2009.414).
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2. Ehospice: find a hospice (http://www.ehospice.com/directory/findahospice.aspx, accessed 27 March 2014)
3. International Association for Hospice and Palliative Care: director of providers (http://hospicecare.com/global-directory-of-providers-organizations/, accessed 27 March 2014).
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Programmatic management of drug-resistant TB

1. The Stop TB strategy. Building on and enhancing DOTS to meet the TB-related Millennium Development Goals. Geneva: World Health Organization; 2006 (WHO/HTM/TB/2006.368).
2. A ministerial meeting of high M/XDR-TB burden countries: Meeting report Beijing, China. Geneva: World Health Organization; 2009 (WHO/HTM/TB/2009.415).
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1. Planning the development of human resources for health for implementation of the Stop TB Strategy – A handbook. Geneva: World Health Organization; 2009 (WHO/HTM/TB/2008.407)
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1. Global Drug Facility Product Catalogue. Geneva: World Heath Organization. (http://www.stoptb.org/gdf/drugsupply/drugs_available.asp, accessed 24 March 2014).
2. DR-TB drugs under the microscope: the sources and prices of medicines. IUATLD and MSF Access Campaign; 2013 (http://www.theunion.org/what-we-do/publications/technical/english/msf_tb_report_utm3rdedition-2013_final.pdf, accessed 24 March 2014).

Training materials and tools

1. MDR-TB-Course. World Medical Association: free self-learning online tool accredited by the South African Medical Association and the Norwegian Medical Association http://www.wma.net/en/70education/10onlinecourses/10mdr_tb/index.html

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8. Blasi F, Dara M, van der Werf MJ, Migliori GB. Supporting TB clinicians managing difficult cases: the ERS/WHO Consilium. European Respiratory Journal 2013;41(3): 491–494.

Useful websites

1. Find TB Resources: http://www.findtbresources.org
2. Global Drug Facility: http://www.stoptb.org/gdf/
3. Global Laboratory Initiative: http://www.stoptb.org/wg/gli/default.asp
4. KNCV Tuberculosis Foundation: http://www.kncvtbc.org/
5. Medecins Sans Frontieres: http://www.msf.org/
6. Partners In Health: http://www.pih.org/
7. Systems for improved access to pharmaceuticals and services http://siapsprogram.org/
8. Stop TB Partnership: http://www.stoptb.org/
9. Treatment Action Group: www.treatmentactiongroup.org/tb
10. TBCARE: http://tbcare.net/
11. The International Union Against Tuberculosis and Lung Disease http://www.theunion.org/
12. US CDC – Centers for Disease Control and Prevention: http://www.cdc.gov/tb/
13. World Health Organization, Stop TB Department: http://www.who.int/tb/publications/en/

ANNEX 2

Weight-based dosing for adults[a]

Weight-based oral anti-TB drug daily dosing in adults ≥30 kg

DRUGS	DAILY DOSE	30–35 KG	36–45 KG	46–55 KG	56–70 KG	>70 KG
Isoniazid	4–6 mg/kg once daily	150 mg	200 mg	300 mg	300 mg	300 mg
Rifampicin	8–12 mg/kg once daily	300 mg	450 mg	450 mg	600 mg	600 mg
Pyrazinamide	20–30 mg/kg once daily	800 mg	1000 mg	1200 mg	1600 mg	2000 mg
Ethambutol	15–25 mg/kg once daily	600 mg	800 mg	1000 mg	1200 mg	1200 mg
Rifabutin	5–10 mg/kg once daily	300 mg	300 mg	300 mg	300 mg	300 mg
Levofloxacin	750–1000 mg once daily	750 mg	750 mg	1000 mg	1000 mg	1000 mg
Moxifloxacin	400 mg once daily	400 mg	400 mg	400 mg	400 mg	400 mg
Ethionamide	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Prothionamide	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Cycloserine	500–750 mg/day in 2 divided doses	500 mg	500 mg	500 mg	750 mg	750 mg
***p*-aminosalicylic acid**[a]	8 g/day in 2 divided doses	8 g	8 g	8 g	8 g	8–12 g
Bedaquiline	400 mg once daily for 2 weeks then 200 mg 3 times per week					
Delamanid	100 mg twice daily (total daily dose = 200 mg)					
Clofazimine	200–300 mg daily (2 first months) then reduce to 100 mg daily (alternative dosing 100 mg daily)					
Linezolid	600 mg once daily	600 mg	600 mg	600 mg	600 mg	600 mg
Amoxicillin/clavulanic acid[b] **7/1**	80 mg/kg/day in 2 divided doses	2600 mg	2600 mg	2600 mg	2600 mg	2600 mg
Amoxicillin/clavulanic acid[b] **8/1**	80 mg/kg/day in 2 divided doses	3000 mg	3000 mg	3000 mg	3000 mg	3000 mg

DRUGS	DAILY DOSE	30–35 KG	36–45 KG	46–55 KG	56–70 KG	>70 KG
Imipenem/cilastatin	1000 imipenem/1000 mg cilastatin twice daily					
Meropenem	1000 mg three times daily (alternative dosing is 2000 mg twice daily)					

Weight-based oral high dose isoniazid

	<30 KG	30–50 KG	>50 KG
DOSE	300 mg	400 mg	600 mg

Weight-based injectable anti-TB daily dosing in adults ≥30 kg

DRUGS	DAILY DOSE	30–33 KG	34–40 KG	41–45 KG	46–50 KG	51–70 KG	>70 KG
Streptomycin	12–18 mg/kg once daily	500 mg	600 mg	700 mg	800 mg	900 mg	1000 mg
Kanamycin	15–20 mg/kg once daily	500 mg	625 mg	750 mg	875 mg	1000 mg	1000 mg
Amikacin	15–20 mg/kg once daily	500 mg	625 mg	750 mg	875 mg	1000 mg	1000 mg
Capreomycin	15–20 mg/kg once daily	500 mg	600 mg	750 mg	800 mg	1000 mg	1000 mg

[a] Adapted from Tuberculosis: Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries. Médecins Sans Frontières and Partners In Health; 2013.

ANNEX 3

Weight-based dosing for children

The dosing tables for children have been adapted from the following:

1. Management of multidrug-resistant tuberculosis in children: A field guide. Sentinel Project on Pediatric Drug-Resistant Tuberculosis/TB CARE II; 2012.
2. Tuberculosis: Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries. Médecins Sans Frontières and Partners In Health; 2013.
3. PIH guide to the medical management of multidrug-resistant tuberculosis, 2nd Edition. Partners In Health and USAID TB CARE II; 2014.

General considerations

- Anti-TB drugs should be dosed according to weight and adjusted regularly as weight increases during treatment.
- When a liquid formulation is available, it should be used for patients less than 15 kg.
- Most second-line TB drugs do not have paediatric liquid or tablet formulations, so it may be necessary to split the pills in order to approximate the correct dose. To split tablets into 0.75, it is suggested to split the tablet in half and then split a half tablet in half. Discard the smaller quarter tablet and give the child a half tablet plus the remaining quarter tablet.
- Doses of most anti-TB drugs have not been established for children below 5 kg, but often the potential benefit outweighs the risks. In such cases, the child should be dosed as close to the middle of the mg/kg range as possible.

Weight-based dosing tables

Isoniazid (7–15 mg/kg for patients less than 30 kg; maximum dose 300 mg daily)

Body weight kg	50 mg per 5 ml oral solution	100 mg tablet	300 mg tablet
5	5 ml	0.5 tab	-
6	6 ml	1.0 tab	-
7	7 ml	1.0 tab	-
8	8 ml	1.0 tab	-
9	9 ml	1.0 tab	-
10	10 ml	1.5 tab	-
11	11 ml	1.5 tab	-

Isoniazid (7–15 mg/kg for patients less than 30 kg; maximum dose 300 mg daily)

Body weight kg	50 mg per 5 ml oral solution	100 mg tablet	300 mg tablet
12	12 ml	1.5 tab	-
13	13 ml	2.0 tab	-
14	14 ml	2.0 tab	-
15	15 ml	2.0 tab	-
16–20		2.0 tab	-
21–30		-	1.0 tab

Notes

The table shows the "regular" dose for children, not high-dose isoniazid, which is rarely used in children.

Children at risk for peripheral neuropathy (e.g. malnutrition or HIV co-infection) should also receive pyridoxine 5–10 mg/day.

Rifampicin (10–20 mg/kg for patients less than 30 kg; maximum dose 600 mg daily)

Body weight kg	100 mg per 5 ml oral suspension	150 mg tablet	300 mg tablet
5	4 ml	0.5 tab	-
6	5 ml	0.5 tab	-
7	5 ml	0.5 tab	-
8	6 ml	1.0 tab	-
9	7 ml	1.0 tab	-
10	8 ml	1.0 tab	-
11	9 ml	1.0 tab	-
12	10 ml	1.0 tab	-
13	10 ml	1.5 tab	-
14	11 ml	1.5 tab	-
15	12 ml	1.5 tab	-
16–30		-	1.0 tab

Notes

Oral solution is preferred for children less than 15 kg.

Ethambutol (15–25 mg/kg, maximum dose 1200 mg daily)

Body weight kg	100 mg tablet	400 mg tablet
5–7	1.0 tab	-
8–13	2.0 tab	-
14–17	3.0 tab	-
18–26	-	1.0 tab
27–30	-	1.5 tab

Note

Older children over 16 kg can use the adult 400 mg tablet in combination with the 100 mg tablet to reduce pill count.

Pyrazinamide (30–40 mg/kg for patients less than 30 kg; maximum dose 2000 mg daily)

Body weight kg	400 mg tablet
5–7	0.50 tab
8–9	0.75 tab
10–14	1.00 tab
15–20	1.50 tab
21–27	2.00 tab
28–30	2.50 tab

Pyrazinamide (30–40 mg/kg for patients less than 30 kg; maximum dose 2000 mg daily)

Body weight kg	500 mg tablet
5–6	0.25 tab
7–9	0.50 tab
10–11	0.75 tab
12–18	1.00 tab
19–25	1.50 tab
26–30	2.00 tab

Note

Pyrazinamide comes in either 400 mg or 500 mg tablets.

Tablets are big enough to split into quarters.

Injectable anti-TB drugs

Drug	Daily dose	Maximum daily dose
Streptomycin	20–40 mg/kg once daily	1000 mg
Amikacin	15–30 mg/kg once daily	1000 mg
Kanamycin	15–30 mg/kg once daily	1000 mg
Capreomycin	15–30 mg/kg once daily	1000 mg

Example: Injectable dose calculation for a child weighing 6.9 kg

- Calculate the low and high doses for the child's weight. For kanamycin:
  - Low dose: 15 mg/kg x 6.9 kg = 103 mg
  - High dose: 30 mg/kg x 6.9 kg = 207 mg
- Choose a convenient dose between the two numbers.
  - Select a dose between the two numbers and toward the higher number. In this case, 200 mg is a convenient dose.
- Calculate the number of ml to draw up in the syringe based on the mg/ml concentration of the preparation.

Levofloxacin

5 years and under: 15–20 mg/kg split into two doses (morning and evening)

Over 5 years: 10–15 mg/kg once daily

Body weight kg	Under 5 years (250 mg tablet)	More than 5 years (250 mg tablet)
10–15	0.50 tab twice daily	-
16–23	0.75 tab twice daily	1.0 tab once daily
24–30	1.00 tab twice daily	1.5 tab once daily

Note

Levofloxacin is dosed twice daily for children 5 years of age and under (total daily dose: 15–20 mg/kg/day) and once daily for children over 5 years of age (total daily dose: 7.5–10 mg/kg/day). This is done because children under 5 years metabolize levofloxacin faster than those older than 5 years.

Once daily dosing at 15 mg/kg resulted in adequate serum concentrations for children less than 5 years in at least one programme and can be used as an alternative if twice daily dosing is not programmatically possible.

Moxifloxacin (7.5–10 mg/kg)	
Body weight kg	**400 mg tablet**
10–17	0.25 tab
18–30	0.50 tab

Note

Later-generation quinolones, such as levofloxacin and moxifloxacin, are recommended instead of ofloxacin as they are more potent. Dosing for ofloxacin is not provided in this guide.

Cycloserine (10–20 mg/kg)		
Body weight kg	**250 mg capsule**	**1 capsule in 10 ml water**
5	0.25 cap	2.5 ml
6–9	0.50 cap	5.0 ml
10–11	0.75 cap	7.5 ml
12–22	1.00 cap	10.0 ml
23–30	2.00 cap	–

Note

For older children who cannot swallow capsules, the capsules can be opened and dissolved in 10 ml water to aid administration.

Prothionamide/ethionamide (15–20 mg/kg)	
Body weight kg	**250 mg tablet**
5–10	0.5 tab
11–18	1.0 tab
19–24	1.5 tab
25–29	2.0 tab

PAS (200–300 mg/kg for patients less than 30 kg)	
Body weight kg	**PASER® Jacobus**
5	500 mg twice daily
6–7	750 mg twice daily
8–10	1000 mg twice daily
11–14	1500 mg twice daily
15–18	2000 mg twice daily
19–22	2500 mg twice daily
23–26	3000 mg twice daily
27–30	3500 mg twice daily

PAS (200–300 mg/kg for patients less than 30 kg)	
kg	**MonoPAS 9.2 g® Macleods**
5–6	1.5 g twice daily
7–8	2.0 g twice daily
9–13	3.0 g twice daily
14–18	4.0 g twice daily
19–24	6.0 g twice daily
25–30	8.0 g twice daily

Note

PASER® is stable for up to eight weeks at 40°C and 75% humidity and therefore can be distributed to the patient on a monthly basis in most environments with no cold chain. If storage of longer than eight weeks is needed, refrigeration below 15°C is required.

PASER® comes with a dosage scoop graduated in milligrams, and MonoPAS 9.2 g® comes with a measuring spoon graduated in grams.

Group 5 anti-TB drugs		
Drug	**Daily dose**	**Maximum daily dose**
Bedaquiline (Bdq)	Dose not yet determined in children	
Delamanid (Dlm)	Dose not yet determined in children	
Linezolid (Lzd)	10 mg/kg given three times daily (pyridoxine should also be given)	600 mg
Clofazimine (Cfz)	Limited data, but 1 mg/kg once daily has been given	200 mg

Group 5 anti-TB drugs		
Drug	**Daily dose**	**Maximum daily dose**
Amoxicillin/clavulanic acid (Amx/Clv)	80 mg/kg (based on the amoxicillin component) in two divided doses	4000 mg amoxicillin and 500 mg clavulanic acid
Meropenem (Mpn)	20–40 mg/kg intravenous every eight hours	6000 mg
Imipenem/cilastatin (Imp/Cln)	Meropenem is preferred in children	

Note

Most of the Group 5 drugs, except amoxicillin/clavulanic acid and linezolid, have limited experience with dosing in children. The data on long-term use of all the Group 5 drugs in children is also limited.

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ANNEX 4.1

'How-to' guide on the use of bedaquiline for MDR-TB treatment

A4.1.1 Background on bedaquiline

Introduction

Bedaquiline belongs to a new class of drugs called diarylquinolines, and is indicated as part of combination therapy in adult patients (≥18 years) with pulmonary multidrug-resistant tuberculosis (MDR- TB). Bedaquiline is the first new drug developed specifically to treat TB in over 40 years.

Bedaquiline was granted accelerated approval by the USA Federal Food and Drug Administration (FDA) in December 2012 *(1)*. The approval is primarily based on an analysis of time to sputum culture conversion from two controlled phase 2 trials in patients with pulmonary MDR-TB, and on a review of the safety data gathered in these studies *(2)*. One of the phase 2 trials - a double-blinded placebo-control trial - demonstrated clinical efficacy with faster and lasting conversions in patients receiving bedaquiline for the first 24 weeks when given on top of a WHO standard MDR regimen. In June 2013, the WHO published interim policy guidance for the use of bedaquiline in conjunction with the WHO-recommended MDR-TB treatments *(3)*.

This annex serves as an operational document to facilitate bedaquiline implementation according to WHO policies.

In this Handbook, bedaquiline is placed with anti-TB drugs belonging to Group 5, primarily because it does not belong to any of the other TB drug families and because of as yet the limited data on its effectiveness and long-term safety in the treatment of drug-resistant TB.

WHO strongly recommends the acceleration of phase 3 trials to generate a more comprehensive evidence base to inform future policy on bedaquiline. The WHO will review, revise, or update the interim guidance *(3)* as additional information on efficacy and safety become available. This may result in the modification of this annex and the WHO website should be checked regularly for updates.

Key facts about bedaquiline *(2,4)*

- Bedaquiline has a novel mechanism of action. The drug specifically targets mycobacterial adenosine triphosphate (ATP) synthase, an enzyme that is essential for the supply of energy to *Mycobacterium tuberculosis* and most other mycobacteria. Strong bactericidal and sterilizing activity against *M. tuberculosis* organisms have been shown in pre-clinical laboratory setting as well as in animal experiments.

- There is reported cross-resistance of bedaquiline with clofazimine (Cfz) due to mutations in Rv0678, a transcriptional repressor of the genes encoding the MmpS5-MmpL5 efflux pump *(5)*.
- Bedaquiline shows linear pharmacokinetics and better absorption when the drug is taken with food versus when taken fasting (resulting in approximately a two-fold increase in serum drug levels).
- The drug is hepatically metabolized (CYP3A4 involvement). The main metabolite is N-monodesmethyl-bedaquiline (M2), which is three to six-fold less active than the parent drug. The M2 metabolite can however result in similar toxicities as bedaquiline.
- The drug has a high volume of distribution, with extensive tissue distribution, and is highly bound to plasma proteins (>99.9%). Bedaquiline has a slow terminal elimination profile, with a terminal half-life of approximately 5.5 months. The long half-life is explained by the slow release of bedaquiline (and M2) from peripheral tissue compartments.
- There is no experience with use of bedaquiline in children, pregnant women, extrapulmonary disease, and the elderly, and there is minimal information on its use in HIV-infected patients, whether on antiretroviral treatment (ART) or not.
- In one of the placebo-controlled trials, there was an observed risk of death: the bedaquiline treatment group experienced 11.4% deaths (9/79) compared to 2.5% in the placebo treatment group (2/81) *(2)*. No evidence that directly linked the drug to the cause of death was however seen. Data do not suggest that QT prolongation in the bedaquiline group contributed to deaths. Despite no discernable pattern or cause, extreme caution is warranted in the use of bedaquiline until a complete safety profile can be established.
- QT prolongation can occur with bedaquiline. The heart's electrical cycle can be measured on an ECG; the QT interval is a measure of the time between the start of the Q wave and the end of the T wave (see Box A4.2) representing the electrical depolarization and repolarization of the left and right ventricles. A lengthened QT interval is a biomarker for ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. Concomitant use with drugs that prolong the QT interval may cause additive QT prolongation, and should be avoided if possible (see Section A4.1.6). Some of the second-line anti-TB drugs are known to prolong the QT interval (see Section A4.1.6).
- Bedaquiline can also cause hepatotoxicity. Conditions and medications associated with hepatotoxicity could pose additional hepatotoxic risks.
- When bedaquiline is added to a regimen, it is only given for the first 24 weeks of treatment (see Section A4.1.2 for dosing schedule).
- Drug susceptibility testing (DST) for bedaquiline has not yet been standardized. Laboratory testing of the minimal inhibitory concentration (MIC) of bedaquiline seems to suggest a break-point for susceptibility of <0.5mcg/ml in agar medium; however, until a specific DST assay for bedaquiline is developed, clinicians will not be able to be guided by MIC values or DST results when composing a regimen..

Adverse effects and risks are explained in more detail throughout this annex so that a health care provider can discuss with the patient the risk/benefits of bedaquiline with proper knowledge. While there is limited data on the safety of bedaquiline and a number of potential adverse effects and risks, bedaquiline may play a crucial role to strengthen the regimen for many patients. Section A4.1.7 discusses the programmatic considerations for introducing bedaquiline.

A4.1.2 Using bedaquiline in patients with MDR-TB

WHO interim policy guidance *(3)*

The WHO issued an interim policy statement in June 2013 to provide guidance on the use of bedaquiline in eligible patient groups *(3)*. The interim policy is based on an evidence assessment and advice provided by an Expert Group convened by the WHO/Stop TB Department in Geneva, Switzerland and resulted in the recommendation that **bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB (conditional recommendation, very low confidence in estimates of effects).**

Given the limited data available on bedaquiline and its use under the various situations that may be encountered in different clinical settings, adequate provisions for safe and effective use of the drug must be in place. Consequently, countries are advised to follow a phased approach to bedaquiline implementation, ideally through observational cohorts, where the following measures are in place. The WHO recommendation for the inclusion of bedaquiline in the adult treatment regimen of MDR-TB is subject to the following five conditions being met *(3)*:

1. **Effective treatment and monitoring:** Treatment must be closely monitored for effectiveness and safety, using sound treatment and management protocols approved by relevant national authorities (see Section A4.1.5).
2. **Proper patient inclusion:** The current recommendation for the use of bedaquiline applies to adults (≥18yrs) with pulmonary TB disease (see absolute, relative contraindications, and cautions below in this section).
   - Special caution and proper clinical judgment should be applied when bedaquiline is used in people aged 65 years and over, or in those with diabetes, HIV, hepatic or severe renal impairment, or those who use alcohol or other substances, given that data on efficacy and safety under such conditions are very limited or unavailable.
   - Use of the drug in children and in pregnant and breastfeeding women is not currently advised due to a lack of evidence on safety, efficacy and proper dosing in these groups.
3. **Informed consent:** Health care workers should follow a due process for informed consent by ensuring that the patient is: i) aware of the novel nature of bedaquiline; ii) appreciates the reason why the drug is being proposed for inclusion in their treatment regimen; and iii) recognizes the possible benefits and potential harms, including the uncertainties that surround them. This informed consent process must be documented and signed by the patient, and applies to all situations where bedaquiline is employed, including under compassionate use programmes (see Section A4.1.9).
4. **Adherence to the principles of designing a WHO-recommended MDR-TB regimen**: Bedaquiline is intended to be introduced alongside other anti-TB drugs in composing an effective second-line regimen based on WHO guidelines; the cardinal rules governing the general composition and duration of MDR-TB regimens remain the same:

   a. The WHO-recommended MDR-TB treatment regimen *(7)* is typically composed of at least pyrazinamide and four second-line drugs considered to be effective (based on DST and/or previous use and/or drug resistance surveillance data): a fluoroquinolone (preferably later-generation), a second-line injectable agent, and two bacteriostatic drugs, preferably prothionamide or ethionamide plus cycloserine or p-aminosalicylic acid.
   It should be noted that there is as yet no evidence that bedaquiline is equivalent to other second-line drugs or can effectively be used as a replacement. When an effective

and reasonably well-tolerated MDR-TB regimen can be composed with conventional second-line drugs, bedaquiline is not necessary. However, use of bedaquiline may be an option to consider in individual patients if a WHO-recommended regimen is not feasible because of:

- In vitro resistance to a drug;
- Known adverse drug reactions, poor tolerance, or contraindication to any component of the combination regimen; or
- Unavailability or lack of a guaranteed supply of a drug. In such circumstances extra measures should be taken to ensure adherence to treatment and reduce the likelihood of creating additional resistance.

b. There is as yet no standardised drug-susceptibility test (DST) method for bedaquiline, nor a commercially available test. Because bedaquiline is a new anti-TB agent, strain resistance to the drug is highly unlikely, and adding it to a MDR-TB regimen should not be problematic in this context. Cross-resistance between bedaquiline and clofazimine has been reported, however, and previous treatment with clofazimine in a patient subsequently considered for treatment with bedaquiline should keep in mind the potential for resistance existing in the infecting strain.

c. There are currently no data on the concurrent use of bedaquiline and delamanid. Until such data become available, no recommendation on the joint administration of these two medicines is possible. There are concerns that, potentially, there could be additive cardiotoxicity because both drugs prolong the QT interval. Also, the effects of combined use on treatment efficacy has not been tested.

d. Bedaquiline should not be added alone to a failing regimen. (Also see Chapter 5 and Section A4.1.3).

5. **Active pharmacovigilance and management of adverse events:** Active pharmacovigilance measures must be in place to ensure early detection and proper management of adverse reactions and potential interactions with other drugs (Section A4.1.5 and A4.1.6).

Absolute contraindications, relative contraindications and cautions

There are a number of relative and absolute contraindications for bedaquiline. For relative contraindications, bedaquiline should be avoided but could be used in situations where the options of treatment are extremely limited and the benefit of bedaquiline outweighs the potential risks (this risk–benefit determination should emerge through discussion with the patient and is based on the patient's clinical situation and the programmatic policy on bedaquiline use).

Absolute contraindications:

- **Patient refuses to consent.** The patient decides to not accept the medication after being properly counselled and informed about the benefits and risks associated with the use of bedaquiline (a suggested informed consent template is provided in Section A4.1.9).
- **Hypersensitivity.** The patient is hypersensitive to the active substance or to any of the excipients in the formulation

- **High risk for cardiac complications.** Patient has a QT interval greater than 500 ms, history of torsades de pointes or cardiac ventricular arrhythmias or severe coronary artery disease.

Relative contraindications (bedaquiline may be used on a case-by-case basis in the following situations when an effective treatment regimen cannot otherwise be provided):

- **Children or persons under 18 years of age.** The safety and dosing of bedaquiline has not been established in children and its use in this group should be avoided until further data are available.
- **Pregnancy.** Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the foetus due to bedaquiline. In these studies, the corresponding plasma exposure (area under curve; AUC) was two-fold higher in rats compared to humans. Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy *(5)*.
- **Nursing mothers.** It is not known if bedaquiline and its metabolites are passed into human breast milk. Because of the potential for adverse reactions in nursing infants, a decision should be made on whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother *(5)*.

Cautions:

- **Geriatric use (use in the elderly).** Clinical studies of bedaquiline did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients *(5)*.
- **Hepatic impairment.** No dose adjustment is necessary for bedaquiline in patients with mild or moderate hepatic impairment. Bedaquiline has not been studied in patients with severe hepatic impairment and should be used with caution in these patients and only when the benefits outweigh the risks *(5)*.
- **Renal impairment.** No dose adjustment is required in patients with mild or moderate renal impairment. Bedaquiline has not been studied in patients with severe renal impairment or end stage renal disease requiring haemodialysis or peritoneal dialysis and should be used with caution in these patients and only when the benefits outweigh the risks *(5)*.
- **Co-administration with anti-HIV medication.** The use of bedaquiline in patients also requiring treatment for HIV infection is addressed in Section A4.1.4
- **Co-administration with QT-prolonging drugs.** The monitoring of the QT segment in patients receiving bedaquiline is addressed in Section A4.1.5.
- **Serum potassium outside the normal range.** Because QT prolongation is associated with hypokalaemia and arrhythmias are associated with hypokalemia or hyperkalaemia, potassium should be corrected before starting bedaquiline and carefully monitored if abnormal ECG is observed.
- While patients with **exclusive extrapulmonary disease** were not included in the bedaquiline trials, there is no absolute contraindication for its use in such patients and inclusion may be considered where any potential harm that bedaquiline may cause is offset by the benefit expected.

- **Concurrent use of delamanid**: no data exist about concomitant use of delamanid and bedaquiline. Given the short half-life of delamanid (38 hours), a five-day washout period of delamanid is recommended before using bedaquiline.
- **Concurrent use of bedaquiline with other Group 5 second-line anti-TB drugs.** No data exist about concomitant use of bedaquiline and Group 5 drugs, though its main metabolizing enzymes are unlikely to have a significant impact on concentrations of companion drugs.
- **Strong inducers/inhibitors of CYP3A.** Because strong inducers (i.e. carbamazepine, phenobarbital, phenytoin) and strong inhibitors (i.e. ketoconazole, itracononazole, clarithromycin) of CYP3A will affect the safety, tolerability or efficacy of bedaquiline to an extent that is not yet known (no public data exist on interaction with these drugs), an alternative to those drugs should be offered to patients before starting use of bedaquiline (see Section A4.4 for known interactions of some ARVs with bedaquiline). If co-administration of bedaquiline with strong inhibitors is necessary then perform more frequent monitoring with ECGs throughout the bedaquiline treatment period.

Section A4.1.8 offers a clinician's checklist to confirm clinical eligibility and to indicate when increased monitoring is indicated.

Length of treatment of bedaquiline-containing regimens

Bedaquiline is used for a maximum period of 24 weeks (6 months) at the start of treatment. Bedaquiline is added to the WHO standard regimen (see Table A4.1.9) and the overall duration of the regimen does not change (see Chapter 5 for recommended length of treatment of standard WHO regimens).

Table A4.1.1 **Length of treatment of bedaquiline-containing regimens**

DRUG	SUGGESTED DURATION OF TREATMENT IN MONTHS WHEN BEDAQUILINE IS ADDED TO THE STANDARD WHO REGIMEN[a]
Bedaquiline (oral)	6[b]
Injectable drug	8
Other oral anti-TB drugs	20

[a] With XDR-TB, the total treatment can be extended to 24 months; however bedaquiline is still only used for the initial six months.

[b] The dosing of the **initial first two weeks** of bedaquiline is different from maintenance dosing (see Section A9.2.3 below).

Bedaquiline is generally never added in the middle of treatment. Instead, when it is determined that there is an indication for bedaquiline, a new regimen is designed according to scenarios in Section A4.1.3.

The dose of bedaquiline

Bedaquiline comes in 100 mg tablets. Bedaquiline is only to be taken at the recommended dose and indicated frequency of administration. The six-month (24 weeks) dosing schedule of the medication is as follows:

- Week 1–2: Bedaquiline 400 mg (4 tablets of 100 mg) daily (seven days per week).
- Week 3–24: Bedaquiline 200 mg (2 tablets of 100 mg), three times per week (with at least 48 hours between doses) for a total dose of 600 mg per week.
- Week 25 (start of month 7) to end of treatment: Continue other second-line anti-TB drugs only, as per WHO standard recommendations. No bedaquiline is used in this phase of treatment.

Bedaquiline can be taken together with other anti-TB drugs and should be taken with a light meal (better absorption of bedaquiline occurs with food); if taking a light meal with bedaquiline and other anti-TB drugs, do not consume milk-containing products at the same time as the calcium in them can decrease the absorption of the fluoroquinolones. Also, avoid large fatty meals as this can impair absorption of some of the other anti-TB drugs (cycloserine, isoniazid, etc) *(6)*. See the drug information sheets (Part 3) for more advice on interactions between food and other anti-TB drugs.

Currently, dose adjustment is not considered to be required under any particular circumstance, even if concomitant agents are known to affect bedaquiline bioavailability. The general principle is to monitor potential adverse events closely and manage them as quickly and effectively as possible (see Section A4.1.5 for more information on monitoring).

If a dose is missed during the first two weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule. From week 3 onwards, if a 200 mg dose is missed, patients should take the missed dose as soon as possible, and then resume the three times a week regimen.

A4.1.3 Constructing a bedaquiline-containing regimen for the treatment of MDR-TB

The following scenarios (Figure A4.1.1–A4.1.4) are based on the principles of regimen design in Chapter 5. The scenarios cover the most common indications for the inclusion of bedaquiline in a MDR-TB regimen.

All the suggested regimens in this section are examples and will likely vary based on the individual clinical circumstances and availability of companion drugs. The regimens and algorithms put forth here have not been tested in either research or field conditions and are based on expert opinion. The algorithms always maintain the principle of never using less than four effective second-line drugs. Often when Group 5 drugs are used, more than four second-line drugs are used to make up for the uncertainty of the efficacy of some of the Group 5 drugs. Finally, the recommendations on the number of Group 5 drugs is based on expert opinion and some experts recommend using more than the minimal suggested number in the algorithms. There is very little experience on the most effective regimens that involve bedaquiline and specific Group 5 drugs.

Figure A4.1.1. Scenario 1: MDR-TB plus resistance to fluoroquinolones with no injectable resistance

STEP 1	**Choose an injectable (Group 2)**	**Kanamycin** **Amikacin** **Capreomycin**
STEP 2	**Choose a higher generation fluoroquinolone (Group 3)**	**Levofloxacin** **Moxifloxacin**

Levofloxacin (in the doses recommended in this handbook) and moxifloxacin can overcome ofloxacin resistance in some circumstances; for most patients the fluoroquinolone is tolerated well and worth using if there is a chance of efficacy. Both moxifloxacin and levofloxacin (to a lesser extent) are known to have additive QT-prolonging effects and should be used with caution.

- If only ofloxacin DST is known (and resistant) use levofloxacin unless it is thought to be compromised (previous use in a failing regimen or known contact with a patient with levofloxacin resistance).
- If levofloxacin resistance is likely (previous exposure, documented resistance, and/or known contact with a patient with levofloxacin resistance), the use of moxifloxacin can be considered.
- If moxifloxacin is testing resistant and/or history suggests it has not been effective (e.g. if used in a failing regimen for an extended time), it should not be used; levofloxacin can be considered instead, given its likely lower overlapping toxicity with bedaquiline. Otherwise, fluoroquinolones might be excluded from use in the regimen.
- Use of the combination of moxifloxacin with bedaquiline and clofazimine (three drugs that strongly prolong the QT interval) should be avoided.

Be aware that bedaquiline has a long half-life and replacing levofloxacin with moxifloxacin after the bedaquiline has stopped could still result in cardiac toxicity.

STEP 3	**Add Group 4 drugs**	**Ethionamide/prothionamide** **Cycloserine/terizidone** **Para-aminosalicylic acid (PAS)**

Use all drugs thought to be effective. If confidence on efficacy is difficult to judge, the drug can be added to the regimen, but should not be counted as one of the four second-line drugs.

STEP 4	**Add Group 1 drugs**	**Pyrazinamide** **Ethambutol**

Pyrazinamide is routinely added in most regimens; ethambutol may also be added if the criteria for an effective drug are met.

STEP 5	**Add bedaquiline and other Group 5 drugs as necessary** *NOTE: Delamanid is avoided as an additional Group 5 drug if bedaquiline is being used*	**Bedaquiline** **Linezolid** **Clofazimine** **Amoxicillin/clavulanate** **Imipenem/cilastatin** **Meropenem** **High-dose isoniazid** **Clarithromycin** **Thioacetazone**

Group 5 drugs other than bedaquiline are added based on the number of Group 4 drugs for which there is a high degree of confidence in efficacy:

- Confidence in all three Group 4 drugs: adding other Group 5 drugs is not necessary.
- Confidence in only two Group 4 drugs: add **one** other Group 5 drug.
- Confidence in only one Group 4 drugs: add **two** other Group 5 drugs.
- Confidence in no Group 4 drugs: add **three** other Group 5 drugs.

Figure A4.1.2. Scenario 2: MDR-TB plus resistance or severe intolerance to all second-line injectable agents and no resistance to fluoroquinolones

STEP 1	**Choose an injectable (Group 2)**	**Kanamycin** **Amikacin** **Capreomycin**
	If the clinical history or DST suggest that resistance exist for all second-line injectable or in case of serious adverse event (nephrotoxicity or hearing loss) consider not using an injectable.	
STEP 2	**Choose a higher generation fluoroquinolone (Group 3)**	**Levofloxacin** **Moxifloxacin**
	Use a later generation fluoroquinolone. Avoid moxifloxacin when using bedaquiline.	
STEP 3	**Add Group 4 drugs**	**Ethionamide/Prothionamide** **Cycloserine/Terizidone** **Para-aminosalicylic acid (PAS)**
	Add all Group 4 drugs thought to be effective. If confidence on efficacy is difficult to judge, the drug can be added to the regimen, but should not be counted as one of the four second-line drugs.	
STEP 4	**Add Group 1 drugs**	**Pyrazinamide** **Ethambutol**
	Pyrazinamide is routinely added in most regimens; ethambutol may also be added if the criteria for an effective drug are met.	
STEP 5	**Add bedaquiline and other Group 5 drugs as necessary** *NOTE: Delamanid is avoided as an additional Group 5 drug if bedaquiline is being used*	**Bedaquiline** **Linezolid** **Clofazimine** **Amoxicillin/clavulanate** **Imipenem/cilastatin** **Meropenem** **High-dose isoniazid** **Clarithromycin** **Thioacetazone**
	Bedaquiline routinely added. Group 5 drugs other than bedaquiline are added based on the number of Group 4 drugs for which there is a high degree of confidence in efficacy: • Confidence in all three Group 4 drugs: adding other Group 5 drugs is not necessary. • Confidence in only two Group 4 drugs: add **one** other Group 5 drug. • Confidence in only one Group 4 drugs: add **two** other Group 5 drugs. • Confidence in no Group 4 drugs: add **three** other Group 5 drugs	

Figure A4.1.3. Scenario 3: MDR-TB plus two or more Group 4 drugs compromised (Group 2 and 3 drugs effective)

STEP 1	**Choose an injectable (Group 2)**	**Kanamycin** **Amikacin** **Capreomycin**
STEP 2	**Choose a higher generation fluoroquinolone (Group 3)**	**Levofloxacin** **Moxifloxacin**
	Use a later generation fluoroquinolone. Avoid moxifloxacin when using bedaquiline.	
STEP 3	**Add Group 4 drugs**	**Ethionamide/Prothionamide** **Cycloserine/Terizidone** **Para-aminosalicylic acid (PAS)**
	Add the Group 4 drug thought to be effective. If confidence on efficacy is difficult to judge, the drug can be added to the regimen, but should not be counted as one of the four second-line drugs.	
STEP 4	**Add Group 1 drugs**	**Pyrazinamide** **Ethambutol**
	Pyrazinamide is routinely added in most regimens; ethambutol may also be added if the criteria for an effective drug are met.	
STEP 5	**Add bedaquiline and other Group 5 drugs as necessary** *NOTE: Delamanid is avoided as an additional Group 5 drug if bedaquiline is being used*	**Bedaquiline** **Linezolid** **Clofazimine** **Amoxicillin/clavulanate** **Imipenem/cilastatin** **Meropenem** **High-dose isoniazid** **Clarithromycin** **Thioacetazone**
	Bedaquiline routinely added. Group 5 drugs other than bedaquiline are added based on the number of Group 4 drugs for which there is a high degree of confidence in efficacy: • Confidence in all three Group 4 drugs: adding other Group 5 drugs is not necessary. • Confidence in only two Group 4 drugs: add **one** other Group 5 drug. • Confidence in only one Group 4 drugs: add **two** other Group 5 drugs. • Confidence in no Group 4 drugs: add **three** other Group 5 drugs.	

Figure A4.1.4. Scenario 4: XDR-TB

STEP 1	**Choose an injectable (Group 2)**	**Kanamycin** **Amikacin** **Capreomycin**
	• If patient's strain is still susceptible to one of the injectable drugs, include in the regimen. • If resistant to all injectable agents, consider not using any injectable or using one that the patient has never received based on clinical judgement (see Box 5.3 in chapter 5).	

STEP 2	**Choose a higher generation fluoroquinolone (Group 3)**	**Levofloxacin** **Moxifloxacin**

In addition to determining organism susceptibility to ofloxacin, every attempt should be made to specifically determine susceptibility also to moxifloxacin and levofloxacin.

- If only ofloxacin DST is known (and resistant) use levofloxacin unless thought to be compromised (previous use in failing regimen or known contact with a patient with levofloxacin resistance).
- If resistance has specifically been shown to ofloxacin and/or levofloxaxin, and moxifloxacin DST is susceptible, consider adding moxifloxacin to the regimen.
- Use of the combination of moxifloxacin with bedaquiline and clofazimine (three drugs that strongly prolong the QT interval) should be avoided.
- If resistance shown to all three Group 3 agents, do not use fluoroquinolones.

Be aware that bedaquiline has a long half-life and replacing levofloxacin with moxifloxacin after the bedaquiline has stopped could still result in cardiac toxicity.

STEP 3	**Add Group 4 drugs**	**Ethionamide/Prothionamide** **Cycloserine/Terizidone** **Para-aminosalicylic acid (PAS)**

Add all Group 4 drugs thought to be effective. If confidence on efficacy is difficult to judge, the drug can be added to the regimen, but should not be counted as one of the four second-line drugs.

STEP 4	**Add Group 1 drugs**	**Pyrazinamide** **Ethambutol**

Pyrazinamide is routinely added in most regimens; ethambutol may also be added if criteria for an effective drug are met.

STEP 5	**Add bedaquiline and other Group 5 drugs** *NOTE: Delamanid is avoided as an additional Group 5 drug if bedaquiline is being used*	**Bedaquiline** **Linezolid** **Clofazimine** **Amoxicillin/clavulanate** **Imipenem/cilastatin** **Meropenem** **High-dose isoniazid** **Clarithromycin** **Thioacetazone**

Bedaquiline routinely added. Group 5 drugs other than delamanid are added based on the number of Group 4 drugs for which there is a high degree of confidence in efficacy:

- Confidence in all (three) Group 4 drugs: add **one** other Group 5 drug.
- Confidence in only two Group 4 drugs: add **two** other Group 5 drugs.
- Confidence in only one or no Group 4 drugs: add **three** or more Group 5 drugs.

If resistant to higher generation fluoroquinolone and/or the two classes of Group 2 injectables (aminoglycosides and polypeptides), can add an additional Group 5 drug to what is being recommended above.

A4.1.4 Concomitant therapy with anti-HIV or other medicines

Consideration should be given to potential drug interactions between bedaquiline and antiretrovirals when choosing a regimen. It should be noted that data from drug–drug interaction studies with bedaquiline and antiretrovirals to date are very limited because these studies were conducted among healthy individuals who did not have HIV or TB, and only a single dose of bedaquiline was given. For these reasons, the effects of antiretroviral medications on bedaquiline concentrations when bedaquiline is given more frequently are unknown. Bedaquiline steady state concentrations have been estimated using established techniques of modelling and simulation, but caution is warranted as these estimations may differ from future field studies of bedaquiline being used in HIV patients on antiretroviral agents.

Bedaquiline is metabolized by the cytochrome P450 3A4 (abbreviated CYP3A4). Efavirenz and nevirapine are inducers of CYP3A4. Ritonavir, a boosting agent for most protease inhibitors, is an inhibitor of CYP3A4. When efavirenz is given together with a single dose of bedaquiline, bedaquiline concentrations are reduced by about 20% *(8)*. But when mathematical modelling is used to estimate steady state bedaquiline concentrations, a 50% reduction is predicted *(9)*. The effect of this reduction in bedaquiline levels on treatment efficacy is unknown; using a higher dose of bedaquiline is one potential strategy for overcoming this drug interaction, but this has not yet been tested and is not recommended at this time. When nevirapine is given together with bedaquiline, bedaquiline concentrations are not significantly reduced, so it is likely that these drugs can be co-administered without dose adjustments.

The use of ritonavir-boosted lopinavir (LPV/r) with bedaquiline is more problematic. Although a single dose drug–drug interaction study showed only a modest increase in concentrations of bedaquiline *(2)* and its main metabolite, it is likely that significant accumulation of bedaquiline and its metabolite will occur with prolonged concomitant use of bedaquiline and LPV/r. Since it is unclear what the clinical effects will be when LPV/r and bedaquiline are used together, this combination should be used with extreme caution and only in a closely monitored setting when other options are not available.

Nucleoside reverse transcriptase inhibitors (NRTI) neither induce nor inhibit CYP3A4 and are unlikely to affect bedaquiline concentrations. Three NRTIs may be considered for patients on bedaquiline, even though these interactions have not been studied. However, triple NRTI regimens are known to result in inferior virologic outcomes compared with standard antiretroviral regimens, especially in patients with viral loads >100 000 copies/ml. Nonetheless, in the context of TB co-treatment triple NRTIs can maintain good clinical and immunological response after virologic suppression on standard ART *(10)*.

Raltegravir, an integrase strand transfer inhibitor (ISTR), neither induces nor inhibits CYP3A4 and is unlikely to affect bedaquiline concentrations. However, raltegravir is generally reserved for third-line antiretroviral regimens and its routine use with bedaquiline is not indicated. If a patient is on a third-line ART regimen with raltegravir prior to starting bedaquiline, the raltegravir should be considered for continuation, but caution is warranted as no experience of using these drugs together exists.

BOX A4.1.1 SUMMARY OF ART REGIMEN OPTIONS FOR PERSONS ON BEDAQUILINE THERAPY

- **Given the limited data on drug–drug interactions of antiretrovirals with bedaquiline, the following options for ART regimens can be considered:**
  - Two NRTIs with nevirapine [e.g. AZT-3TC (or FTC)-NVP]
  - A NtRTI, a NRTI with nevirapine [e.g. TDF-3TC-(or FTC)-NVP]
  - Triple NRTI (e.g. AZT-3TC (or FTC)-ABC)*
- **General recommendations**
  - Avoid efavirenz containing regimens
  - Avoid regimens with protease inhibitors
  - More frequent monitoring of QT interval prolongation (every month)
  - Be aware of potential additive liver toxicity with NVP and Bdq.

NRTI = nucleoside reverse-transcriptase inhibitor

NtRTI = nucleotide reverse-transcriptase inhibitor

3TC = lamivudine; AZT = zidovudine; NVP = nevirapine; FTC = emtricitabine; TDF = tenofovir

* Limited evidence on triple NRTI regimens (AZT-3TC/FTC-ABC) are associated with a lower ability to obtain good viral suppression and should only be used when other options are not possible (10).

Concomitant therapy with other medicines

Overlapping toxicities are also a concern with the use of bedaquiline. Other second-line anti-TB drugs and ART are shown in Chapter 11, Table 11.3. Because the common drug combinations of ART can result in QT prolongation, monthly monitoring with ECGs is indicated while on ART. If the bedaquiline is stopped in a patient on ART because of QT prolongation, the ART is often continued except if dangerous arrhythmias are present, then all QT-prolonging drugs are stopped.

A summary of ART regimen options for persons on bedaquiline therapy is provided in Box A4.1.1. The suggested regimens in Box A4.1.1 are based on expert opinion and very limited data.

A4.1.5 Monitoring and managing patients receiving bedaquiline

The safety of bedaquiline has not been conclusively established. Special attention should therefore be paid to ensure that adverse reactions – in particular hepatic and cardiac – are detected early or promptly managed. Patients receiving bedaquiline are to be clinically monitored closely throughout their treatment. As for the monitoring of other medications, programmes should strive to provide the monitoring tests, as well as any ancillary drugs prescribed for adverse effects, free of charge or at the lowest possible cost to the patient.

The most frequent adverse drug reactions (>10% of patients) during treatment with bedaquiline in the controlled trials were nausea, arthralgia and headache. General monitoring and management of these and other common adverse effects experienced by patients receiving second-line anti-TB drugs are described in Chapter 11, and also apply to patients receiving bedaquiline. This includes monitoring the bacteriological and clinical responses (Chapter 10), which do not differ from normal monitoring described in this Handbook.

Two other less commonly observed but potentially serious adverse effects related to bedaquiline use in clinical trials need special consideration. These are QT interval prolongation and hepatic-related adverse drug reactions.

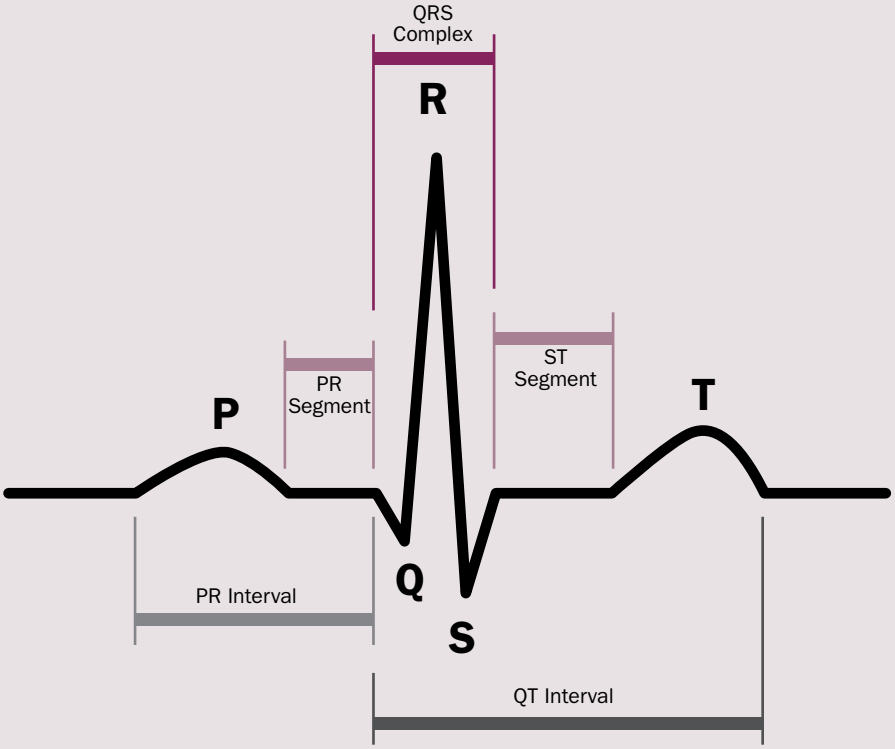
QT interval monitoring. QT prolongation can result in ventricular arrhythmias (torsade de pointes) and result in death, and it is imperative that ECG measurements are taken before treatment with bedaquiline is started, and regularly during bedaquiline use. The QT interval must be corrected for the heart rate (adjustment is referred to as QT-corrected or QTc). The Fredericia correction method (QTcF) is preferred. QT interval monitoring should preferably be done using ECG machines that directly report the QTc interval. If this is not possible, Box A4.2 describes how the correction can be calculated using measurements on a graduated ECG rhythm strip.

Box A4.3 describes the frequency and key actions for QT interval monitoring for patients on bedaquiline. The following are important notes on QT interval monitoring:

- The QT interval must always be corrected for heart rate.
- A value of greater than 450/470 ms is considered prolonged in male/female patients. If a male/female patient taking bedaquiline has a QTcF value of greater than 450/470 ms (or an increase of greater than 60 ms from baseline) on his or her ECG, electrolyte testing and more frequent ECG monitoring should be performed. A QTcF interval of more than 500 ms is considered dangerous and is reason to stop the use of bedaquiline and all other QT prolonging drugs in the regimen (see Box A4.1.3 for further details).

BOX A4.1.2 DEFINITION OF THE QTC INTERVAL

- The QT interval in an ECG is measured from the start of the Q wave to the end of the T wave (see diagram below).



- When monitoring the effect of bedaquiline, the QT interval needs to be adjusted (corrected) for the heart rate. Many ECG machines today provide an output of the corrected QT interval (QTc) automatically. If you are using a machine that does not, the following instructions can help you make the necessary correction.
  - The preferred way to calculate the QTc is the Fredericia method (QTcF), which is derived by dividing the QT interval by the cubed root of the interval in seconds between the peak of two successive R waves (RR) read from the ECG strip:

$$QT_{cF} = \frac{QT}{\sqrt[3]{RR}}$$

- Whenever an abnormal QTc value is found, the ECG and calculations should be repeated.
- A normal value for the corrected QTcF interval is equal to or less than 0.45 seconds (450 ms) in males or 0.47 seconds (470 ms) in females.

BOX A4.1.3 FREQUENCY OF QT INTERVAL MONITORING AND MANAGEMENT OF QT INTERVAL PROLONGATION

- An ECG should be obtained before initiation of treatment, and at least two, 2, 4, 8, 12 and 24 weeks after starting treatment with bedaquiline. Monitoring ECGs should be done monthly if other QT-prolonging drugs are included in the regimen).
- Serum potassium (K+), ionized calcium (Ca++) and magnesium (Mg++) levels should be obtained at baseline and corrected if abnormal. Every effort should be made to have accurate testing for electrolytes. K+, Mg++ and ionized Ca++ should be monitored monthly while on bedaquiline. An abnormal value for electrolytes should be corrected. Most commonly, low values are due to second-line anti-TB injectable drugs.
- Whenever low potassium is detected, it should trigger urgent management with replacement and frequent repeat potassium testing (often daily) to document that the potassium is moving in the correct direction. If potassium is low, always check magnesium and calcium and replace as needed (If unable to check, strongly consider oral empiric replacement doses of magnesium and calcium). Be aware that in patients who are critically ill, low calcium levels can be simply due to hypoalbuminaemia, which has no clinical significance because the active fraction (ionized) is not affected. However, to prevent missing a second hypocalcaemic disorder, measure the ionized calcium level whenever the albumin level is low.
- Whenever significant QTcF prolongation is detected (absolute value >450 ms in males or >470 ms in females, or an increase of > 60 ms from baseline):
  - Repeat ECG to confirm prolongation.
  - Check K+, Mg++ and ionized Ca++ and correct levels if found to be abnormal. Withhold bedaquiline and injectable agent (if patient is still using) until the electrolytes have normalized.
  - If the QTcF interval remains above normal value but still below 500 ms (and the patient is stable and electrolyte values are within normal limits) repeat weekly ECGs to confirm that QTcF interval is stable.
  - If the QTc interval is >500 ms (confirmed by repeat ECG) discontinue bedaquiline and all other QT-prolonging drugs in the regimen.
- Bedaquiline and all other QT-prolonging drugs are to be discontinued if the patient develops clinically significant ventricular arrhythmia.
- If bedaquiline is stopped to deter QT prolongation, monitor ECGs at least weekly to confirm that the QTcF interval has returned to baseline.
- If cardiac symptoms appear (tachycardia, syncope, palpitations, weakness or dizziness), obtain an ECG to check the QT interval and rule out an arrhythmia.
- Because of the long half-life of bedaquiline, if the ECG has QT prolongation at week 24, ongoing weekly monitoring should take place until the QT interval normalizes (even though the drug is no longer being given).

Low or high serum electrolyte concentrations in the presence of a QT interval prolongation predisposes to arrhythmias.

Liver function monitoring. Because a high incidence of liver toxicity have been seen in patients on bedaquiline, liver enzymes should be monitored monthly. If aminotransferase elevations are accompanied by total bilirubin elevation >2x upper limit of normal (ULN), or aminotransferase elevations are >5x the upper limit of normal, bedaquiline needs to be discontinued (Box A4.1.4). Also see Chapter 12 for suggestions on the management of hepatotoxicity.

BOX A4.1.4 KEY CONSIDERATIONS IN MONITORING AND MANAGING HEPATIC TOXICITY IN PATIENTS ON BEDAQUILINE

- Alcohol and other hepatotoxic drugs should be avoided while on bedaquiline, especially in patients with diminished hepatic reserve (e.g. chronic hepatitis or cirrhosis).
- Monitor symptoms and laboratory tests (alanine transaminase (ALT), aspartate aminotransferase (AST), and bilirubin) at baseline, monthly while on treatment, and thereafter as needed.
- An increase in serum aminotransferases to >3x upper limit of the normal should be followed by repeat testing within 48 hours. Testing for viral hepatitis should be performed and other hepatotoxic medications reviewed and be considered for discontinuation.
- Evidence of new or worsening liver dysfunction (including clinically significant elevation of aminotransferases and/or bilirubin and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients on bedaquiline should prompt additional evaluation by the prescriber.
- Discontinue bedaquiline if:
  - Aminotransferase elevations are accompanied by total bilirubin elevation >2 times the upper limit of normal;
  - Aminotransferase elevations are >5 times the upper limit of normal;
  - Aminotransferase elevations persist beyond two weeks;
  - Consider other anti-TB drugs (i.e. isoniazid, rifampicin, pyrazinamide, ethionamide or PAS) as causative drug. If another drug is identified as the likely cause of drug hepatitis, consider re-challenging with bedaquiline.

Other monitoring considerations

- ***Haemoptysis and chest pain.*** Haemoptysis and chest pain were more commonly seen in one clinical trial with bedaquiline, although the reasons were unclear. Therefore, patients presenting with haemoptysis or chest pain should be clinically investigated, including chest radiograph, pulse oximetry and ECG.
- ***Pancreatitis***. Pancreatitis was not seen more commonly in clinical trials that used bedaquiline versus placebo. Nonetheless, increase in pancreatic enzymes have been observed in patients taking bedaquiline, although it was rare and not determined whether the drug was the cause. Consider a baseline lipase or amylase at the start of bedaquiline treatment, and repeat if signs of pancreatitis develop.

Safety concerns are best addressed using the active TB drug-safety monitoring and management approach, see Section A4.1.7 for more information.

A4.1.6 Drug–drug interactions with bedaquiline

As mentioned above, bedaquiline is metabolized in the liver by the CYP3A4 enzymes. Many drugs can either induce or inhibit this system, resulting in drug–drug interactions. Interaction with CYP3A4 inducers can lead to loss of efficacy of bedaquiline (due to low blood concentration from increased metabolism of the drug), and conversely, interaction with strong and moderate inhibitors of CYP3A4 can lead to higher exposure (higher blood levels) of bedaquiline.

Currently, there is no information available on how dosing should be adjusted in the face of strong drug–drug interactions. Care must be taken in prescribing certain drugs.

Co-administration of strong CYP3A4 inducers, such as rifamycins (e.g. rifampin), should be avoided while on treatment with bedaquiline *(5)*. It is not known if rifabutin, which is a weaker inducer of CYP3A4 than rifampicin can be used with bedaquiline.

Co-administration of bedaquiline with strong CYP3A4 inhibitors may increase the systemic exposure to bedaquiline, which could potentially increase the risk of adverse reactions. Therefore, the use of strong CYP3A4 inhibitors used systemically for more than 14 consecutive days should be avoided while on bedaquiline, unless the benefit of treatment with the drug combination outweighs the risk. Appropriate clinical monitoring for adverse reactions is recommended and discussed in Section A4.1.5.

Ketoconazole is an example of a strong CYP3A4 inhibitor. Co-administration of 400 mg bedaquiline once daily for 14 days and ketoconazole 400 mg once daily for four days in healthy subjects increased the exposure (AUC) to bedaquiline by 22% *(5)*.

No significant drug–drug interactions are thought to occur with pyrazinamide or isoniazid. No dose-adjustment of isoniazid or pyrazinamide is required during co-administration with bedaquiline. In a placebo-controlled clinical trial in patients on bedaquiline, no major impact of co-administration of bedaquiline on the pharmacokinetics of ethambutol, kanamycin, pyrazinamide, ofloxacin or cycloserine was observed *(5)*.

The drug–drug interactions with bedaquiline and ART are discussed in Section A4.4

Additive or synergistic QT prolongation was observed when bedaquiline was co-administered with other drugs that prolong the QT interval. Many drugs are known to prolong the QT interval and the full drug prescribing information should always be consulted before using a drug in a patient taking bedaquiline. Some of the common drugs that can prolong the QT interval include:

- Moxifloxacin, gatifloxacin (levofloxacin to a lesser degree).
- Clofazimine.
- Macrolide antibacterial drugs (erythromycin, clarithromycin, azithromycin).
- Serotonin 5-HT3 receptor antagonist (like ondansetron, an anti-nausea drug commonly used in MDR-TB).
- Azole antifungal agents (e.g., ketonazole, itraconzaole, fluconazole).
- ART. The common three drug combinations used in ART can result in QT prolongation (also see section A4.1.4).
- Some antimalarials (quinine sulfate, chloroquine).
- Some medicines to treat a psychiatric disorder (e.g. chlorpromazine, haloperidol, thioridazine).

If possible, avoid the use of QT-prolonging drugs with bedaquiline. If it is absolutely necessary to include a QT-prolonging drug, increase ECG monitoring as described in Section A4.1.5.

Drugs that lower electrolytes (i.e. injectable agents) can result in a higher potential for arrhythmias (including sudden death) due to QT prolongation. While this is not a drug–drug interaction per se, the concomitant use of injectable agents and bedaquiline do require added electrolyte monitoring as described in Section A4.1.5.

A4.1.7 Programmatic considerations for introducing bedaquiline in the management of MDR-TB

Good programmes managing drug-resistant TB will have the following goals when rolling out the use of bedaquiline.

- To provide early access to drugs to patients with limited treatment options.
- To limit the risk to the patient by monitoring for and managing adverse events.
- To protect emergence of resistance to bedaquiline.
- To ensure that the highest standards of clinical ethical conduct and human rights are respected.

Because bedaquiline is a new drug, and currently limited only to the treatment of MDR-TB, widespread field experience on its safety and efficacy is not yet available. It is necessary, therefore, that information on adverse effects monitoring and management for all patients on bedaquiline be kept track of through active TB drug-safety monitoring and management (aDSM). WHO has developed detailed descriptions of approaches to pharmacovigilance, which would generally also apply to the programmatic use of the drug at country-level *(8)*. It would be assumed that in any country programme where MDR-TB patients are treated

according to a national policy, essential infrastructure (diagnostic and clinical), drug access (budget, procurement and distribution), and data gathering have been adequately developed. All of these would be applicable to the introduction and use of bedaquiline in MDR-TB treatment programmes, and are summarised in Box A4.1.5.

BOX A4.1.5 CONSIDERATIONS FOR PROGRAMMATIC USE OF BEDAQUILINE IN MDR-TB TREATMENT AT THE COUNTRY LEVEL

- **Programmatic goals are to:**
  - Provide early access to a promising new drug to patients with limited therapeutic options.
  - Protect the efficacy of the new drug: avoid resistance arising.
  - Limit risk to the patient: monitor for and manage adverse events.
  - Ensure that highest standards of clinical ethical conduct and human rights are respected.
- **Checklist**
  - Well-functioning MDR-TB programme in place.
  - Diagnostic laboratory capability for second-line DST according to WHO-recommended procedures.
  - Clinical monitoring capability, in particular for ECG, liver function and electrolytes.
  - Quantification and drug procurement in place and the full range of necessary MDR-TB Committee available to support and monitor treatment providers.
  - Regulatory and importation issues addressed.
  - National guidelines adjusted to accommodate use of new drugs.
  - Consent forms designed and available.
  - Ethics/IRB support in place as required by local law and practices.
- **Setting up and maintaining a pharmacovigilance system for bedaquiline as per WHO policy (see chapter 11)**

A4.1.8 Clinicians checklist for eligible patients

As an aid to determining **eligibility** of a patient for assignment to a bedaquiline-containing treatment regimen, a checklist is proposed in Box A4.1.6 and a template is provided for obtaining **informed consent** from the patient before starting bedaquiline therapy.

BOX A4.6.1 CLINICIAN'S CHECKLIST OF ESSENTIAL PARAMETERS FOR SELECTION OF MDR-TB PATIENTS WITH BEDAQUILINE

Parameters	Tick Yes or No
• Patient is at least 18 years old.	☐ YES ☐ NO
• Patient is known or suspected to be diseased with a multiple-resistant strain of tuberculosis and therefore eligible for treatment with second-line anti-TB drugs.	☐ YES ☐ NO
• Additional laboratory data has been obtained on the susceptibility profile of the patient's TB isolate to the following agents: fluoroquinolones (ofloxacin and moxifloxacin), and second-line parenteral agents (kanamycin, amikacin and capreomycin).	☐ YES ☐ NO
• The drug resistance profile of the patient's isolate suggests that the WHO standard recommended regimen for treatment of MDR-TB cannot be provided.	☐ YES ☐ NO
• Clinically significant ventricular arrhythmia is absent.	☐ YES ☐ NO
• Baseline and repeat ECG shows normal QT interval.	☐ YES ☐ NO
• Aminotransferase and total bilirubin within normal limits.	☐ YES ☐ NO
• The patient's serum albumin, potassium, calcium, and magnesium have been obtained at baseline and levels are within normal limits.	☐ YES ☐ NO
• Informed consent for treatment with bedaquiline has been obtained (see Section A4.1.9).	☐ YES ☐ NO

If the answer is 'yes' to all questions, the patient can be enrolled on treatment with bedaquiline as per the algorithms in figures A4.1.1–A4.1.4.

If the answer is 'no' to any of the above, further consideration and review is needed before enrolment in a treatment regimen with bedaquiline.

Getting a 'no' response to any of the above is not an absolute contraindication to using bedaquiline, only that the situation should be reviewed and the risk benefit of bedaquiline be reconsidered under the circumstance.

A4.1.9 Educating the patient and informed consent for patients eligible for treatment with bedaquiline[1]

This section contains templates for educating the patient on the use of bedaquiline and for obtaining informed consent. These templates can be modified by a programme. The informed consent process is divided into two parts.

Instructions to a health care provider on patient education and informed consent for bedaquiline are given in Box A4.1.7.

- **Informed Consent Part I – Medication guide for patients taking bedaquiline**. The patient will receive a copy of this medication guide (Box A4.1.8).
- **Informed Consent Part II – Certificate of consent for bedaquiline.** This part is for signatures if the patient agrees to receive bedaquiline. The patient also receives a copy of this document (Box A4.1.9).

BOX A4.1.7 INSTRUCTIONS TO A HEALTH CARE PROVIDER ON PATIENT EDUCATION AND INFORMED CONSENT FOR BEDAQUILINE

Introduction

Briefly state who you are and explain to patients that you are inviting them to accept bedaquiline as part of the drug regimen necessary to treat their disease. Inform patients that they may talk to anyone they feel comfortable talking with about the drug and that they can take time to reflect on whether they want to receive it or not. Assure the patient that if they do not understand some of the words or concepts, that you will take time to explain them as you go along and that they can ask questions now or later.

Proposed text: *I am X, working for the Y Clinic. At Y Clinic, we have a new drug available for the treatment of those forms of tuberculosis that cannot easily be treated with commonly used drugs. You are suffering from a difficult-to-treat form of the tuberculosis, which is called drug-resistant TB. I am going to give you information about the drug, bedaquiline, its potential benefits, and also the potential risks associated with its use. This drug has been tested in patients like you, and has been approved for use in TB patients by the drug control authorities in the European Union and the World Health Organisation. You do not have to decide today whether or not you would want to receive this new drug. Before you decide, you can talk to anyone you feel comfortable with about the information you have received and how to respond to it.*

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.

Reasons why bedaquiline is being offered to the patient

Explain **in lay terms** why you are offering to add bedaquiline to the treatment regimen. The language used should clarify rather than confuse. Use local and

[1] Adapted from the template for Informed Consent for Clinical Studies developed by the WHO Ethics Research Committee (http://www.who.int/entity/rpc/research_ethics/InformedConsent-clinicalstudies.doc, accessed 27 March 2014).

simplified terms. Avoid using terms like pathogenesis, antibiotic, adverse effects, cardiac, hepatic, etc.

Proposed text: *Tuberculosis is a serious disease that can be fatal. There are many TB cases who are especially difficult to treat with the drugs that are currently used; some patients with resistant TB may have limited treatment options. There is a new drug that has become available recently, and that may work better. Bedaquiline has been observed to have side-effects on the heart and liver in particular, and special tests will be offered to you during treatment to check for these.*

Explain how the treatment will be taken by the patient

Briefly state the type of intervention that will be undertaken. This will be expanded upon in the procedures section but it may be helpful and less confusing to the participant if they know from the very beginning that the drug will be taken by mouth for a period of six months, along with several other drugs administered by mouth or by injection.

Proposed text: *You will need to take four tablets of bedaquiline daily for two weeks, and two tablets on Mondays, Wednesdays and Fridays for a further five and a half months thereafter. It would be necessary to take these tablets here at the clinic in the morning. There will be other drugs to take also for a total of 20 months at least. Bedaquiline is best taken with a light meal. It is important to take the medication as prescribed to avoid the further development of resistance to the drugs you are taking.*

Explain to the patient that taking bedaquiline is their choice (it is voluntary)

Indicate clearly that they can choose to receive the drug or not. State what the alternative – in terms of the treatment offered by the clinic – will be, if they decide not to accept bedaquiline as part of their treatment. State, *only if it is applicable,* that they will still receive all the services they usually do whether they choose to take the drug or not. This can be repeated and expanded upon later in the form as well, but it is important to state clearly at the beginning of the form that receiving the drug is voluntary so that the other information can be heard in this context.

Example: *Your choice to receive bedaquiline for treating your disease is entirely voluntary. It is your choice whether to receive it or not. Whether you choose to accept the medication or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to receive bedaquiline, you will be offered the treatment that is routinely offered in this clinic/hospital for drug resistant tuberculosis, and we will tell you more about it later. You may change your mind later and stop receiving bedaquiline even if you agreed earlier.*

Go over the medication guide for patients taking bedaquiline (See Box A4.1.8)

Go over each section of the medication guide with the patient.

Write in the contact information of one or more persons at the bottom of the medication guide.

BOX A4.1.8

Informed Consent Part I:

Medication guide for patients taking bedaquiline tablets

Read this medication guide before you start taking bedaquiline and each time before your monthly visit. This information does not tell your health care provider about your medical treatment or any medical conditions.

What is the most important information i should know about bedaquiline?

Bedaquiline is a drug used to treat multidrug-resistant tuberculosis (MDR-TB) lungs in people with limited treatment options. MDR-TB is a serious disease that can result in death and for which there are few treatment choices. More people treated with bedaquiline cleared TB from their sputum compared to people who did not receive bedaquiline. In one clinical trial, fewer deaths were seen in people who were not treated with bedaquiline compared to people who did receive bedaquiline.

It is important to complete the full course of treatment of bedaquiline and your other TB medicines and not skip doses. Skipping doses may decrease the effectiveness of the treatment and increase the likelihood that your TB disease will not be treatable by bedaquiline or other medicines.

Bedaquiline can cause serious side-effects.

- Heart rhythm problems can happen with bedaquiline.

It is not known if bedaquiline is safe in:

- Children under 18 years of age
- Pregnancy
- In patients with heart, kidney, liver or other health problems.

Before you take bedaquiline, tell your health care provider if:

- You have had an abnormal heart rhythm or other heart problems.
- Anyone in your family has or has had a heart problem called ‘congenital long QT syndrome’.
- You have liver or kidney problems or any other medical conditions, including HIV infection.
- You are pregnant or plan to become pregnant. It is not known if bedaquiline will harm your unborn baby.
- You are breastfeeding or plan to breastfeed. It is not known if bedaquiline passes into breast milk. You and your health care provider should decide if you will take bedaquiline or breastfeed.
- You are taking any prescription and non-prescription medicines, vitamins and herbal supplements.

How should I take bedaquiline?

- Bedaquiline must always be taken with other medicines to treat TB. Your health care provider will decide which other medicines you should take with bedaquiline.
- Always take bedaquiline with a light meal.
- Swallow the tablets whole with water.

- Take bedaquiline for a total of 24 weeks (6 months).
  - Week 1 and Week 2: Take 400 mg (4 tablets) once a day, 7 days a week
  - Week 3 to Week 24: Take 200 mg (2 tablets) three times a week. For example, you may take bedaquiline on Monday, Wednesday and Friday of every week.
- You will need to take your other TB medicines for longer than 24 weeks, and at least for 20 months in total (the injectable drug is usually given for up to 8 months).
- Your treatment will be provided under directly observed treatment (DOT), with a patient-centred approach, which means that a health care provider will accompany you during the treatment and that your information, psychological and material needs will be addressed in order to enable your adherence to treatment.
- Do not skip bedaquiline doses. If you skip doses, or do not complete the total 24 weeks of bedaquiline your treatment may not work as well and your TB may be harder to treat.
- If for some reason you miss a dose, inform the person responsible for your treatment right away, they will tell you what to do.

What should I avoid while taking bedaquiline?

- You should not drink alcohol while taking bedaquiline.
- There are some medications that cannot be taken safety with bedaquiline. Make sure to inform your doctor if you are taking medicines or if medicines are recommended to you by a health care practitioner while you are on treatment for TB with bedaquiline.

What are the possible side-effects of bedaquiline?

- Serious heart rhythm changes. Tell your health care provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you faint. Your heart will be monitored periodically with a machine that checks that the heart rhythm is normal.
- Liver problems (hepatotoxicity). Liver toxicity can present in many ways. Tell your doctor of symptoms such as nausea or vomiting, stomach pain, fever, weakness, itching, unusual tiredness, loss of appetite, light coloured stools, dark colored urine, yellowing of your skin or yellowing of the white of your eyes.
- Other side-effects of bedaquiline include nausea, joint pain, headache, an abnormal laboratory test associated with damage to the pancreas, coughing up blood, chest pain, loss of appetite, and/or rash.

It is possible that it may also cause some problems that we are not aware of. However, you will be followed closely for any unwanted effects or any problems. Other medicines to decrease the symptoms of the side-effects or reactions may also be given.

Always tell your health care provider of any side-effects or problems you are having. Sometimes because of side-effects bedaquiline or other drugs may need to be stopped.

What monitoring tests do I need while on bedaquiline?

- You will need the same monitoring test that all patients on MDR-TB treatment need. In addition, you will need heart monitoring, extra blood tests for the liver and your electrolytes. Consult with your health-care provider about the appropriate schedule of all your monitoring tests and regular doctor visits.

General information about the risk versus the benefit of taking bedaquiline

- RISK: It is possible that you will be at greater risk of not feeling well than you would otherwise because of certain side-effects due to the drug. It is possible that adverse side-effects could be serious and even result in death.
- BENEFIT: There is a greater chance that you will be cured of tuberculosis than if you did not take the medicine. You will possibly also become better very much sooner than if you only took the standard medicines for treatment of resistant TB. Also, it is probably less likely that the drugs you are taking will develop resistance if you are taking bedaquiline.

Confidentiality and sharing of information

- Because bedaquiline is a new drug for which we have limited experience, we are collecting information on patients taking it.
- The information that we collect from you will be kept confidential and no one but the clinical staff will be able to see your medical information.
- Any information collected to help us better use the drug in future patients will be unlinked to your name (made anonymous) before we share or analyse it.

Costs

- If you choose to take bedaquiline and cannot afford it, it may be provided free of charge to you. Many programmes will provide bedaquiline free of charge to all patients whether or not they can afford it.

Right to refuse or withdraw

- You do not have to agree to take bedaquiline if you do not wish to do so and refusing to accept the drug as part of your treatment schedule will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic.
- If you agree to take bedaquiline, you may choose to discontinue it at any point for any reason without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way.

Contact person

If you have any questions, you may contact any of the following persons:

Name_____. Title_____. Phone_____.

Name_____. Title_____. Phone_____.

Name_____. Title_____. Phone_____.

Name of responsible physician: _____

Name of clinic/hospital/institution: _____

BOX A4.1.9

Informed Consent Part II:
Certificate of consent

This section should be written in the first person and have a statement similar to the one in bold below. If the participant is illiterate but gives oral consent, a witness must sign the relevant section below. The person going over the informed consent must sign this form. The certificate of consent should avoid statements that have "I understand…." phrases. The understanding should perhaps be better tested through targeted questions during the reading of the information sheet, or through the questions being asked at the end of the reading of the information sheet, if the patient is reading the information sheet him/herself.

Example: *I have read the provided information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent to receive bedaquiline for treating the drug-resistant tuberculosis disease that I am suffering from.*

Print Name of Patient: _____

Signature of Patient: _____

Date: _____

Day/month/year

If illiterate, a literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the care providers). Patients who are illiterate should include their thumbprint.

I have witnessed the accurate reading of the consent form to the potential recipient of bedaquiline, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness:_____ AND Thumbprint of patient

Signature of witness: _____ or

Date: _____

Day/month/year

Statement by the person taking consent

I have accurately read out the information sheet to the potential bedaquiline recipient, and to the best of my ability made sure that the patient understands that the following will be done:

1. Special tests will be conducted to verify eligibility for receiving bedaquiline. These will include ECG assessments, blood tests and additional laboratory tests to determine the full drug resistance profile of the patient's infecting isolate;
2. Tests will be repeated at regular intervals, and are necessary to enable proper monitoring of response to treatment, both from an efficacy and a safety point of view; and
3. Bedaquiline will be administered as part of the drug regimen for a period of six months.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this informed consent form has been provided to the participant.

Print name of person taking the consent: _____

Signature of person taking the consent: _____

Date: _____

Day/month/year

A4.1.10 References

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ANNEX 4.2

'How-to' guide on the use of delamanid for MDR-TB treatment

A4.2.1 Background on delamanid

Introduction

Delamanid is a nitro-dihydro-imidazo-oxazole derivative, inhibiting a novel target in *Mycobacterium tuberculosis* cell wall mycolic acid synthesis *(1)*. The drug received marketing authorization from the Committee for Medicinal Products for Human Use for the treatment of MDR-TB patients in the European Union *(2)*. Delamanid has demonstrated potent pre-clinical *in vitro* and *in vivo* activity against both drug-susceptible and drug-resistant strains of *M. tuberculosis (1)*. The evidence for efficacy and safety has been gathered primarily in a two-month Phase II, multicentre, randomized, double-blind, stratified (by extent of pulmonary disease), placebo-controlled clinical trial in three parallel groups of male and female patients (18–64 years old) with pulmonary, sputum culture positive MDR-TB *(3)*. That study was followed by a six-month, open-label, multicentre clinical trial in which subjects who successfully completed the initial two-month study were eligible to enrol *(4)*.

In interim policy guidance issued by the WHO for the use of delamanid in conjunction with other WHO-recommended MDR-TB treatment regimens *(5)*, delamanid is placed with anti-TB drugs belonging to Group 5, primarily because of limited data on efficacy and long-term safety in the treatment of DR-TB. In this annex, recommendations on the therapeutic use of the drug follow the WHO interim policy guidance. WHO will review, revise and/or update the interim guidance *(5)* as additional information on efficacy and safety become available. This may result in the modification of this annex, and the WHO website should be checked regularly for updates.

Key facts about delamanid

- Delamanid is active against drug-susceptible and drug-resistant *M. tuberculosis* strains. Specifically, it inhibits mycobacterial cell wall synthesis by interfering with the biosynthesis of methoxy-mycolic and keto-mycolic acids. *In vitro* studies demonstrated that the drug is at least as potent as isoniazid *(1)*. Unlike isoniazid, however, delamanid does not inhibit α-mycolic acid synthesis.
- Delamanid is highly active against intracellular *M. tuberculosis* in human macrophages.
- There is no known cross-resistance of delamanid with any existing anti-TB drugs.

- Strong bactericidal and sterilizing activity against *M. tuberculosis* organisms have been shown in pre-clinical laboratory and animal experiments *(1)*.
- There are no published data on the use of delamanid in pregnant women, patients older than 65 years, or in patients with extra-pulmonary tuberculosis. There is limited data on delamanid use in patients with HIV infection, in children, and in patients with XDR-TB.
- Delamanid is metabolized by cytochrome P450 enzymes like CYP3A4, and formation of its main metabolite is regulated by plasma albumin. It is neither an inducer nor an inhibitor of key drug metabolizing enzymes, and hence unlikely to have a significant impact on concentrations of companion drugs.
- Delamanid absorption is increased after a standard meal.
- QT prolongation can occur with delamanid. QTc prolongation is closely correlated with the major delamanid metabolite DM-6705.
  - Concentration effect analysis demonstrated an association between DM-6705, a globally appearing metabolite of delamanid, and the QT effect, which is consistent with time-matched ECG analysis and supported by pre-clinical data.
  - The complete metabolic profile of delamanid in humans has not yet been fully elucidated. Therefore the potential for drug–drug interactions of clinical significance to occur with delamanid and the possible consequences – including the total effect on the QTc interval – cannot be predicted with confidence.
  - The delamanid safety profile has been characterized through six months of treatment. A dose-dependent effect on QTc was observed with mean changes in QTc of 14.6 ms and 18.9 ms after delamanid 100 mg BID + optimized background regimen and 200 mg BID + optimized background regimen, respectively.
  - Maximal change in QTcF occurred after eight weeks of treatment. Beyond this period (and until the end of the treatment) QTc prolongation did not increase further.
  - QTcF outlier analysis demonstrated that most patients who had a biomarker of cardiac repolarization risk had, in addition to delamanid use, other previously identified risk factors, including female sex, cardiovascular disease including various AV and bundle branch blocks, and hypokalaemia.
  - No cases of torsades de pointes or recurrence of previous dysrhythmias have been reported to date following delamanid use.
  - Concomitant use with drugs that prolong the QT interval may cause additive QT prolongation and should be avoided if at all possible.

- Delamanid is generally well-tolerated. Other than QT prolongation, adverse events observed in clinical studies with delamanid were generally mild to moderate, not different from those seen in control subjects receiving placebo, and were consistent with known side-effect profiles of drugs in the optimized background regimen. Hepatotoxicity was not a concern with the use of delamanid.
- Mortality associated with use of delamanid has not been reported in published clinical studies.
- Drug–drug interaction studies in healthy subjects show no clinically significant interactions when delamanid is co-administered with tenofovir, efavirenz or lopinavir/ritonavir.

A4.2.2 Using delamanid in patients with MDR-TB

WHO interim policy guidance *(5)*

WHO issued interim policy guidance in October 2014 on the use of delamanid *(6)*. The interim policy guidance is based on an evidence assessment and advice provided by an Expert Group convened by the WHO Global TB Programme in Geneva, Switzerland and resulted in the recommendation that **delamanid may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB (conditional recommendation; very low confidence in estimates of effect).**

In view of the insufficient experience with the use of delamanid under the different conditions that may be expected in treatment programmes and the uncertainty about its overall added value in the treatment of MDR-TB patients, WHO recommends that the use of delamanid in the treatment regimen of MDR-TB be made subject to the following five conditions.

1. **Proper patient inclusion:** The current recommendation for the use of delamanid applies to adults (age ≥18 years) with pulmonary MDR-TB disease, including people living with HIV. Special caution and proper clinical judgment should be applied when delamanid is used in people 65 years and older, or in those with diabetes, hepatic or severe renal impairment, or those who use alcohol or other substances, given that data on efficacy and safety under such conditions are extremely limited or unavailable.

   Use of the drug in children and in pregnant and breastfeeding women is not currently advised due to a lack of evidence on safety, efficacy and proper dosing in these groups.

   Because delamanid is shown to cause prolongation of the QT interval, patients with a QTcF >500ms should not receive the drug.

   When an effective and reasonably well-tolerated MDR-TB regimen can be composed with conventional second-line drugs, the routine addition of delamanid may not be warranted and the implications of additional health service costs should be considered. MDR-TB patients in whom delamanid may have a particular role include those with:

   - higher risk for poor outcomes (e.g. drug intolerance or contraindication, extensive or advanced disease);
   - additional resistance to quinolones or injectable drugs;
   - XDR-TB (see figure A4.2.5 for additional considerations to apply when the drug is used in XDR-TB patients).

   While patients with exclusive extrapulmonary disease were not included in the delamanid trials, there is no absolute contraindication for its use in such patients and inclusion may be considered where any potential harm that delamanid may cause is offset by the benefit expected.

2. **Adherence to the principles of designing a WHO-recommended MDR-TB regimen:** Delamanid is intended to be introduced alongside other anti-TB drugs in composing an effective second-line regimen based on WHO guidelines; the cardinal rules governing the general composition and duration of MDR-TB regimens remain the same.

a. The WHO-recommended MDR-TB treatment regimen is typically composed of at least pyrazinamide and four second-line drugs considered to be effective (based on DST and/or previous use and/or drug resistance surveillance data): a fluoroquinolone (preferably later-generation), a second-line injectable agent, and two bacteriostatic drugs, preferably prothionamide or ethionamide plus cycloserine or p-aminosalicylic acid *(6)*. As yet, there is no evidence that delamanid is equivalent to other second-line drugs or can be effectively used as a replacement.

b. MDR-TB patients with confirmed resistance or intolerance to either fluoroquinolones or the second-line injectable drugs represent a particular treatment challenge. In such cases, delamanid may have a crucial role to play in strengthening a regimen, bringing the number of drugs likely to be effective to a minimum of four, and reducing the risk of acquisition of additional resistance and progression towards XDR-TB.

c. A DST method for delamanid is undergoing validation through the SRL network; WHO will evaluate the validation data in order to issue recommendations for DST of delamanid later in 2015. DSTs for second-line drugs other than fluoroquinolones and injectables (e.g. kanamycin, amikacin, capreomycin) are not accurate or reproducible, and MDR-TB patients may respond poorly to treatment for reasons other than drug resistance. A change in medication may, therefore, have to be based on persistence of positive sputum culture, or reversion to positive following initial culture conversion, rather than DST.

d. While experience in the use of delamanid in the management of XDR-TB is limited, there may be a benefit given the limitations in designing an effective regimen. In such patients, delamanid may lower the need to include other drugs belonging to Group 5 that have unproven anti-TB activity or a lower safety profile. However, special caution is necessary when delamanid is used with a fluoroquinolone or a Group 5 drug, given the potential for synergistic drug–drug interactions effects, particularly on QT prolongation.

e. There are currently no data on the simultaneous use of bedaquiline and delamanid in the same patient. Until such data become available, no recommendation on the joint administration of these two medicines is possible within the scope of this interim guidance.

f. In line with general principles of TB therapeutics, delamanid should not be introduced into a regimen in which the other companion drugs are known or believed to be ineffective, or are failing to show effectiveness. This means that delamanid should not be added alone to a failing regimen. Given the emergence of resistance to delamanid observed in the available data, all possible measures should be taken to protect the efficacy of the drug.

g. The recommended dose of delamanid in adults is 100 mg twice a day, irrespective of body weight, for a period of six months. As bioavailability was higher when given after a standard meal, delamanid should preferably be administered during or just after a meal. There was no evidence that delamanid 200mg twice a day was more effective than the 100 mg dose, and the higher dose was associated with higher rates of adverse events including QT interval prolongation. It should be particularly noted that supervision of delamanid intake should be adapted to twice a day.

3. **Treatment is closely monitored:** Adherence to best practices when administering treatment is imperative to ensure optimal drug effectiveness and safety. It is therefore recommended that the following measures are in place.

a. Sound treatment and management protocols, including clear patient eligibility criteria, locally appropriate procedures for informed consent, and defined roles and responsibilities of all professionals involved. Safety concerns are best addressed through active pharmacovigilance *(7)*. The treatment protocols should allow for the prospective capture of data on key variables for both effectiveness and safety, making sure that good practices (such as those applied in the conduct of observational studies) are adhered to.

b. Treatment protocols are preferably submitted to and approved by the relevant national authority in the country prior to patient enrolment on treatment.

c. Preferably, oversight of treatment programmes is provided by an independent group of experts in clinical management and public health (e.g. a national MDR-TB advisory group).

d. The potential for emergence of delamanid resistance during the course of therapy requires that all measures to enable patient adherence are in place before starting treatment.

4. **Active pharmacovigilance and proper management of adverse drug reactions and prevention of drug–drug interactions:** Alongside measures to monitor treatment adherence and effectiveness, special vigilance is needed for monitoring adverse events, including potential reactions to delamanid that are as yet undescribed.

a. Given that the results of Phase III trials are expected in the next few years, it is particularly important that the introduction of delamanid is accompanied by an enhanced monitoring for adverse events. For this purpose, spontaneous reporting is not expected to represent an appropriate level of care and active pharmacovigilance techniques, such as active TB drug-safety monitoring and management (aDSM), will be needed to improve the early detection of adverse drug reactions (see Chapter 11).

b. Any adverse event should be reported to the national pharmacovigilance centre. As for any other drug in an MDR-TB regimen, the patient should be encouraged to report to the attending health worker any adverse event that occurs during the time the drug is being taken. Such occurrences should also trigger a rapid response to manage untoward effects in the patient.

c. When introducing delamanid into a regimen, there is also the potential for its interaction with other medications administered concurrently, with additive or synergic adverse effects. Other second-line drugs that are likely to be administered with delamanid, notably fluoroquinolones and clofazimine, may potentially increase the risk of cardiotoxicity. Although there are data showing QT prolongation when delamanid is administered simultaneously with levofloxacin, no data are available on concomitant use with moxifloxacin and/or clofazimine. Also, some antiretroviral medications can cause modest QT prolongation, especially ritonavir-containing regimens. Therefore, monitoring of patients for cardiac dysrhythmias or QT prolongation (i.e. using ECG), and for electrolyte imbalances (especially serum potassium) that can predispose to cardiotoxicity is imperative.

d. Drug–drug interaction studies of delamanid with tenofovir, efavirenz and lopinavir/ritonavir, respectively, conducted among healthy individuals who did not have HIV or TB, suggested that no dose adjustments were needed when delamanid was used with any of these antiretroviral agents. However, there is no published evidence so far on the use of delamanid in HIV-infected MDR-TB patients on ART. Therefore, people living with HIV

who will be receiving delamanid as part of MDR-TB treatment should have their ART regimens designed in close consultation with HIV clinicians and ART specialists.

e. Lastly, caution is advised in patients with pre-existing health conditions that may be exacerbated or worsened by delamanid. Currently there are no data on the efficacy and safety of delamanid in patients with co-morbid conditions such as diabetes, liver and/or renal dysfunction, malignancies, alcohol and substance use, and therefore careful screening for these conditions prior to treatment initiation is advised. Hypersensitivity reactions to delamanid have not yet been described, but vigilance is nevertheless required.

5. **Patient informed consent:** Health workers should follow the due process for informed consent by ensuring that the patient: i) is aware of the novel nature of delamanid; ii) appreciates the reason why the drug is being proposed to be included in their treatment regimen; and iii) recognizes the possible benefits and potential harms, including the uncertainties that surround outcomes. This informed consent process applies to all situations where delamanid is employed, including under compassionate use programmes. In some settings, as per national or local policy, it is required that the informed consent is made in writing for enrolment on MDR-TB treatment.

Absolute contraindications, relative contraindications, and cautions

There are a number of relative and absolute contraindications for delamanid. For relative contraindications, delamanid should generally be avoided but there may be exceptional circumstances where individual clinical judgement of the potential risks and benefits might lead to a decision to use the drug.

Absolute contraindications:

- **Patient refuses to consent.** The patient decides to not accept the medication after being properly counselled and informed about benefits and risks associated with the use of delamanid (a suggested informed consent form is provided in Section 5.9).
- **Hypersensitivity to the active substance or to any of the excipients in the formulation**
- **Serum albumin <2.8 g/dL** (see Section A4.2.6)
- **High risk for cardiac complications**. Patient has a QT interval >500 ms, history of torsade de pointes or cardiac ventricular arrhythmias or severe coronary artery disease.

Relative contraindications:

- **Children or persons under 18 years old.** The safety and dosing of delamanid have not been established in children and its use in this group should be avoided (pediatric trials are ongoing to address these two issues)[1].
- **Pregnancy.** Reproduction studies performed in animals have shown reproductive toxicity. While animal reproduction studies are not always predictive of human response, delamanid should not be used during pregnancy.
- **Nursing mothers.** It is not known if the metabolites of delamanid are present in breast milk of humans. Because of the potential for adverse reactions in nursing infants, a decision

[1] https://clinicaltrials.gov/ct2/show/NCT01859923?term=delamanid&rank=1; https://clinicaltrials.gov/ct2/show/NCT01856634?term=delamanid&rank=4, accessed 23 March, 2014)

should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Cautions:

- **Geriatric use (use in the elderly).** Clinical studies of delamanid did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently to younger patients.
- **Hepatic impairment.** No dose adjustment is necessary for delamanid in patients with mild hepatic impairment. Delamanid has not been studied in patients with moderate or severe hepatic impairment and should be used with caution in these patients and only when the benefits outweigh the risks.
- **Renal impairment.** Less than 5% of an oral dose of delamanid is recovered from urine. Mild renal impairment (50 mL/min < CrCLN < 80 mL/min) does not appear to affect delamanid exposure and no dose adjustment is considered necessary in patients with mild or moderate renal impairment. Delamanid has not been studied in patients with severe renal impairment or end stage renal disease requiring haemodialysis or peritoneal dialysis and should be used with caution in these patients and only when the benefits outweigh the risks.
- **Co-administration with anti-HIV medication.** The use of delamanid in patients also requiring treatment for HIV infection is addressed in Section A4.2.4.
- **Co-administration with QT-prolonging drugs.** The monitoring of the QT segment in patients receiving delamanid is addressed in Section A4.2.5.
- **Serum potassium outside the normal range.** Because QT prolongation is associated with hypokalaemia and arrhythmias are associated with hypokalaemia or hyperkalaemia, potassium should be corrected before starting delamanid and carefully monitored if abnormal ECG is observed.
- While patients with exclusive **extrapulmonary disease** were not included in the delamanid trials, there is no absolute contraindication for its use in such patients and inclusion may be considered where any potential harm that delamanid may cause is offset by the benefit expected.
- **Concurrent or previous use of bedaquiline.** No data exist about concomitant use of delamanid and bedaquiline. Given the short half-life of delamanid (38 hours), a five-day washout period of delamanid is recommended before using bedaquiline.
- **Concurrent use of delamanid with Group 5 second-line anti TB drugs.** No data exist about concomitant use of delamanid and Group 5 drugs, though its main metabolizing enzymes are unlikely to have a significant impact on concentrations of companion drugs.
- **Strong inducers/inhibitors of CYP3A.** Because strong inducers (i.e. carbamazepine, phenobarbital, phenytoin) and strong inhibitors (i.e. ketoconazole, itrachononazole, clarithromycin) of CYP3A will affect the safety, tolerability or efficacy of delamanid to an extent that is not yet known (no public data exist on interaction with these drugs), alternative to those drugs should be offered to patients before starting use of delamanid (see Section A4.2.4 for known interactions of some antiretrovirals with delamanid). If co-administration of delamanid with strong inhibitors is necessary then perform more frequent monitoring with ECGs throughout the delamanid treatment period.

Section A4.2.8 offers a clinician's checklist to confirm clinical eligibility and to indicate when increased monitoring is indicated.

Length of treatment of delamanid-containing regimens

The overall duration of MDR-TB treatment must conform to the WHO criteria: Minimum requirement is for eight months of intensive phase treatment, followed by at least a further 12 months of continuation phase treatment. Delamanid is used for six months (24 weeks) (see Table A4.2.1) as part of the intensive treatment phase.

Table A4.2.1 Length of treatment of delamanid-containing regimens

Drug	Suggested duration of treatment (in months) when delamanid is added to the standard WHO regimen[a]
Delamanid (oral)	6
Injectable drug	6–8
Other oral anti-TB drugs	20

[a] With XDR-TB, the total treatment can be extended to 24 months; however delamanid is still only used for the initial six months.

The dose of delamanid

Delamanid comes in 50 mg tablets. The dosing schedule of the medication is as follows:

- Delamanid 100 mg (2 tablets of 50 mg) twice daily (200 mg total daily dose). Delamanid should be given seven days per week for 24 weeks together with second-line drugs for MDR-TB treatment.
- Delamanid can be taken at the same time as the other anti-TB drugs in the regimen and should be taken with a standard meal.

At this time, dose adjustment is not considered to be required with concomitant use of weak inhibitors or inducers CYP3A4 isozymes.

A4.2.3 Constructing a delamanid-containing regimen for the treatment of MDR-TB

The following scenarios are based on the principles of regimen design in Chapter 5 of this Handbook. They cover the most common indications for the inclusion of delamanid in a MDR-TB regimen.

Note that all suggested regimens in this section are examples and will likely vary based on the individual clinical circumstances and availability of companion drugs. The regimens and algorithms have not necessarily been tested in either research or field conditions and what is proposed is largely based on expert opinion.

Furthermore, the scenarios presented here for delamanid, and in particular Scenario 0, are based on the observation from limited clinical data indicating that the addition of delamanid to regimens for treating MDR-TB that were resistant to rifampicin and isoniazid but otherwise susceptible to second-line anti-TB drugs, gave the highest efficacy whereas use of delamanid as part of the best available regimens that could be constructed for treating XDR-TB was associated with the lowest efficacy *(2)*.

If ethambutol is used in MDR-TB treatment together with delamanid (e.g. in Scenarios 0–4 described in Figures A4.2.0 to A4.2.4), it should be noted that delamanid increases steady state exposures to ethambutol, on average, by approximately 25% *(2)*. This is not considered to be clinically significant in that delamanid is not recommended to be used in patients with severe renal impairment.

Of particular importance is the fact that QTcF prolongations of more than 60ms from baseline in patients receiving delamanid in clinical studies were associated with concomitant fluoroquinolone use. Where co-administration is unavoidable in order to construct an adequate treatment regimen for MDR-TB, frequent monitoring of ECGs is recommended throughout the full delamanid treatment period (see Section A4.2.5).

Figure A5.2.0. Scenario 0: MDR-TB plus evidence of (or unknown) susceptibility to Groups 2 and 3 agents and with risk of poor treatment outcome[a]

STEP 1	**Choose an injectable (Group 2)**	**Kanamycin** **Amikacin** **Capreomycin**
STEP 2	**Choose a higher generation fluoroquinolone (Group 3)**	**Levofloxacin** **Moxifloxacin**
	Use a later generation fluoroquinolone. Avoid moxifloxacin when using delamanid.	
STEP 3	**Add two Group 4 drugs**	**Cycloserine/terizidone** **Para-aminosalicylic acid (PAS)** **Ethionamide/prothionamide**
	Use at least two Group 4 drugs thought to be effective.	
STEP 4	**Add Group 1 drugs**	**Pyrazinamide** **Ethambutol**
	Pyrazinamide is routinely added in most regimens; ethambutol may also be added if the criteria for an effective drug are met.	

STEP 5	**Add delamanid**	**Delamanid** **Linezolid** **Clofazimine** **Amoxicillin/clavulanate** **Imipenem/cilastatin** **Meropenem** **High-dose isoniazid** **Clarithromycin** **Thioacetazone**
	Delamanid is routinely added in this scenario as a Group 5 drug.	

[a] Extensive disease, intolerance to any of the drugs, or increased likelihood of acquired resistance, treatment failure or death.

Figure A4.2.1. Scenario 1: MDR-TB plus resistance to fluoroquinolones with no injectable resistance

STEP 1	**Choose an injectable (Group 2)**	**Kanamycin** **Amikacin** **Capreomycin**
STEP 2	**Choose a higher generation fluoroquinolone (Group 3)**	**Levofloxacin** **Moxifloxacin**
	Levofloxacin and moxifloxacin can overcome ofloxacin resistance in some circumstances; for most patients the fluoroquinolone is tolerated well and worth using if there is a chance of efficacy. Both moxifloxacin and levofloxacin (to a lesser extent) are known to have additive QT prolonging effects and should be used with caution when delamanid is also included (see also Section A5.4 below). Note: • If only ofloxacin DST is known (and resistant) use levofloxacin unless it is thought to be compromised (previous use in a failing regimen or known contact with a patient with levofloxacin resistance). • If levofloxacin resistance is likely (previous exposure, documented resistance, and/or known contact with a patient with levofloxacin resistance), the use of moxifloxacin can be considered. • If moxifloxacin resistance is likely and/or history suggests it has not been effective (e.g. if used in a failing regimen for an extended time), it should not be used; levofloxacin can be considered instead, given its lower (but not absent) overlapping toxicity with delamanid. Otherwise, fluoroquinolones might be excluded from use in the regimen. • Use of the combination of moxifloxacin with delamanid and clofazimine (three drugs that strongly prolong the QT interval) should be avoided.	
STEP 3	**Add Group 4 drugs**	**Ethionamide/prothionamide** **Cycloserine/terizidone** **Para-aminosalicylic acid (PAS)**
	Use all drugs thought to be effective.	

STEP 4	**Add Group 1 drugs**	**Pyrazinamide** **Ethambutol**
	Pyrazinamide is routinely added in most regimens; ethambutol may also be added if the criteria for an effective drug are met.	
STEP 5	**Add delamanid and other Group 5 drugs as necessary** *NOTE: Bedaquiline is avoided as an additional Group 5 drug if delamanid is being used*	**Delamanid** **Linezolid** **Clofazimine** **Amoxicillin/clavulanate** **Imipenem/cilastatin** **Meropenem** **High-dose isoniazid** **Clarithromycin** **Thioacetazone**
	Delamanid routinely added. Group 5 drugs other than delamanid are added based on the number of Group 4 drugs for which there is a high degree of confidence in efficacy: Confidence in all three Group 4 drugs: adding other Group 5 drugs is not necessary. Confidence in only two Group 4 drugs: add **one** other Group 5 drug. Confidence in only one Group 4 drugs: add **two** other Group 5 drugs. Confidence in no Group 4 drugs: add **three** other Group 5 drugs.	

Figure A4.2.2. Scenario 2: MDR-TB plus resistance or severe intolerance to all second-line injectable agents

STEP 1		**Kanamycin** **Amikacin** **Capreomycin**
	If the clinical history or DST suggest that resistance exist for all second-line injectable or in case of serious adverse event (nephrotoxicity or hearing loss) consider not using an injectable.	
STEP 2	**Choose a higher generation fluoroquinolone (Group 3)**	**Levofloxacin** **Moxifloxacin**
	Use a later generation fluoroquinolone. Avoid moxifloxacin when using delamanid.	
STEP 3	**Add Group 4 drugs**	**Ethionamide/Prothionamide** **Cycloserine/Terizidone** **Para-aminosalicylic acid (PAS)**
	Add all Group 4 drugs thought to be effective.	
STEP 4	**Add Group 1 drugs**	**Pyrazinamide** **Ethambutol**
	Pyrazinamide is routinely added in most regimens; ethambutol may also be added if the criteria for an effective drug are met.	

STEP 5	**Add delamanid and other Group 5 drugs as necessary** *NOTE: Bedaquiline is avoided as an additional Group 5 drug if delamanid is being used*	**Delamanid** **Linezolid** **Clofazimine** **Amoxicillin/clavulanate** **Imipenem/cilastatin** **Meropenem** **High-dose isoniazid** **Clarithromycin** **Thioacetazone**
	Delamanid routinely added. Group 5 drugs other than delamanid are added based on the number of Group 4 drugs for which there is a high degree of confidence in efficacy: • Confidence in all three Group 4 drugs: adding other Group 5 drugs is not necessary. • Confidence in only two Group 4 drugs: add **one** other Group 5 drug. • Confidence in only one Group 4 drugs: add **two** other Group 5 drugs. • Confidence in no Group 4 drugs: add **three** other Group 5 drugs.	

Figure A4.2.3. Scenario 3: MDR-TB plus two or more Group 4 drugs compromised (Group 2 and 3 drugs effective)

STEP 1	**Choose an injectable (Group 2)**	**Kanamycin** **Amikacin** **Capreomycin**
STEP 2	**Choose a higher generation fluoroquinolone (Group 3)**	**Levofloxacin** **Moxifloxacin**
	Use a later generation fluoroquinolone. Avoid moxifloxacin when using delamanid.	
STEP 3	**Add Group 4 drugs**	**Ethionamide/Prothionamide** **Cycloserine/Terizidone** **Para-aminosalicylic acid (PAS)**
	Add the Group 4 drug thought to be effective.	
STEP 4	**Add Group 1 drugs**	**Pyrazinamide** **Ethambutol**
	Pyrazinamide is routinely added in most regimens; ethambutol may also be added if the criteria for an effective drug are met.	

STEP 5	**Add delamanid and other Group 5 drugs as necessary** *NOTE: Bedaquiline is avoided as an additional Group 5 drug if delamanid is being used*	**Delamanid** **Linezolid** **Clofazimine** **Amoxicillin/clavulanate** **Imipenem/cilastatin** **Meropenem** **High-dose isoniazid** **Clarithromycin** **Thioacetazone**

Delamanid routinely added. Group 5 drugs other than delamanid are added based on the number of Group 4 drugs for which there is a high degree of confidence in efficacy:

- Confidence in all three Group 4 drugs: adding other Group 5 drugs is not necessary.
- Confidence in only two Group 4 drugs: add **one** other Group 5 drug.
- Confidence in only one Group 4 drugs: add **two** other Group 5 drugs.
- Confidence in no Group 4 drugs: add **three** other Group 5 drugs.

Figure A4.2.4. Scenario 4: XDR-TB

STEP 1	**Choose an injectable (Group 2)**	**Kanamycin** **Amikacin** **Capreomycin**

- If patient's strain is still susceptible to one of the injectable drugs, include in the regimen.
- If resistant to all injectable agents, consider not using any injectable or using one that the patient has never received based on clinical judgement (see Box 5.3 in chapter 5).

STEP 2	**Choose a higher generation fluoroquinolone (Group 3)**	**Levofloxacin** **Moxifloxacin**

In addition to determining organism susceptibility to ofloxacin, every attempt should be made to specifically determine susceptibility also to moxifloxacin and levofloxacin.

- If only ofloxacin DST is known (and resistant) use levofloxacin unless thought to be compromised (previous use in failing regimen or known contact with a patient with levofloxacin resistance).
- If resistance has specifically been shown to ofloxacin and/or levofloxaxin, and moxifloxacin DST is susceptible, consider adding moxifloxacin to the regimen.
- Use of the combination of moxifloxacin with delamanid and clofazimine (three drugs that strongly prolong the QT interval) should be avoided.
- If resistance shown to all three Group 3 agents, do not use fluoroquinolones.

STEP 3	**Add Group 4 drugs**	**Ethionamide/Prothionamide** **Cycloserine/Terizidone** **Para-aminosalicylic acid (PAS)**
	Add all Group 4 drugs thought to be effective.	
STEP 4	**Add Group 1 drugs**	**Pyrazinamide** **Ethambutol**
	Pyrazinamide is routinely added in most regimens; ethambutol may also be added if the criteria for an effective drug are met.	
STEP 5	**Add delamanid and other Group 5 drugs** *NOTE: Bedaquiline is avoided as an additional Group 5 drug if delamanid is being used*	**Delamanid** **Linezolid** **Clofazimine** **Amoxicillin/ clavulanate** **Imipenem/cilastatin** **Meropenem** **High-dose isoniazid** **Clarithromycin** **Thioacetazone**
	Delamanid routinely added. Group 5 drugs other than delamanid are added based on the number of Group 4 drugs for which there is a high degree of confidence in efficacy: • Confidence in all (three) Group 4 drugs: add **one** other Group 5 drug. • Confidence in only two Group 4 drugs: add **two** other Group 5 drugs. • Confidence in only one or no Group 4 drugs: add **three** or more Group 5 drugs. • If resistant to higher generation fluoroquinolone and/or the two classes of Group 2 injectables (aminoglycosides and polypeptides), can add an additional Group 5 drug to what is being recommended above.	

A4.2.4 Concomitant therapy with anti-HIV or other medicines

Drug interaction studies with delamanid and antiretrovirals have been conducted as multiple dose studies among healthy individuals who did not have HIV or TB. Delamanid (100 mg twice daily) was given with the anti-HIV medicines tenofovir (300 mg daily) or lopinavir/ritonavir (400/100 mg daily) or efavirenz (600 mg daily). Co-administration of delamanid with lopinavir/ritonavir increased delamanid and DM-6705 exposure modestly, by about 25%. Delamanid did not affect tenofovir, lopinavir or ritonavir exposures. Co-administration with efavirenz did not affect concentrations of either delamanid or efavirenz. Therefore, no dose adjustments are needed when delamanid is used with any of these antiretroviral agents *(2)*.

Because some antiretroviral medicines can cause modest QT prolongation, monthly monitoring with ECGs may be particularly important while on ART, especially with ritonavir-containing regimens. If delamanid is stopped because of QT prolongation in a patient taking concomitant

ART, ART might be continued, except if dangerous arrythymias are present, in which case all QT-prolonging drugs are stopped.

It should be noted that there is no published data on the use of delamanid in HIV-infected individuals receiving concomitant therapy against HIV. However, given the clear benefits of ART among patients with HIV and MDR-TB co-infection, ART should be included in patients with HIV infection being treated for MDR-TB with a delamanid-containing regimen. Non-protease inhibitor-containing regimens are the preferred ART when that option exists. When there is no option but to use a protease inhibitor, it is suggested to adhere to frequent ECG monitoring (see Section 5.5).

Metabolic drug interactions: Delamanid does not inhibit CYP450 isoenzymes, but might itself be affected by the co-administration of strong inducers of cytochrome P450 3A4 (See Section A5.6). Efavirenz, a moderate inducer of P450 enzymes, did not meaningfully reduce delamanid exposure when the two drugs were given together.

Overlapping toxicities: Moxifloxacin is known to cause QT interval prolongation and was not used in the delamanid phase II trials. 96% of patients in the delamanid studies received a fluoroquinolone together with delamanid, mostly throughout the trials; 60% received levofloxacin and in most patients the dose was 750mg, the currently recommended dose for TB. A study in healthy volunteers *(3)* indicated that **levofloxacin 1000 mg and 1500 mg caused a 4.4 to 7.4 ms increase in QT at peak daily effect** compared to a 13.2 ms increase caused by 400 mg of moxifloxacin (the recommended dose for TB).

Potential overlapping toxicities should be considered when delamanid is used together with other second-line anti-TB drugs, ART, or other medications. Particular attention should be paid to concurrent use of delamanid with drugs that prolong the QT interval. A summary based on expert opinion is presented in Chapter 11 (Table 11.3).

A4.2.5 Monitoring and managing patients receiving delamanid

The most frequent adverse drug reactions (>10.0% of patients) during treatment with delamanid in the controlled trials were nausea (38%), vomiting (33%), and dizziness (30%). Other important adverse drug reactions were anxiety, paraesthesia, and tremor. General monitoring and management of these and other common adverse effects experienced by patients receiving second-line anti-TB drugs are described in Chapter 1 of this Handbook, and also apply to patients receiving delamanid. This includes monitoring the bacteriological and clinical responses (Chapter 10), which do not differ from normal monitoring described in this Handbook.

QT prolongation was seen among patients receiving delamanid, but the clinical consequences of these cardiac effects in a larger population of patients receiving the drug are unknown. Therefore, special attention should be paid to ensuring that cardiac toxicity is avoided or promptly managed, and it is recommended that patients receiving delamanid are clinically monitored for response to therapy and adverse effects (including the use of ECGs and active

pharmacovigilance practices). Programmes should strive to provide the monitoring tests, as well as any ancillary drugs prescribed for adverse effects (as a result of delamanid or any other anti-TB drug), free of charge or at the lowest possible cost to the patient.

A less common but potentially serious adverse effect related to delamanid use in clinical trials has been observed that needs special consideration: Hypoalbuminaemia (specifically below 2.8 g/dl) and/or hypokalaemia, shown to be major contributing factors to QT interval prolongation, is a prominent safety concern. Very frequent monitoring of albumin levels, serum electrolytes and ECG is therefore required (see Box A4.2.2).

QT interval monitoring. QT prolongation can result in ventricular arrhythmias (torsade de pointes) and may result in death, and it is imperative that ECG measurements are taken before treatment with delamanid is started, and regularly during its use. The QT interval must be corrected for the heart rate (adjustment is referred to as QT-corrected or QTc). The Fredericia correction method (QTcF) is preferred. QT interval monitoring should preferably be done using ECG machines that directly report the QTc interval. If this is not possible, Box A4.2.1 describes how the correction can be calculated using measurements on a graduated ECG rhythm strip.

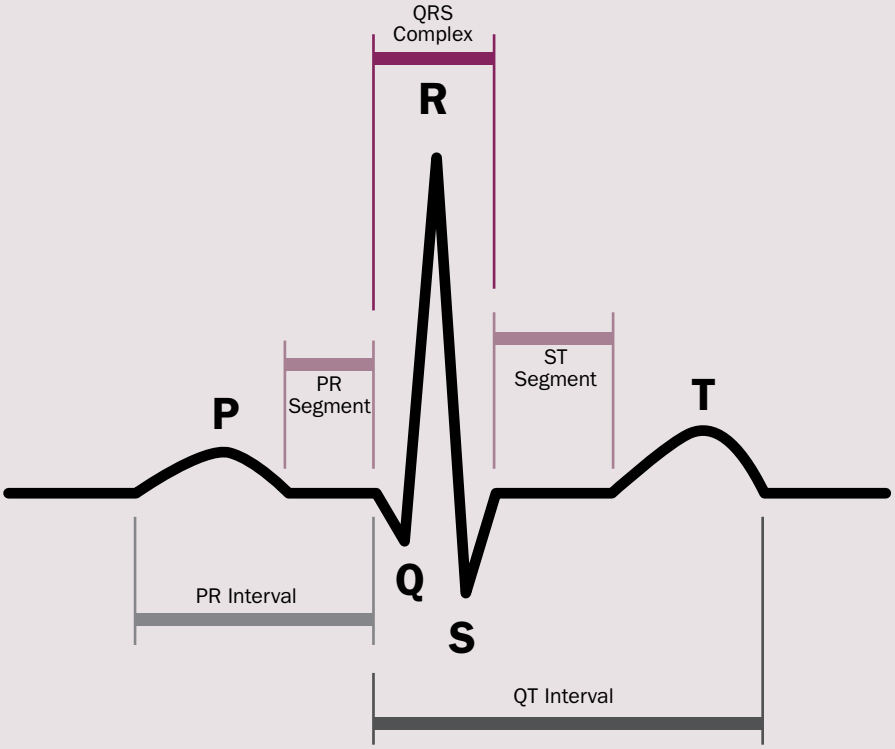
Box A4.2.2 describes the frequency and key actions for QT interval monitoring for patients on delamanid. The following are important notes on QT interval monitoring:

- The QT interval is usually automatically provided during ECG assessment and must always be corrected (QTc) for heart rate.
- The preferred method for calculating QTc is based on the Fredericia Formula (QTcF):
  - **QTcF= QT Interval / 3√ (RR interval)** where the RR Interval = 60/HR
- Some ECG machines provide a QTc based on Bazett's Formula (OTcB):
  - **QTcB= QT Interval / √ (RR interval)** where the RR Interval = 60/HR
- Note the difference: For QTcB the **root** of the R-R value is used, for QTcF the **cube root** of the R-R value is used instead. This is considered the preferred method.
- A value of greater than 450ms (males) or 470ms (females) is considered prolonged. If a patient taking delamanid has a QTcF value of greater than 480 ms (or an increase of greater than 60 ms from baseline) on his or her ECG, electrolyte testing and more frequent ECG monitoring should be performed. A QTcF interval of more than 500 ms is considered dangerous and is reason to stop the use of delamanid and all other QT prolonging drugs in the regimen (see Box A4.2.3 for further details).

Other monitoring considerations. Safety concerns are best addressed using the active TB drug-safety monitoring and management (aDSM), see Section A4.2.7.

BOX A4.2.1 DEFINITION OF THE QTC INTERVAL

- The QT interval in an ECG is measured from the start of the Q wave to the end of the T wave (see the diagram below).



- When monitoring the effect of delamanid, the QT interval needs to be adjusted (corrected) for the heart rate. Many ECG machines today provide an output of the corrected QT interval (QTc) automatically. If you are using a machine that does not, the following instructions can help you make the necessary correction.
  - The preferred way to calculate the QTc is the Fredericia method (QTcF), which is derived by dividing the QT interval by the cubed root of the interval in seconds between the peak of two successive R waves (RR) read from the ECG strip:

$$QT_{cF} = \frac{QT}{\sqrt[3]{RR}}$$

- Whenever an abnormal QTc value is found, the ECG and calculations should be repeated.
- A normal value for the corrected QTcF interval is equal to or less than 0.45 seconds (450 ms) in males or 0.47 seconds (470 ms) in females.

BOX A4.2.2 FREQUENCY OF QT INTERVAL MONITORING AND MANAGEMENT OF QT INTERVAL PROLONGATION

- An ECG should be obtained before initiation of treatment, and at least 2, 4, 8, 12 and 24 weeks after starting treatment with delamanid. Monitoring ECGs should be done monthly if taking other QT prolonging drugs (i.e. moxifloxacin, clofazimine, bedaquiline etc.).
- Delamanid is contraindicated in patients with albumin <2.8 g/dl. Albumin levels should be obtained at baseline and corrected if abnormal. Exogenous albumin cannot be used for the purpose of raising serum albumin levels. The most effective method of minimizing hypoalbuminaemia and restoring serum oncotic pressure is by creating a positive nitrogen balance. This is usually accomplished by enteral protein feeding. Reversal of the inflammatory state during treatment for TB should also naturally lead to the normalization of serum albumin levels.
- Patients who commence delamanid with serum albumin between 2.9–3.4 g/dl or experience a fall in serum albumin into this range during treatment should receive weekly monitoring of ECGs until serum albumin levels have been restored to normal.
- Serum potassium (K+), ionized calcium (Ca++) and magnesium (Mg++) levels should be obtained at baseline. Every effort should be made to have accurate testing for electrolytes.
- An abnormal value for electrolytes should be corrected before starting delamanid. Most commonly, low values are due to second-line anti-TB injectable drugs.
- K+, Mg++ and ionized Ca++ should be monitored monthly while on delamanid.
- Whenever low potassium is detected, it should trigger urgent management with replacement and frequent repeat potassium testing (often daily) to document that the potassium is moving in the correct direction. If potassium is found to be low, always check magnesium and calcium and replace as needed. (If unable to check, strongly consider oral empiric replacement doses of magnesium and calcium). Be aware that in patients who are critically ill, low calcium levels can be due to hypoalbuminaemia and has no clinical significance because the active fraction (ionized) is not affected. However, to prevent missing a second hypocalcaemic disorder, measure the ionized calcium level whenever the albumin level is low.
- Whenever significant QTcF prolongation is detected (absolute value >450 ms in males or >470 ms in females, or an increase of > 60 ms from baseline):
  - Repeat ECG to confirm prolongation.
  - Check K+, Mg++ and ionized Ca++ and correct levels if found to be abnormal. Withhold delamanid and injectable agent (if patient is still using) until the electrolytes have normalised.
  - If the QTcF interval is above normal value but still below 500 ms (and the patient is stable and electrolyte values are within normal limits) repeat weekly ECGs to confirm that QTcF interval is stable.

- If the QTc interval is >500 ms (confirmed by repeat ECG) discontinue delamanid and all other QT prolonging drugs in the regimen.

- Delamanid and all other QT prolonging drugs are to be discontinued if the patient develops clinically significant ventricular arrhythmia.
- If delamanid is stopped to deter QT prolongation, monitor ECGs at least weekly to confirm that the QTcF interval has returned to baseline.
- If cardiac symptoms appear (tachycardia, syncope, palpitations or weakness/dizziness), obtain an ECG to check the QT interval and to rule out an arrhythmia.

A4.2.6 Drug–drug interactions with delamanid

Delamanid is a pro-drug that must be reduced in the body to its active des-nitro metabolite. Plasma albumin and CYP3A4 regulate the formation and metabolism of DM-6705 respectively. DM-6705 contributes to QTc prolongation.

Many drugs can either induce or inhibit the CYP3A4 system, resulting in drug–drug interactions. As mentioned earlier, clinical studies have shown that interaction with strong CYP3A4 inducers can lead to loss of efficacy of delamanid (due to low blood concentration from increased metabolism of the drug).

Currently, there is no information available on how dosing should be adjusted in the face of strong drug–drug interactions. Consequently, dose adjustment is not recommended. Care must be taken in prescribing certain drugs.

Co-administration of strong CYP3A4 inducers, such as rifamycins (e.g. rifampin), should be avoided while on treatment with delamanid *(2)*. It is not known if rifabutin, which is a weaker inducer of CYP3A4 than rifampicin, can be used with delamanid. Co-administration of delamanid with strong CYP3A4 inducers such as rifampicin may significantly decrease the systemic exposure to delamanid, which could potentially increase the risk of loss of efficacy and development of drug resistance.

No significant drug–drug interactions are thought to occur with pyrazinamide or isoniazid. No dose-adjustment of isoniazid or pyrazinamide is required during co-administration with delamanid. In a clinical drug–drug interaction study in healthy subjects, delamanid was administered alone (200 mg daily), with a fixed-dose combination preparation of rifampicin/isoniazid/pyrazinamide (300/720/1800 mg daily) plus ethambutol (1100 mg daily) for 15 days *(2)*. Exposure of concomitant TB drugs (RHZ) was not affected by delamanid. Co-administration with delamanid increased steady state plasma concentrations of ethambutol by approximately 25%. The clinical relevance of this observation is not known.

The drug–drug interactions with delamanid and ART are discussed above in Section A4.2.4. When given in combination with anti-HIV medicines tenofovir, lopinavir/ritonavir and efavirenz, delamanid, did not affect the exposure to these medicines (<25% difference). Delamanid exposure was slightly increased when given with ritonavir-boosted lopinavir.

In the clinical studies, use of moxifloxacin and clofazimine has been avoided. Data regarding QT prolongation when delamanid is co-administered with other drugs that prolong the QT interval are not available. One exception is levofloxacin, which showed additive effect on QTcF interval prolongation (see Section A4.2.4).

Many drugs, however, are known to prolong the QT interval and the full drug prescribing information should always be consulted before using a drug in a patient taking delamanid. Some of the common drugs that can prolong the QT interval include:

- Moxifloxacin, gatifloxacin, levofloxacin (to a lesser degree).
- Clofazimine.
- Macrolide antibacterial drugs (erythromycin, clarithromycin, azithromycin).
- Serotonin 5-HT3 receptor antagonist (such as ondansetron, an anti-nausea drug commonly used in MDR-TB).
- Azole antifungal agents (e.g. ketonazole, itraconzaole, fluconazole).
- ARTs: The common three-drug combinations used in ART can result in QT prolongation (also see Section A4.2.4).
- Some antimalarials (e.g. quinine sulfate, chloroquine).
- Some medicines to treat psychiatric disorders (e.g. chlorpromazine, haloperidol, thioridazine).

If possible, avoid the use of QT-prolonging drugs with delamanid. If it is absolutely necessary to include a QT-prolonging drug, increase ECG monitoring as described in Section A4.2.5. Drugs that lower electrolytes (i.e. injectable agents) can result in a higher potential for arrhythmias (including sudden death) due to QT prolongation. While this is not a drug–drug interaction per se, the concomitant use of injectable agents and delamanid do require added electrolyte monitoring as described in Section A4.2.5.

A4.2.7 Programmatic considerations for introducing delamanid in the management of MDR-TB

Because delamanid is a new drug with currently limited application in the treatment of MDR-TB, widespread field experience with efficacy and safety is not yet available. It is necessary, therefore, that information on adverse effects monitoring and management for all patients on delamanid be tracked through a pharmacovigilance method. WHO has developed detailed active TB drug-safety monitoring and management (aDSM) descriptions of approaches to pharmacovigilance, which generally also apply to the programmatic use of the drug at country-level *(7)*.

In any country programme where MDR-TB patients are treated according to a national policy, essential infrastructure (diagnostic and clinical), drug access (budget, procurement and distribution), and data gathering should have been adequately developed. All of these would be applicable to the introduction and use of delamanid in MDR-TB treatment programmes, and are summarised in Box A4.2.3.

BOX A4.2.3 CONSIDERATIONS FOR PROGRAMMATIC USE OF DELAMANID IN MDR-TB TREATMENT AT THE COUNTRY LEVEL

- **Programmatic goals are to:**
  - Provide early access to a promising new drug to patients with limited therapeutic options.
  - Protect the efficacy of the new drug: avoid resistance arising.
  - Limit risk to the patient: monitor for and manage adverse events.
  - Ensure that highest standards of clinical ethical conduct and human rights are respected.
- **Checklist**
  - Well-functioning MDR-TB programme in place.
  - Diagnostic laboratory capability for second-line DST according to WHO-recommended procedures.
  - Clinical monitoring capability, in particular for ECG, liver function and electrolytes.
  - Quantification and drug procurement in place and the full range of necessary MDR-TB Committee available to support and monitor treatment providers.
  - Regulatory and importation issues addressed.
  - National guidelines adjusted to accommodate use of new drugs.
  - Consent forms designed and available.
  - Ethics/IRB support in place as required by local law and practices.
- **Setting up and maintaining a pharmacovigilance system for bedaquiline as per WHO policy (see chapter 11)**

A4.2.8 Clinician checklist for eligible patients

As an aid to determining eligibility of a patient for assignment to a delamanid-containing treatment regimen, a checklist is proposed in Box A4.2.4 and a template offered for obtaining informed consent from the patient before starting delamanid therapy.

BOX A4.2.4 CLINICIAN CHECKLIST OF ESSENTIAL PARAMETERS FOR SELECTION OF MDR-TB PATIENTS ELIGIBLE FOR TREATMENT WITH DELAMANID

Parameters	Tick Yes or No
• Patient is at least 18 years old.	☐ YES ☐ NO
• Patient is known or suspected to be diseased with a multidrug-resistant strain of tuberculosis and therefore eligible for treatment with second-line anti-TB drugs.	☐ YES ☐ NO
• Additional laboratory data has been obtained on the susceptibility profile of the patient's TB isolate to the following agents: fluoroquinolones (ofloxacin and moxifloxacin), and second-line parenteral agents (kanamycin, amikacin, and capreomycin).	☐ YES ☐ NO
• Clinically significant ventricular arrhythmia is absent.	☐ YES ☐ NO
• Baseline and repeat ECG shows normal QT interval.	☐ YES ☐ NO
• The patient's serum albumin, potassium, calcium and magnesium have been obtained at baseline and levels are within normal limits.	☐ YES ☐ NO
• Due process for consent for treatment with delamanid has been followed (see Section A4.2.9)	☐ YES ☐ NO

If the answer is 'yes' to all questions, the patient can be enrolled on treatment with delamanid as per the algorithms in figures A4.1.1–A4.1.4.

If the answer is 'no' to any of the above, further consideration and review is needed before enrolment in a treatment regimen with delamanid.

Getting a 'no' response to any of the above is not an absolute contraindication to using delamanid, only that the situation should be reviewed and the risk benefit of delamanid be reconsidered under the circumstance.

A4.2.9 Educating the patient and informed consent for patients eligible for treatment with delamanid[2]

This section contains templates for educating the patient on the use of delamanid and for obtaining informed consent. These templates can be modified. The informed consent process is divided into two parts.

Instructions to a health care provider on patient education and informed consent for delamanid are given in Box A4.2.5.

- **Informed Consent Part I – Medication guide for patients taking delamanid**. The patient will receive a copy of this medication guide (Box A4.2.6).

[2] Adapted from the template for Informed Consent for Clinical Studies developed by the WHO Ethics Research Committee (http://ww.who.int/entity/rpc/research_ethics/InformedConsent-clinicalstudies.doc).

- **Informed Consent Part II – Certificate of consent for delamanid.** This part is for signatures only if national authorities require written informed consent and the patient agrees to receive delamanid. The patient also receives a copy of this document (Box A4.2.7).

BOX A4.2.5 INSTRUCTIONS TO A HEALTH CARE PROVIDER ON PATIENT EDUCATION AND INFORMED CONSENT FOR DELAMANID

Introduction

Briefly state who you are and explain to patients that you are inviting them to accept delamanid as part of the drug regimen necessary to treat their disease. Inform patients that they may talk to anyone they feel comfortable talking with about the drug and that they can take time to reflect on whether they want to receive it or not. Assure the patient that if they do not understand some of the words or concepts, that you will take time to explain them as you go along and that they can ask questions now or later.

Proposed text: *I am X, working for the Y Clinic. At Y Clinic, we have a new drug available for the treatment of those forms of tuberculosis that cannot easily be treated with commonly used drugs. You are suffering from a difficult-to-treat form of tuberculosis, which is called drug-resistant TB. I am going to give you information about the drug, delamanid, its potential benefits, and also the potential risks associated with its use. This drug has been tested in patients like you, and has been approved for use in TB patients by the drug control authorities in the European Union, Japan and the World Health Organization. You do not have to decide today whether or not you would want to receive this new drug. Before you decide, you can talk to anyone you feel comfortable with about the information you have received and how to respond to it.*

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.

Reasons why delamanid is being offered to the patient

Explain *in lay terms* why you are offering to add delamanid to the treatment regimen. The language used should clarify rather than confuse. Use local and simplified terms. Avoid using terms like pathogenesis, antibiotic, adverse effects, cardiac, hepatic, etc.

Proposed text: *Tuberculosis is a serious disease that can be fatal. There are many TB cases that are especially difficult to treat with the drugs that are currently used; some patients with resistant TB may have limited treatment options. There is a new drug which has become available recently, and that may work better. Delamanid has been observed to have side-effects on the heart in particular, and special tests will be offered to you during treatment to check for these.*

Explain how the treatment will be taken by the patient

Briefly state the type of intervention that will be undertaken. This will be expanded upon in the procedures section but it may be helpful and less confusing to the participant if they know from the very beginning that the drug will be taken by mouth twice a day for a period of six months, along with several other drugs administered by mouth or by injection.

Proposed text: *You will need to take four tablets of delamanid daily for six months, two in the morning and two in the evening. It would be necessary to take two of the tablets here at the clinic in the morning. There will be other drugs to take also for a total of 20 months at least. The remaining two tablets will need to be taken in the evening in the presence of a treatment supporter. Delamanid is best taken with a light meal. It is important to take the medication as prescribed to avoid the further development of resistance to the drugs you are taking.*

Explain to the patient that taking delamanid is their choice (it is voluntary)

Indicate clearly that they can choose to receive the drug or not. State what the alternative – in terms of the treatment offered by the clinic – will be, if they decide not to accept delamanid as part of their treatment. State that they will still receive all the services they usually do whether they choose to take the drug or not. This can be repeated and expanded upon later in the form as well, but it is important to state clearly at the beginning of the form that receiving the drug is voluntary so that the other information can be heard in this context.

Example: *Your choice to receive delamanid for treating your disease is entirely voluntary. It is your choice whether to receive it or not. Whether you choose to accept the medication or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to receive delamanid, you will be offered the treatment that is routinely offered in this clinic/hospital for drug resistant TB, and we will tell you more about it later. You may change your mind later and stop receiving delamanid even if you agreed earlier.*

Go over the medication guide for patients taking delamanid (See Box A4.2.8)

Go over each section of the medication guide with the patient.

Write in the contact information of one or more persons at the bottom of the medication guide.

BOX A4.2.6 INSTRUCTIONS TO A HEALTH CARE PROVIDER ON PATIENT EDUCATION AND INFORMED CONSENT FOR DELAMANID

Informed Consent Part I:

Medication guide for patients taking delamanid tablets

Read this medication guide before you start taking delamanid and each time before your monthly visit. This information does not tell your health care provider about your medical treatment or any medical conditions.

What is the most important information i should know about delamanid?

Delamanid is a drug used to treat multidrug-resistant tuberculosis (MDR-TB) in people with limited treatment options. MDR-TB is a serious disease that can result in death and for which there are few treatment choices. More people treated with delamanid cleared TB from their sputum compared to people who did not receive delamanid. In one clinical trial, fewer deaths were seen in people who were treated with delamanid compared to people who did not receive delamanid.

It is important to complete the full course of treatment of delamanid and your other TB medicines and not skip doses. Skipping doses may decrease the effectiveness of the treatment and increase the likelihood that your TB disease will not be treatable by delamanid or other medicines.

Delamanid can cause serious side-effects.

- Heart rhythm problems can happen with delamanid.
- It is not known if delamanid is safe in:
  - Children under 18 years
  - Pregnancy
  - In patients with heart, kidney, liver or other health problems.

Before you take delamanid, tell your health care provider if:

- You have ever had an abnormal heart rhythm or other heart problems.
- Anyone in your family has or has had a heart problem called congenital long QT syndrome.
- You have liver or kidney problems or any other medical conditions, including HIV infection.
- You are pregnant or plan to become pregnant. It is not known if delamanid will harm your unborn baby.
- You are breastfeeding or plan to breastfeed. It is not known if delamanid passes into breast milk. You and your health care provider should decide if you will take delamanid or breastfeed.
- You are taking any prescription and non-prescription medicines, vitamins and herbal supplements.

How should I take delamanid?

- Delamanid must always be taken with other medicines to treat TB. Your health care provider will decide which other medicines you should take with delamanid.
- Delamanid must be taken twice a day.
- Always take delamanid with a standard meal.
- Swallow the tablets whole with water.
- Take delamanid for a total of 24 weeks (6 months). Take 100 mg (2 tablets) early in the morning and again 100 mg (two tablets) in the evening, every day of the week.
- You will need to take your other TB medicines for longer than 24 weeks, and at least for 20 months in total (the injectable drug is usually given for up to eight months).
- Your treatment will be provided under directly observed treatment (DOT), with a patient-centred approach, which means that a health care provider will accompany you during the treatment (morning dose and evening dose) and that your information, psychological and material needs will be addressed in order to enable you to adhere to treatment. Do not skip delamanid doses. If you skip doses, or do not complete the total 24 weeks of delamanid your treatment may not work as well and your TB may be harder to treat.
- If for some reason you miss a dose, inform the person responsible for your treatment right away, they will tell you what to do.

What should I avoid while taking delamanid?

You should not drink alcohol while taking delamanid.

There are some medications that cannot be taken safely with delamanid. Make sure to inform your doctor if you are taking medicines or if medicines are recommended to you by a health care practitioner while you are on treatment for TB with delamanid.

What are the possible side-effects of delamanid?

- Serious heart rhythm changes. Tell your health care provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you faint. Your heart will be monitored periodically with a machine that checks that the heart rhythm is normal.
- Other side-effects of delamanid include nausea, vomiting and dizziness. Other important adverse drug reactions are anxiety, tremor, or a feeling of pins and needles in your hands or feet. Tell your doctor about symptoms such as nausea or vomiting, dizziness, anxiety, itching, or tremor.

It is possible that it may also cause some problems that we are not aware of. However, you will be followed closely for any unwanted effects or any problems. Other medicines to decrease the symptoms of the side-effects or reactions may also be given.

Always tell your health care provider of any side-effects or problems you are having. Sometimes because of side-effects delamanid or other drugs may need to be stopped.

What monitoring tests do I need while on delamanid?

- You will need the same monitoring test that all patients on MDR-TB treatment need. In addition, you will need heart monitoring, and extra blood tests. Consult with your health care provider about the appropriate schedule of all your monitoring tests and regular doctor visits.

General information about the risk versus the benefit of taking delamanid

- RISK: It is possible that you will be at greater risk of not feeling well than you would be otherwise because of certain side effects due to the drug.
- BENEFIT: There is a greater chance that you will be cured of TB than if you did not take the medicine. You will possibly also become better sooner than if you only took the standard medicines for treatment of resistant TB. Also, it is probably less likely that the drugs you are taking will develop resistance if you are taking delamanid.

Confidentiality and sharing of information

- Because delamanid is a new drug for which we have limited experience we are collecting information on patients taking it.
- The information that we collect from you will be kept confidential and no one but the clinical staff will be able to see your medical information.
- Any information collected to help us better use the drug in future patients will be unlinked to your name (made anonymous) before we share or analyse it.

Costs

If you choose to take delamanid and cannot afford it, it may be provided free of charge to you. Many programmes will provide delamanid free of charge to all patients whether or not they can afford it.

Right to refuse or withdraw

- You do not have to agree to take delamanid if you do not wish to do so and refusing to accept the drug as part of your treatment schedule will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic.
- If you agree to take delamanid, you may choose to discontinue it at any point for any reason without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way.

Contact person

If you have any questions, you may contact any of the following persons:

Name_____Title_____.Phone_____.

Name_____Title_____.Phone_____.

Name_____Title_____.Phone_____.

Name of responsible physician: _____

Name of clinic/hospital/institution: _____

BOX A4.2.7

Informed Consent Part II:

Certificate of consent

This section should be written in the first person and have a statement similar to the one in bold below. If the participant is illiterate but gives oral consent, a witness must sign the respective section below. The person going over the informed consent must sign this form. The certificate of consent should avoid statements that have "I understand…." phrases. The understanding should perhaps be better tested through targeted questions during the reading of the information sheet, or through the questions being asked at the end of the reading of the information sheet, if the patient is reading the information sheet him/herself.

I have read the provided information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent to receive delamanid for treating the drug-resistant tuberculosis disease that I am suffering from.

Print name of patient: _____

Signature of patient: _____

Date: _____ (Day/month/year)

If illiterate, a literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the care providers). Patients who are illiterate should include their thumbprint.

I have witnessed the accurate reading of the consent form to the potential recipient of delamanid, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness: _____ AND thumbprint of patient

Signature of witness: _____ or

Date: _____ (Day/month/year)

Statement by the person taking consent

I have accurately read out the information sheet to the potential delamanid recipient, and to the best of my ability made sure that the patient understands that the following will be done:

1. Special tests will be conducted to verify eligibility for receiving delamanid. These will include ECG assessments, blood tests and additional laboratory tests to determine the full drug resistance profile of the patient's isolate.
2. Tests will be repeated at regular intervals, and are necessary to enable proper monitoring of response to treatment, both from an efficacy and a safety point of view.
3. Delamanid will be administered as part of the drug regimen for a period of six months.

I confirm that the participant was given an opportunity to ask questions, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this informed consent form has been provided to the participant.

Print name of person taking the consent: _____

Signature of person taking the consent: _____

Date: _____ (Day/month/year)

A4.2.10 References

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2. Deltyba – EPAR product information. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002552/WC500166232.pdf
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ANNEX 4.3

Key points on the summary of evidence in the use of bedaquiline and delamanid in MDR-TB treatment

		Bedaquiline	Delamanid
Evidence base	• Randomized clinical trials (RCT)	• RCT for 24 weeks: double blind placebo-controlled. • 160 patients were randomised to receive Bdq or placebo in addition to a MDR-TB background regimen.	• RCT for 8 weeks with observational open-label extension for further 24 weeks (total 32 weeks). • 481 patients were randomized to receive Dlm or placebo on top of a MDR-TB background regimen.
	• Evidence assessment	• GRADE Evidence Profile:	• GRADE Evidence Profile:
	– Quality (GRADE)	– Quality 'Very low' to 'Low'	– Quality 'Very low' to 'Moderate'
	– Risk of bias	– No serious risk of bias except for assessment of emergence of drug resistance	– Serious risk of bias except for SAEs and QT prolongation
	– Inconsistency	– Not serious	– Not serious
	– Indirectness	– Serious indirectness across all indicators assessed	– Serious risk of indirectness except for QT prolongation[1] assessment (not serious)
	– Imprecision	– 'Serious' to 'Very serious'	– 'Serious'
Efficacy[2]	• Primary and secondary endpoints	• Primary: Time to sputum culture conversion (after all subjects have completed the 24-week treatment period) • Secondary: Proportion of subjects with culture conversion at 24 weeks	• Primary: Sputum culture conversion at 8 wks. • Secondary: Time to sputum culture conversion; Sustained SCC; Favourable outcome (WHO definition); Mortality

1 QT not specifically considered for Bdq outside of the SAE category

2 Not directly comparable due to differences in study design.

3 Somoskovi A, Bruderer V, Hömke R, Bloemberg GV, Böttger EC (2015) A mutation associated with clofazimine and bedaquiline cross-resistance in MDR-TB following bedaquiline treatment Eur Respir J 2015; 45: 554-557

4 Andries K, Villellas C, Coeck N, Thys K, Gevers T, et al. (2014) Acquired Resistance of Mycobacterium tuberculosis to Bedaquiline. PLoS ONE 9(7): e102135. doi:10.1371/journal.pone.0102135

		Bedaquiline	Delamanid
	• Drug resistance	• Cross resistance to clofazimine reported[3]. Acquired resistance to Bdq observed[4].	• Dlm resistance observed in 4/205 patients
	• Outcome measures (WHO criteria)	• Statistically significant higher treatment success in Bdq arm compared to the MDR-TB background regiment; statistically significant shorter time to culture conversion and statistically higher proportion of culture conversion at 24 weeks in Bdq arm; statistically significant higher mortality in Bdq arm.	• Statistically significant higher treatment success in Dlm arm compared to the MDR-TB background regiment; statistically significant lower mortality in Dlm arm.
	• Specific forms of TB:		
	– Susceptible TB	– Not studied in RCT	– Not studied in RCT
	– Extra-P TB	– Not studied in RCT	– Not studied in RCT
	– XDR-TB	– XDR-TB patients excluded in RCT.	– XDR-TB patients included in RCT [data on XDR-TB limited due to small number of patients (23 patients)].
	• Special groups (children, pregnant women, elderly patients)	• Not studied in RCT	• Not studied in RCT
	• HIV and concomitant use of ART	• Minimal information on use in HIV-infected patients	• No information on use in HIV-infected MDR-TB patients on ART
Safety	• SAEs (including mortality)[5]	• Increased mortality observed, QT prolongation	• No increased risk of mortality observed, QT prolongation
	• AEs	• Most common (>10% of cases): headache, nausea, arthralgia	• Most common (>10% of cases): nausea, vomiting, dizziness
	• Absolute medical contraindications	• Severe cardiac disease or QTc >500 ms	• Severe cardiac disease or QTc >500 ms, albumin less than 2.8 g/dL
	• Drug–drug interactions	• Significant interactions with drugs that inhibit or induce the CYP3A4 enzymes. Additive cardiotoxicity with drugs that prolong the QT interval (moxifloxacin, clofazimine, efavirenz, lopinavir/ritonavir are not recommended in concomitant use with Bdq). Prolonged terminal elimination half-life (about 5.5 months).	• Significant interactions only with drugs that strongly inhibit or induce the CYP3A4 enzymes. Additive cardiotoxicity with drugs that prolong the QT interval (data available showing QT prolongation when Dlm is administered with Lfx, but no data available on concomitant use with Mfx and Cfz; no DDI with efavirenz, tenofovir, lopinavir/ritonavir for Dlm dosed at 100 mg BD).
	• Concomitant or sequential use of Bdq and Dlm	• Not studied.	• Not studied.

[5] Mortality differences are not directly comparable due to differences in study design.

ANNEX 4.4

Summary information on clinical and programmatic aspects of the new anti-TB drugs bedaquiline and delamanid

General considerations:

Bedaquiline or delamanid may be added to WHO regimens in adult populations with MDR-TB as described in Annexes 4.1 and 4.2 respectively. **Because of lack of data, concomitant use of bedaquiline and delamanid is not recommended at this stage.** In order to guide decision-making in choosing between bedaquiline and delamanid when both are available for use at country-level, please refer to Annex 4.5. Adequate provisions for safe and effective use of either drug must be in place. Addition of the drug should be done under best practices of safety and efficacy monitoring and with active pharmacovigilance. There is no evidence that directly compares the efficacy or safety of one drug versus the other. It is recommended that the new drugs be introduced in operational research conditions with relevant ethical approval and patient informed consent.

Category		Bedaquiline	Delamanid
Indications	**New drug may be added to a WHO-recommended second-line regimen in adult patients with pulmonary MDR-TB**	Conditional recommendation; very low confidence in estimates of effect	Conditional recommendation; very low confidence in estimates of effect
	Use of the new drug in adult patients with MDR-TB may be considered by programmes with low treatment success rates despite good programmatic conditions	Given uncertainties about the relative benefits and harms when using bedaquiline, caution is advised when other options to compose an effective MDR-TB treatment regimen using conventional second-line medication still exist. Because of the increased mortality associated with bedaquiline use (1) and its long half-life, strong caution needs to be exercised when used in MDR-TB treatment regimens.	Given the insufficient experience with the use of delamanid under the different conditions that may be expected in treatment programmes, and the uncertainty about its overall added value in the treatment of MDR-TB patients, routine addition of delamanid may not be warranted when an effective and reasonably well-tolerated MDR-TB regimen can be composed; however, because of decreased mortality associated with delamanid use (2) and its good safety profile, the routine inclusion of delamanid in adults with MDR-TB may be considered (see Annex 4.2, section A4.2.3, scenario 0).

Category		Bedaquiline	Delamanid
	The use of new drugs may be considered when an effective treatment regimen according to WHO recommendations cannot be designed.	Bedaquiline or delamanid may be used as a Group 5 drug in addition to a regimen designed according to WHO recommendations in patients presenting with: • MDR-TB plus additional risk of poor outcomes (eg. drug intolerability)* • MDR-TB plus resistance to fluoroquinolones • MDR-TB plus resistance to both classes of Group 2 second-line injectable agents (aminoglycosides and polypeptides) or severe intolerance to second-line injectable agents • MDR-TB plus two or more Group 4 (Eto, Pto, Cs, PAS) drugs compromized or severe intolerance shown to these drugs • XDR-TB Refer to Annex 4.5 for a situation-based guide to choosing between bedaquiline and delamanid. Annexes 4.1 and 4.2 provide detailed descriptions for each drug in regimens that might be considered under various treatment scenarios.	
	Extra-pulmonary MDR-TB	While patients with exclusive extrapulmonary disease were not included in product development trials, the use of the drug in extrapulmonary MDR-TB patients may be considered, extrapolating from the data in patients with pulmonary MDR-TB.	
Special Situations	**Cardiac disease**	Absolute contraindication: patients with a QT interval >500 ms, history of torsades de pointes (except for delamanid) or cardiac ventricular arrhythmias or severe coronary artery disease.	
	Pregnancy*	No evidence to recommend use.	No evidence to recommend use. Studies in animals have shown reproductive toxicity.
	Children*	No evidence to recommend use.	
	Nursing mothers*	Unknown whether product or its metabolites are excreted in human milk. Pharmacokinetic data in animals have shown excretion of the drug and/or its metabolites in milk. Discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother's condition.	
	Pancreatitis	No specific precautions.	No specific precautions.
	Hypoalbuminaemia (albumin below 2.8 g/dL)	No specific precautions.	Contraindicated in patients with albuminaemia below 2.8 g/dL.
	Electrolyte imbalance	Not recommended while serum potassium level is abnormal (normal range 3.5–5.2 mmol/L).	
	Renal impairment	No dose adjustment for mild renal impairment. Use with caution in moderate to severe renal impairment.	
	Hepatic impairment	Use with caution in mild to severe hepatic impairment. No dose adjustment for mild hepatic impairment.	

Category		Bedaquiline	Delamanid
Monitoring	**ECG monitoring**	Before initiation of treatment, and at least at 2, 4, 8, 12 and 24 weeks after starting treatment. ECGs should be done at least monthly if other drugs that prolong the QT interval are included in the regimen. Given the long half-life of bedaquiline (5.5 months), one or more ECGs should be done after 24 weeks, based on clinical judgement.	Before initiation of treatment, and at least at 2, 4, 8, 12 and 24 weeks after starting treatment. ECGs to be done at least monthly if other drugs that prolong the QT interval are included in the regimen. Patients who commence delamanid with serum albumin between contraindicated when albumin is below 2.9–3.4 g/dl or experience a fall in serum albumin into this range during treatment should receive weekly monitoring of ECGs until serum albumin levels have been restored to normal.
	Magnitude of QT prolongation	In a placebo-controlled study, the mean increases from reference in QTcF** grew gradually larger over the first 8 weeks of bedaquiline treatment and then remained more or less stable until Week 24. The largest mean increase from reference in QTcF at a pre-dose time point in the first 24 weeks was 15.4 ms in the "any bedaquiline group" (at Week 24) and 7.7 ms in the "any placebo group" (at Week 20). After Week 24, QTcF increases in the "any bedaquiline group" gradually became less pronounced (3).	In a placebo controlled study in patients receiving 100 mg delamanid twice daily the mean placebo-corrected increases in QTcF from baseline were 7.6 ms at 1 month and 12.1 ms at 2 months. 3% of patients experienced an increase of 60 ms or greater at some point during the trial and 1 patient exhibited a QTcF interval > 500 ms (4).
	Liver function tests	Monitor symptoms and laboratory tests (ALT, AST, and bilirubin) at baseline, monthly while on treatment, and thereafter as needed.	Monitor symptoms and laboratory tests (ALT, AST, and bilirubin) at baseline, and thereafter as needed.
	Albumin	No specific precautions.	At baseline: Caution when albumin level below 3.4 g/dL, with weekly ECG monitoring until level returns to normal.
	Electrolytes	Serum potassium, calcium, and magnesium should be obtained at baseline and corrected if abnormal before use of the drug. Follow-up monitoring of electrolytes should be performed if QT prolongation is detected.	

Category		Bedaquiline	Delamanid
Drug–drug interactions	**Use of delamanid after a patient has taken bedaquiline**	Given the long half-life of bedaquiline (5.5 months), a six month drug-elimination period is recommended before using delamanid.	
	Use of bedaquiline after a patient has taken delamanid	Given the short half-life of delamanid (38 hours), a five-day washout period of delamanid is recommended before using bedaquiline.	
	Concomitant use of bedaquiline and delamanid.	Safety of use together is not established. Until more data is available, no recommendation for or against simultaneous use can be made. Concomitant use of bedaquiline and delamanid is the responsibility of individual expert clinicians and should only be considered for individual patients with no other therapeutic options, after careful risk-benefit assessments, and under close monitoring.	
	Use of drugs that prolong QT interval	If possible, avoid the use of other drugs that prolong the QT interval with bedaquiline or delamanid. If it is absolutely necessary, ECGs should be done at least monthly if other drugs that prolong the QT interval are included in the regimen. Some of the common drugs used in MDR-TB management that can prolong the QT interval include: moxifloxacin, levofloxacin (to a lesser degree), clofazimine, and ondansetron.	
	Concomitant use with drugs that induce cytochrome P450 3A4 (abbreviated CYP3A4)	Contraindicated with concomitant administration of strong inducers. Bedaquiline is metabolized by CYP3A4 isozymes and there is a risk of reduced efficacy when used alongside other drugs that induce CYP3A4 isozymes.	Avoid concomitant administration of strong inducers (e.g. rifamycins, carbamazepine). No clinically relevant reduction in delamanid exposure was observed with weak inducers.
	Use of drug with drugs that inhibit the cytochrome P450 3A4 (abbreviated CYP3A4)	Avoid. Risk of increased toxicity when used alongside other drugs that inhibit CYP3A4 isozymes. If co-administration of bedaquiline with any strong inhibitor of CYP3A (e.g. ritonavir, ketoconazole) is necessary, perform more frequent monitoring of ECGs throughout the bedaquiline treatment period.	Limited experience. If co-administration of delamanid with any strong inhibitor of CYP3A (e.g. ritonavir, ketoconazole) is necessary, perform more frequent monitoring of ECGs throughout the delamanid treatment period.
	ARVs	Avoid efavirenz, protease inhibitors and ritonavir.	No or insignificant interactions observed with efavirenz, tenofovir, lopinavir/ritonavir for delamanid dosed at 100mg BD.

Category		Bedaquiline	Delamanid
Resistance	**Cross-resistance**	Reported cross-resistance with clofazimine (CFZ) due to mutations in Rv0678, a transcriptional repressor of the genes encoding the MmpS5-MmpL5 efflux pump (5), an important sensitizer of bedaquiline and clofazimine (6).	Does not show cross-resistance with any of the currently used anti-tuberculosis drugs; however, emergence of delamanid resistance has been reported in 4/205 patients involved in the randomized control trial.
Implementation and operational feasibility	**Drug characteristics**	Better absorbed when taken with food; slow elimination (half-life of 5.5 months).	Better absorbed when taken with food; half-life of 38 hours.
	Clinical monitoring (essential requirements)	ECG, electrolytes, hepatic function tests.	ECG, electrolytes, serum albumin.
	Patient supervision	DOT, once daily for 2 weeks, thereafter 3 times per week, for 6 months. Other drugs in the MDR-TB regimen require daily DOT throughout.	DOT, twice daily for 6 months. Other drugs in the MDR-TB regimen require daily DOT throughout.
	Active pharmacovigilance	Required	Required
	Informed consent	Required in writing as per local law and practice.	Required in writing as per local law and practice.
	Cost	Tiered pricing, currently adding 15–25% to cost of MDR-TB regimen based on lowest tier.	No information available as of 17 March 2015.

(Eto: ethionamide; Pto: prothionamide; Cs: cycloserine; PAS: para-aminosalicylic acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase).

* Because MDR-TB may have a high mortality rate, use of new drugs might be considered for cases with increased risk of adverse treatment outcomes.

** QTcF – The QT interval with the Fredericia correction method.

References

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2. The use of delamanid in the treatment of multidrug-resistant tuberculosis: Interim policy guidance. Geneva: World Health Organization; 2014 (WHO/HTM/TB2014.23).
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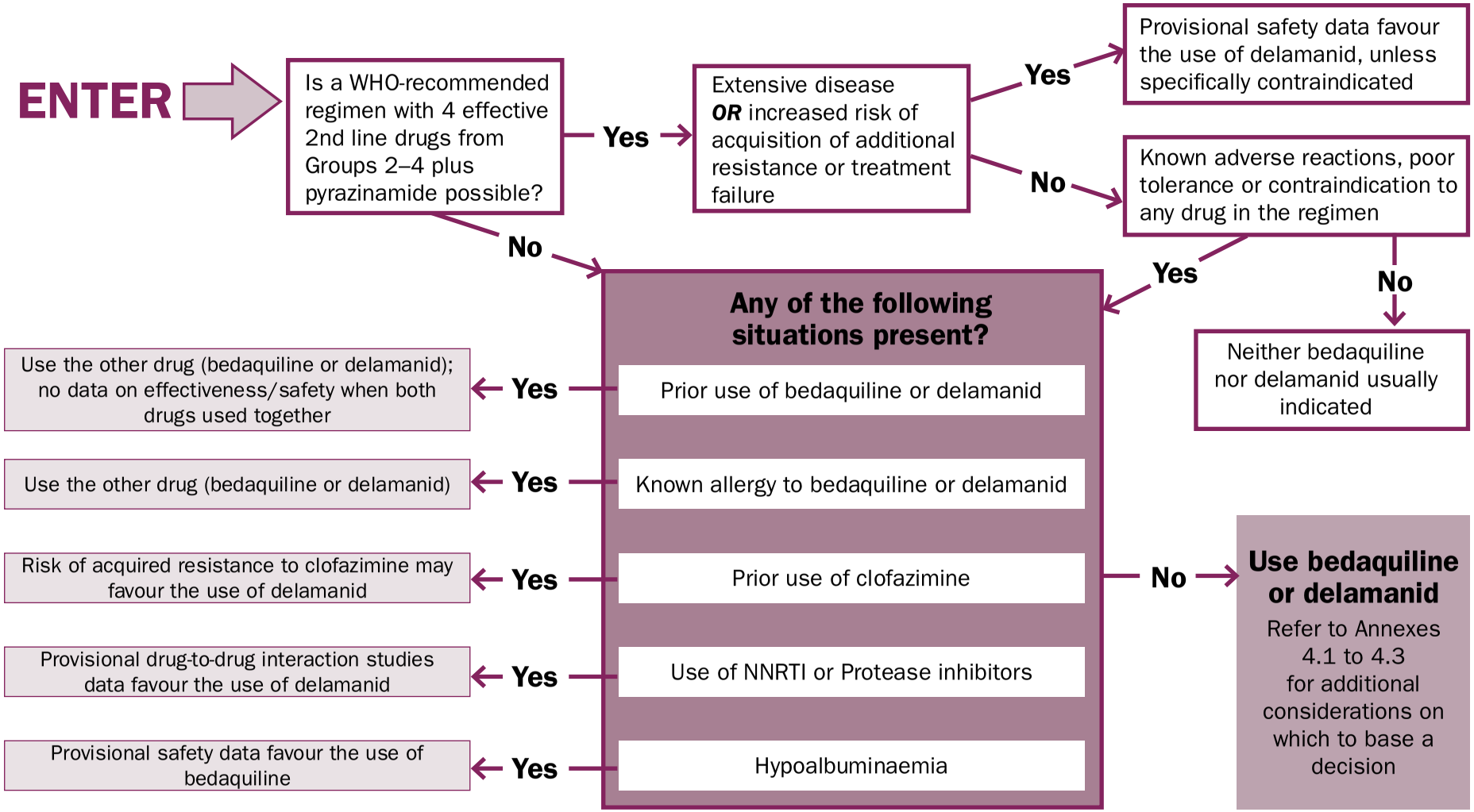
ANNEX 4.5

Deciding between bedaquiline and delamanid for the treatment of MDR-TB

(when both drugs are available for the full duration of treatment, and based on WHO interim policy on each drug)



ANNEX 5

Indicators for monitoring drug-resistant TB programmes

INDICATOR GROUP	INDICATOR NUMBER AND NAME	CALCULATION	STRATIFICATION	EXPRESSED AS	DATA SOURCES	LEVEL	PERIOD OF ASSESSMENT	NOTES
Detection (DR-TB)	1) TB patients with result for isoniazid and rifampicin drug susceptibility testing (DST)	Numerator: Number of TB cases (in each risk category) with DST result for both isoniazid and rifampicin during the period of assessment. Denominator: Number of TB cases identified (in each risk category) during the period of assessment.	By new, retreatment and each other risk category specified in the national policy	Absolute numbers, proportion	Numerator: Laboratory register; Denominator: Basic TB register and Treatment card. For some risk categories (eg, contacts of MDR-TB) the information may have to be traced from elsewhere in the medical records.	National, regional, district & WHO	6 months	To be computed separately for patients detected with rifampicin-resistant TB (RR-TB) alone in sites using Xpert MTB/RIF For annual reporting to WHO (absolute numbers): DST coverage stratified by new, retreatment and previous history unknown
Detection (DR-TB)	2) Confirmed MDR-TB cases detected among TB patients tested for susceptibility to isoniazid and rifampicin	Numerator: Number of confirmed MDR-TB cases (in each risk category) during the period of assessment. Denominator: Number of TB cases (in each risk category) with DST result for both isoniazid and rifampicin during the period of assessment.	By new, retreatment and each other risk category specified in the national policy	Absolute numbers, proportion	Numerator: Laboratory register; Denominator: identical to the numerator of Detection Indicator 1.	National, regional, district & WHO	6 months	To be computed separately for patients detected with rifampicin-resistant TB (RR-TB) alone in sites using Xpert MTB/RIF For annual reporting to WHO (absolute numbers): RR-/MDR-TB cases stratified by new, retreatment and previous history unknown
Detection (DR-TB)	3) Confirmed MDR-TB cases tested for susceptibility to any fluoroquinolone and any second-line injectable drug	Numerator: Number of confirmed MDR-TB cases tested for susceptibility to a fluoroquinolone and a second-line injectable anti-TB medication during the period of assessment. Denominator: Number of confirmed MDR-TB cases during the period of assessment.	None	Absolute numbers, proportion	Numerator: Laboratory register; Denominator: identical to the (non-disaggregated) numerator of Detection Indicator 2.	National, regional, district & WHO	6 months	To be computed only for patients with confirmed MDR-TB For annual reporting to WHO (absolute numbers)

INDICATOR GROUP	INDICATOR NUMBER AND NAME	CALCULATION	STRATIFICATION	EXPRESSED AS	DATA SOURCES	LEVEL	PERIOD OF ASSESSMENT	NOTES
Detection (DR-TB)	4) Confirmed XDR-TB cases detected among MDR-TB patients tested for susceptibility to any fluoroquinolone and any second-line injectable drug	Numerator: Number of confirmed XDR-TB cases during the period of assessment. Denominator: Number of confirmed MDR-TB cases tested for susceptibility to a fluoroquinolone and a second-line injectable anti-TB medication during the period of assessment.	None	Absolute numbers, proportion	Numerator: Laboratory register; Denominator: identical to the numerator of Detection Indicator 3.	National, regional, district & WHO	6 months	To be computed only for patients with confirmed MDR-TB, given that the XDR-TB definition requires resistance to isoniazid as well For annual reporting to WHO (absolute numbers)
Detection (DR-TB)	5) Interval between presumption of RR-/ MDR-TB and DST results	The duration in days between the date when the TB patient was identified as being in a risk category as per the national policy and the date of the DST results for isoniazid and rifampicin. The calculation is done on all cases with DST or Xpert MTB/RIF results (sensitive or resistant) entered in the Laboratory register during the period of assessment. The number of episodes included in the calculation should also be indicated.	None	Number of episodes included in the calculation; mean interval and range (min-max) in days	Date of presumption of RR-/MDR-TB: Basic TB register, Treatment card, other information Date of DST results: Laboratory register	National, regional, district	6 months	In sites using Xpert MTB/ RIF the date of the first result showing rifampicin resistance is used, regardless of whether the same patient was confirmed to be MDR-TB or not subsequently Not reported to WHO
Enrolment (DR-TB)	1) MDR-TB cases (presumptive or confirmed) enrolled on MDR-TB treatment	Definition: Number of RR-/ MDR-TB cases (presumptive or confirmed) registered and started on a prescribed MDR-TB treatment regimen during the period of assessment. Comparator: Number of RR-/ MDR-TB cases (presumptive or confirmed) eligible for treatment with second-line drugs during the period of assessment.	age < 15y / 15y +; males / females	Absolute numbers, ratio of newly enrolled to eligible	Number of cases started on treatment: Second-line TB treatment register; Number of eligible cases: Basic TB register and Laboratory register	National, regional, district & WHO	6 months	Patients detected with rifampicin-resistant TB (RR-TB) in sites using Xpert MTB/RIF to be included in the denominator as well as numerator For annual reporting to WHO (absolute numbers)

INDICATOR GROUP	INDICATOR NUMBER AND NAME	CALCULATION	STRATIFICATION	EXPRESSED AS	DATA SOURCES	LEVEL	PERIOD OF ASSESSMENT	NOTES
Enrolment (DR-TB)	2) Confirmed RR-/MDR-TB cases enrolled on MDR-TB treatment regimen	Definition: Number of confirmed RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment regimen during the period of assessment. Comparator: Number of confirmed RR-/MDR-TB cases detected during the period of assessment.	Cases with HIV on ART / Cases with HIV but not known to be on ART	Absolute numbers, ratio of newly enrolled to detected cases	Number of confirmed RR-/MDR-TB cases started on treatment: Second-line TB treatment register; Number of confirmed RR-/MDR-TB cases: Laboratory register, identical to the (non-disaggregated) numerator of Detection Indicator 2 inclusive of any other RR-TB cases.	National, regional, district & WHO	6 months	Patients detected with rifampicin-resistant TB (RR-TB) in sites using Xpert MTB/RIF to be included in the denominator as well as numerator For annual reporting to WHO (absolute numbers, non-disaggregated)
Enrolment (DR-TB)	3) Confirmed XDR-TB cases enrolled on XDR-TB treatment regimen	Definition: Number of confirmed XDR-TB cases registered and started on a prescribed XDR-TB treatment regimen during the period of assessment. Comparator: Number of confirmed XDR-TB cases detected during the period of assessment.	None	Absolute numbers, ratio of newly enrolled to detected cases	Number of confirmed XDR-TB cases started on treatment: Second-line TB treatment register; Number of confirmed XDR-TB cases: Laboratory register, identical to the (non-disaggregated) numerator of Detection Indicator 4.	National, regional, district & WHO	6 months	To be computed only for patients with confirmed XDR-TB as per definition (i.e. including resistance to isoniazid) For annual reporting to WHO (absolute numbers)
Enrolment (DR-TB)	4) Interval between RR-/MDR-TB diagnosis and start of MDR-TB treatment	The duration in days between the date of RR-/MDR-TB confirmation and the date when the patient started a prescribed second-line drug regimen. The calculation is done on all confirmed RR-/MDR-TB cases recorded on the Second-line TB treatment register during the period of assessment. If treatment was started before the confirmatory DST was reported then the interval is marked as zero days. The number of episodes included in the calculation should also be indicated.	None	Number of episodes included in the calculation; mean interval and range (min-max) in days	Second-line TB treatment register, Laboratory register	National, regional, district	6 months	In sites using Xpert MTB/RIF the date of the first result showing rifampicin resistance is used, regardless of whether the same patient was confirmed to be MDR-TB or not subsequently Not reported to WHO

INDICATOR GROUP	INDICATOR NUMBER AND NAME	CALCULATION	STRATIFICATION	EXPRESSED AS	DATA SOURCES	LEVEL	PERIOD OF ASSESSMENT	NOTES
Interim results (DR-TB)	1) RR-/MDR-TB cases on MDR-TB treatment regimen with negative culture by six months.	Numerator: Number of confirmed pulmonary RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment with negative results for culture in month 6 of their treatment. Denominator: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment.	None	Absolute numbers, proportion	Second-line TB treatment register	National, regional, district	3 months	Patients with rifampicin-resistant TB (RR-TB) in sites using Xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator Applies only to pulmonary cases; all cases included in denominator Not reported to WHO
Interim results (DR-TB)	2) RR-/MDR-TB cases on MDR-TB treatment regimen who died by six months.	Numerator: Number of confirmed RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment who died of any cause by the end of month 6 of their treatment. Denominator: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment.	None	Absolute numbers, proportion	Second-line TB treatment register	National, regional, district	3 months	Patients with rifampicin-resistant TB (RR-TB) in sites using Xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator Not reported to WHO
Interim results (DR-TB)	3) RR-/MDR-TB cases on MDR-TB treatment regimen who were lost to follow-up by six months.	Numerator: Number of confirmed RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment who were lost to follow-up by the end of month 6 of their treatment Denominator: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment	None	Absolute numbers, proportion	Second-line TB treatment register	National, regional, district	3 months	Patients with rifampicin-resistant TB (RR-TB) in sites using Xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator Not reported to WHO
Interim results (DR-TB)	4) Patients on MDR-TB treatment regimen found not to have RR-/MDR-TB.	Number of patients started on a prescribed MDR-TB treatment regimen during the period of assessment and later found not to have RR-/MDR-TB.	None	Absolute numbers	Second-line TB treatment register	National, regional, district	3 months	Not reported to WHO

INDICATOR GROUP	INDICATOR NUMBER AND NAME	CALCULATION	STRATIFICATION	EXPRESSED AS	DATA SOURCES	LEVEL	PERIOD OF ASSESSMENT	NOTES
Interim results (DR-TB)	5) Patients on XDR-TB treatment regimen found not to have XDR-TB.	Number of patients started on a prescribed XDR-TB treatment regimen during the period of assessment and later found not to have XDR-TB.	None	Absolute numbers	Second-line TB treatment register	National, regional, district	3 months	Not reported to WHO
Final outcomes (DR-TB)	1) RR-/MDR-TB patients cured	Numerator: The number of confirmed pulmonary RR-/MDR-TB cases registered for MDR-TB treatment during the period of assessment assigned an outcome Cured. Denominator: Number of confirmed RR-/MDR-TB cases registered for treatment and starting a prescribed MDR-TB treatment regimen during the period of assessment.	XDR-TB / non-XDR-TB; HIV positive cases	Absolute number, proportion	Second-line TB treatment register	National, regional, district & WHO	A calendar year	Patients with rifampicin-resistant TB (RR-TB) in sites using Xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator Applies only to pulmonary cases; all cases included in denominator For annual reporting to WHO (absolute numbers, if possible stratification of XDR-TB vs non-XDR MDR-TB cases)
Final outcomes (DR-TB)	2) RR-/MDR-TB patients completing treatment	Numerator: The number of confirmed RR-/MDR-TB cases registered for MDR-TB treatment during the period of assessment assigned an outcome Treatment completed. Denominator: Number of confirmed RR-/MDR-TB cases registered for treatment and starting a prescribed MDR-TB treatment regimen during the period of assessment.	XDR-TB / non-XDR-TB; HIV positive cases	Absolute number, proportion	Second-line TB treatment register	National, regional, district & WHO	A calendar year	Patients with rifampicin-resistant TB (RR-TB) in sites using Xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator For annual reporting to WHO (absolute numbers, if possible stratification of XDR-TB vs non-XDR MDR-TB cases)

INDICATOR GROUP	INDICATOR NUMBER AND NAME	CALCULATION	STRATIFICATION	EXPRESSED AS	DATA SOURCES	LEVEL	PERIOD OF ASSESSMENT	NOTES
Final outcomes (DR-TB)	3) RR-/MDR-TB patients whose treatment failed	Numerator: The number of confirmed RR-/MDR-TB cases registered for MDR-TB treatment during the period of assessment assigned an outcome Treatment failed. Denominator: Number of confirmed RR-/MDR-TB cases registered for treatment and starting a prescribed MDR-TB treatment regimen during the period of assessment.	XDR-TB / non-XDR-TB; HIV positive cases	Absolute number, proportion	Second-line TB treatment register	National, regional, district & WHO	A calendar year	Patients with rifampicin-resistant TB (RR-TB) in sites using Xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator For annual reporting to WHO (absolute numbers, if possible stratification of XDR-TB vs non-XDR MDR-TB cases)
Final outcomes (DR-TB)	4) RR-/MDR-TB patients who died	Numerator: The number of confirmed RR-/MDR-TB cases registered for MDR-TB treatment during the period of assessment assigned an outcome Died. Denominator: Number of confirmed RR-/MDR-TB cases registered for treatment and starting a prescribed MDR-TB treatment regimen during the period of assessment.	XDR-TB / non-XDR-TB; HIV positive cases	Absolute number, proportion	Second-line TB treatment register	National, regional, district & WHO	A calendar year	Patients with rifampicin-resistant TB (RR-TB) in sites using Xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator For annual reporting to WHO (absolute numbers, if possible stratification of XDR-TB vs non-XDR MDR-TB cases)
Final outcomes (DR-TB)	5) RR-/MDR-TB patients lost to follow-up	Numerator: The number of confirmed RR-/MDR-TB cases registered for MDR-TB treatment during the period of assessment assigned an outcome Lost to follow-up. Denominator: Number of confirmed RR-/MDR-TB cases registered for treatment and starting a prescribed MDR-TB treatment regimen during the period of assessment.	XDR-TB / non-XDR-TB; HIV positive cases	Absolute number, proportion	Second-line TB treatment register	National, regional, district & WHO	A calendar year	Patients with rifampicin-resistant TB (RR-TB) in sites using Xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator For annual reporting to WHO (absolute numbers, if possible stratification of XDR-TB vs non-XDR MDR-TB cases)

INDICATOR GROUP	INDICATOR NUMBER AND NAME	CALCULATION	STRATIFICATION	EXPRESSED AS	DATA SOURCES	LEVEL	PERIOD OF ASSESSMENT	NOTES
Final outcomes (DR-TB)	6) RR-/MDR-TB patients not evaluated for outcome	Numerator: The number of confirmed RR-/MDR-TB cases registered for MDR-TB treatment during the period of assessment assigned an outcome Not evaluated for outcome. Denominator: Number of confirmed RR-/MDR-TB cases registered for treatment and starting a prescribed MDR-TB treatment regimen during the period of assessment.	XDR-TB / non-XDR-TB; HIV positive cases	Absolute number, proportion	Second-line TB treatment register	National, regional, district & WHO	A calendar year	Patients with rifampicin-resistant TB (RR-TB) in sites using Xpert MTB/RIF who are on treatment to be included in the denominator as well as numerator For annual reporting to WHO (absolute numbers, if possible stratification of XDR-TB vs non-XDR MDR-TB cases)

ANNEX 6

Schedule of clinical and laboratory follow up[2]

General follow-up schedule for MDR-TB patients

MONTH	CLINICAL CONSULT	WEIGHT	SMEAR	CULTURE	DRUG SUSCEPTIBILITY TESTING	CHEST RADIOGRAPH	LFT	CR, K	TSH	AUDIO-METRY	HIV TESTING
0 (baseline)	√	√	√	√	√	√	√	√	√	√	√
1	Every two weeks	√	√	√				√		√	Repeat if indicated
2		√	√	√				√		√	
3		√	√	√				√	√	√	
4	Monthly	√	√	√	If culture pos.			√		√	
5		√	√	√				√		√	
6		√	√	√	If culture pos.	Optional		√	√	√	
7		√	√	√				√		√	
8		√	√	√	If culture pos.			√		√	
9		√	√	√				If on inj.	√	If on inj.	
10		√	√	√	If culture pos.			If on inj.		If on inj.	
11		√	√	√				If on inj.		If on inj.	
12		√	√	√	If culture pos.	Optional		If on inj.	√	If on inj.	
Until completion			Monthly	Monthly	If culture pos.	Optional			Every three months		

Abbreviations: pos. = positive; inj = injectable drug; LFT = liver function testing (liver enzymes); Cr = creatinine; K = potassium.

[2] This annex is adapted from The PIH guide to the medical management of multidrug-resistant TB. 2nd Edition. Boston: Partners In Health; 2013. Patient on treatment with bedaquiline, delamanid, or with QT prolonging drugs need special follow up with ECG (See Annexes 4.1 and 4.2).

More frequent screening may be advisable for certain types of patients

- Creatinine and potassium may be done weekly in the first month of treatment in the elderly, HIV co-infected, and those with pre-existing renal disease.
- Liver function tests may be done monthly in patients with liver disease, the HIV co-infected, and for those taking bedaquiline.
- TSH test may be done every six months in HIV-negative patients receiving ethionamide (or prothonamide) or para-aminosalicylic acid (PAS) but not taking both together in the regimen.
- Regular HIV serology testing in high HIV prevalence settings.

Additional screening tests for specific drugs

- AZT: when starting, check baseline haemoglobin, after one month, and then every three months afterwards.
- Linezolid: check baseline haemoglobin and complete blood count (CBC) at baseline and then monthly.
- Gatifloxacin: check fasting blood sugar at baseline and then monthly.
- Bedaquiline or delamanid: check an ECG (QT interval) before initiation of treatment, and then at two , four, eight, 12 and 24 weeks after starting treatment (more frequently if heart conditions, hypothyroidism or electrolyte disturbances are present). Check baseline potassium, calcium and magnesium. If QT prolongation is detected, check serum potassium, calcium, magnesium and baseline lipase and repeat if abdominal pain develops.
- Ethambutol or linezolid: use the Ishihara test for visual changes (test all patients at baseline as a certain percentage of people have colour blindness as a genetic variation; repeat if there is suspicion of a change in vision).

Less frequent culture monitoring may be acceptable in some settings

- Programmes with very limited culture capacity may consider doing smears monthly but cultures every other month for the continuation phase.
- Monthly culture monitoring is likely to identify possible treatment failure earlier than less frequent monitoring.

Follow-up after successful completion of MDR-TB treatment

- Check sputum culture at six and 12 months after completion date to evaluate for possible recurrence.

ANNEX 7

Management of electrolyte disturbances[3]

Possible anti-TB drug causes: Cm, Km, Am, S

Possible antiretroviral treatment causes: tenofovir disoproxil fumarate (TDF) (rare)

Suggested management strategy

1. Monitor serum potassium, magnesium and calcium frequently in patients with vomiting/diarrhoea and patients receiving injectables.
2. Hypokalaemia is defined as serum potassium <3.5 mEq/l.
3. Severe hypokalaemia or symptomatic hypokalaemia is <2.0 mEq/l.
4. Hypomagnesaemia is defined as serum magnesium <1.5 mEq/l.
5. Hospitalization is necessary in severe cases of hypokalaemia.
6. Check for signs of dehydration in patients with vomiting and diarrhoea. Start oral or intravenous rehydration therapy immediately until volume status is normal.
7. Replete potassium and magnesium; see tables for guidance.
8. Hypokalaemia may be refractory if concurrent hypomagnesaemia is not also corrected.
9. If unable to check serum magnesium, give empiric oral replacement therapy in all cases of hypokalaemia with magnesium gluconate, 1000 mg twice daily.
10. Check ECG in patients with significant serum electrolyte disturbances. Drugs that prolong the QT interval should be discontinued in patients with evidence of QT interval prolongation.
11. Electrolyte abnormalities are reversible upon discontinuation of the injectable. Even after suspending the injectable, it may take weeks or months for this syndrome to disappear, so electrolyte replacement therapy should continue for several months after completion of the injectable phase of multidrug-resistant tuberculosis (MDR-TB) treatment.

Comments

Hypokalaemia and hypomagnesaemia are often asymptomatic.

- Moderate cases may present with fatigue, myalgias, cramps, paresthesias, lower extremity weakness, behaviour or mood changes, somnolence and confusion.
- Severe disturbances can lead to tetany, paralysis and life-threatening cardiac arrhythmias.

[3] This annex is adapted from The PIH guide to the medical management of multidrug-resistant TB. 2nd Edition. Boston: Partners In Health; 2013.

Hypokalaemia and hypomagnesaemia are common in patients receiving MDR-TB treatment. Common causes are:

- Vomiting and diarrhoea.
- Renal tubular toxicity from the injectable (probably more common in capreomycin than the aminoglycosides).
  - Injectables can cause a syndrome of electrolyte wasting, including potassium, magnesium, calcium and bicarbonate.
  - This syndrome is more common and severe in HIV co-infected patients; and hospitalization and aggressive serum electrolyte monitoring and correction may be necessary.
- Formulations of oral potassium chloride vary by manufacturer and country. Slow-release versions are common in resource-limited settings. The amount of potassium is often different than the tablet size. For example, one 200 mg tablet of Slow-K contains 8 mEq of potassium.
  - Oral potassium, magnesium or calcium should be administered either two hours before or four to six hours after fluoroquinolones as they can interfere with fluoroquinolone absorption.
  - Oral potassium can cause nausea and vomiting. Oral magnesium can cause diarrhoea.
- Dietary intake of potassium should be encouraged. Bananas, oranges, tomatoes and grapefruit juice are good sources of supplementation.
- Amiloride 5 to 10 mg orally daily or spironolactone 25 mg orally daily may decrease potassium and magnesium wasting due to the injectable and may be useful in severe cases that are refractory to replacement therapy.

Potassium replacement therapy

POTASSIUM LEVEL	DOSING	MONITORING FREQUENCY
4.0 or more	None	Monthly
3.6–4.0	None	Monthly
3.3–3.5	40 mEq orally daily	Monthly
2.9–3.2	60–80 mEq orally daily	Weekly
2.7–2.8	60 mEq orally three times a day	One to two days
2.4–2.6	80 mEq orally every eight hours	Daily
<2.4	10 mEq/hr IV and 80 mEq orally every six to eight hours	One hour after infusion, every six hours with IV replacement

Note: The normal preparation of a potassium chloride infusion is 40 mEq in 200 ml of normal saline. Do not exceed an infusion rate of 20 mEq/hr (100 ml/hr).

Magnesium replacement therapy

MAGNESIUM LEVEL	TOTAL DAILY DOSE	MONITORING FREQUENCY
2.0 or more	None	Monthly
1.5–1.9	1000 mg–1200 mg	Monthly
1.0–1.4	2000 mg	One to seven days
<1.0	3000 mg–6000 mg	Daily

Note: Quantities greater than 2000 mg are usually given by IV or intramuscular (IM). The normal preparation is magnesium sulfate 2 g in 100 ml or 4 g in 250 ml of 5% dextrose or normal saline. Do not exceed an infusion rate of 150 mg/min (2 g in 100 ml administered over one to two hours, 4 g in 250 ml administered over two to four hours).

Calcium replacement therapy

CALCIUM LEVEL (TOTAL NONIONIZED CALCIUM VALUE ADJUSTED FOR LOW ALBUMIN)	DOSING	MONITORING FREQUENCY
>8.5 mg/dl (>4.2 mEq/l)	None	
7.5–8.4	500 mg three times a day	Monthly
7.0–7.4	1000 mg three times a day	One to two weeks
<7.0	Consider intravenous and taper to 1000 mg three times a day	One to four days

Note: Normal calcium is 8.5–10.3 mg/dl (2.12–2.57 mmol/l). To adjust for low albumin in nonionized values of calcium, use this formula: Corrected calcium = 0.8 x (4.0 – measured albumin) + reported calcium. If ionized calcium is being tested, it does not need to be adjusted for low albumin and normal value is 4.5–5.6 mg/dl (1.11–1.30 mmol/l).

ANNEX 8

Management strategy for hearing loss[4]

Possible anti-TB drug causes: S, Km, Am, Cm, Clr

Possible antiretroviral treatment causes: tenofovir disoproxil fumarate (TDF) (rare)

Suggested management strategy

1. Develop a management protocol and train all staff responsible for delivering treatment of MDR-TB on its implementation
2. Inform patient about the early symptoms of ototoxicity, such as tinnitus and dizziness.
3. Perform a monthly audiometry of every patient on injectables, starting with a baseline at the time of enrolment on treatment.
4. If the patient is experiencing clinically significant ototoxicity, decrease the dosing frequency of the injectable to two to three times a week. Consider switching to capreomycin.
5. Stop the injectable if symptoms worsen despite dose adjustment, and add additional anti-TB drugs to reinforce the regimen.
   - Even when additional drugs are not available, stopping the injectable agent can be considered based on the patient's desire to maintain hearing.
   - Ototoxicity is one of the few adverse effects that can be permanent and may necessitate discontinuation of a class of agents.
   - If tinnitus and unsteadiness develop and these are attributable to vestibular toxicity, stop the injectable agent. Persistent vertigo and ataxia is an intolerable toxicity and not reversible.

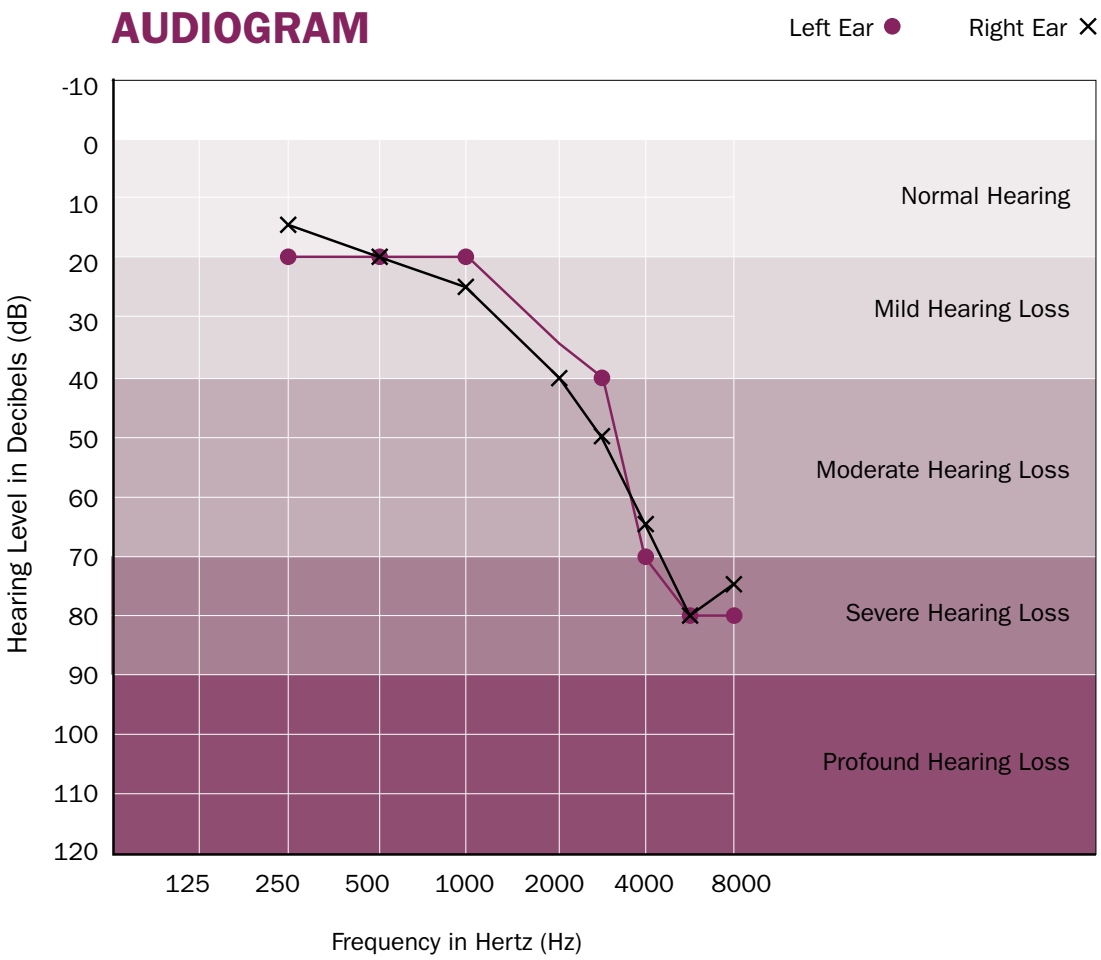
Comments

- Ototoxicity refers to damage of the hearing apparatus of the inner ear, including the cochlea, vestibule, semicircular canals and cranial nerve VIII.
- Symptoms include hearing loss and tinnitus, as well as vestibular symptoms such as disequilibrium and vision problems.
- Ototoxicity is commonly observed in patients receiving large cumulative doses of injectable agents. Capreomycin may be less ototoxic than aminoglycosides.
- Some degree of hearing loss occurs with most patients taking an injectable, but high-frequency loss may not significantly affect the patient's quality of life.
- Patients with previous exposure to aminoglycosides may have already sustained a degree of hearing loss. These patients are at the highest risk of incurring further ototoxicity. In such patients, audiometry may be helpful in guiding therapy to prevent further damage.

[4] This annex is adapted from The PIH guide to the medical management of multidrug-resistant tuberculosis, 2nd Edition. Boston: Partners In Health; 2013.

- Concomitant use of furosemide, particularly in the setting of renal insufficiency, may exacerbate ototoxic effects of the injectables.
- Hearing loss and vestibular dysfunction are generally not reversible upon discontinuation of therapy.
- Mild disequilibrium can also be caused by cycloserine, fluoroquinolones, ethionamide/prothionamide, isoniazid or linezolid. Stopping all anti-TB drugs for several days can help to distinguish the cause of disequilibrium.
- Some patients may choose to tolerate significant hearing loss to achieve a higher chance of cure. This should be discussed between the patient and a physician trained in MDR-TB. Continuing the injectable in such situations almost always results in permanent hearing loss.
- There is little experience to date regarding substitution with newer agents such as bedaquiline or delamanid when signs of auditory or vestibular toxicity appear, but may prove to be a useful strategy.
- The benefit of hearing aids is minimal to moderate in overcoming auditory toxicity but may be helpful in some patients. Strict adherence to the current WHO interim policy on bedaquiline is recommended in that case.

Example of an audiogram showing high-frequency hearing loss due to aminoglycosides



Source: Auditory neuroscience: making sense of sound. (http://auditoryneuroscience.com/acoustics/clinical_audiograms, accessed 30 June 2013)

Notes on audiogram

- This audiogram represents high-frequency hearing loss, which is often the first sign of auditory toxicity due to injectable agents.
- The patient with this audiogram could still hear conversations. Frequencies around 2000 Hz are the most important for understanding conversations, and the patient has only moderate hearing loss in this area.
- Often patients do not notice hearing loss above 4000 Hz.
- An audiogram that demonstrates hearing loss as illustrated above is a good example of a situation where suspending (or substituting) a different anti-TB drug is indicated; this can prevent further loss of hearing.

Whenever hearing loss has developed, advise and guide patient regarding suitable options for rehabilitation. Such options include use of hearing devices such as hearing aids and cochlear implants; sign language education; and social and psychological support. The national TB programme may need to establish collaboration with appropriate specialists to develop referral protocols for effective management of persons developing severe ototoxic effects of MDR-TB treatment.

ANNEX 9

"How-to" guide for forecasting drugs needs and tools for quantification and forecasting

A9.1 How to forecast (steps to follow):

National tuberculosis control programmes (NTPs) need to be able to determine how many drugs are needed and to monitor if there is risk of stockouts, overstocks or expiration. The use of accurate assumptions for quantification of all steps is essential. This requires the central NTP to collaborate with treatment facilities and warehouse personnel to collect and consolidate accurate information on patient treatment and stock position of second-line anti-TB drugs. Coordination of the NTP with the procurement unit is also important to facilitate drug orders and deliveries.

The following formula is used for quantification for total drug requirement:

Total drug requirement = (consumption of new patients)
+ (consumption of ongoing patients) – (stock on hand)

When starting up a drug-resistant TB programme, if there are no patients under treatment yet, both consumptions mentioned above are zero. However, delivery schedules and quantities need to be analysed with the stock on hand and the expiration details. Schedule the deliveries by splitting quantities to avoid possible expiration.

Steps in forecasting of second-line anti-TB drug:

1. Obtain the following information and use the formula below to get the drug requirement for new patient enrolment:
   - Number of new patients enrolled
   - Treatment regimen being used and duration of treatment for both intensive and continuation phases (calculated in days per month x months of treatment)
   - Average daily dose per drug
   - Percentage (%) of utilization per drug
     This refers to the % of patients who will use the drug, or the number of expected patients who will use the drug over the total number of patients. If out of 10 new patients enrolled all will be using Pto, then the % of utilization of Pto is 100%. A % utilization

of 10% for Cm and 90% for km means that if the new patients enrolled are 100, then 10 patients are expected to receive Cm and 90 of them are expected to receive km.

Consumption of new patients = (# of new patients) x (% of utilization) x (average dose) x (duration of treatment in days) x (months of treatment).

For example, the programme is about to enrol 100 patients in the next year with the following treatment regimen: 8 Km(Cm) Lfx Pto Cs / 12 Lfx Pto Cs, where 10% of the patients are expected to take Cm and 90% will be on Km.

Quantification for these new patients will then be:

DRUG	NUMBER OF PATIENTS	% UTILIZATION	AVERAGE DAILY DOSE	DURATION OF TREATMENT: DAYS X MONTHS	TOTAL DRUG REQUIREMENT FOR NEW PATIENTS
Km 1 g vial	100	90%	1 vial	26 days x 8 months	18 720 vials
Cm 1 g vial	100	10%	1 vial	26 days x 8 months	2080 vials
Lfx 250 mg tablet	100	100%	3 tablets	26 days x 20 months	156 000 tablets
Pto 250 mg tablet	100	100%	3 tablets	26 days x 20 months	156 000 tablets
Cs 250 mg capsule	100	100%	3 capsules	26 days x 20 months	156 000 capsules

2. Add the drug requirement for ongoing patients (depending on the number of patients under treatment, a paper based or excel system might become a real challenge to calculate these requirements without more advanced tools or electronic platforms. See available tools and description in Annex 2).
3. Subtract the stock on hand including the quantities in the pipeline.

A9.2 Tools for quantification and forecasting

1. WHO second-line anti-TB drug estimation and request tool – in Excel
   - Helpful in starting up a drug-resistant TB programme
   - Accommodates standardized, individualized and empiric treatment regimen
   - Accommodates increasing patients enrolment for scale up of programme
   - Plans the quantities and delivery schedule of medicines
   - Includes the costing of medicines for funding and budgeting purposes
   - Cannot add more drugs not listed in the tool
   - Does not consider existing stock on hand and drugs in the pipeline
   - Does not consider continuing/ongoing patients

2. QuanTB – Tuberculosis Medicines Quantification Tool (http://siapsprogram.org/quantb/)
   - Helpful in starting and continuing TB and drug-resistant TB programmes
   - Accommodates first- and second-line standardized, individualized and empiric treatment regimen
   - Can add or edit medicines and treatment regimens in the tool; available in multiple languages
   - Considers existing stock on hand and drugs in the pipeline
   - Estimates drug requirements of ongoing and new cases as they progress through treatment phases based on their actual regimen
   - Estimates months of stock and quantities of medicines likely to expire
   - Plans quantities for regular and emergency delivery schedules of the medicines
   - Accommodates increasing patient enrolments for programme scale up and develop alternative caseload and regimen scenarios to phasein or phaseout
   - Includes the costing of medicines for funding and budgeting purposes
   - Provides a dashboard to serve as an early warning mechanism for expiring medicines, stockout, and overstock

3. GDF second-line anti-TB drug forecasting tool – in Excel
   - Helpful in starting up and continuing a drug-resistant TB programme
   - Accommodates standardized, individualized and empiric treatment regimen
   - Able to monitor drug utilization and drug status monthly
   - Estimates when the programme has possibility of stockout and/or wastage due to expiration
   - Estimates quantities of medicines due for expiration
   - Considers ongoing patients and estimates future drug requirements based on their actual regimen
   - Considers existing stock in hand and drugs in the pipeline
   - Accommodates increasing patient enrolments for scale up of the programme
   - Direct collaboration to drug point persons from the treatment centres and the warehouses

4. e-TB Manager (www.etbmanager.org)
   - Web-based tool where the drug management module is linked with the case and laboratory module
   - Comprehensive drug management module which includes not just the component for forecasting but other aspects of drug management, such as real time stock position, medicine request and medicine transfer
   - Helpful in continuing the MDR-TB programme
   - Considers ongoing patients and estimates future drug requirements based on their actual regimen entered in the system
   - Accommodates increasing patient enrolments for scale up of the programme
   - Estimates when the programme has possibility of stockout and/or wastage due to expiration
   - Estimates quantities of medicines due for expiration

- Considers existing stock on hand in the forecast
- Able to monitor drug utilization and drug status

Other electronic systems have been implemented to register TB patient data, such as OpenMRS, OpenXdata, Imogène systems and WEB-TBS. While these systems have space to register patient treatment doses they do not have functionalities for drug quantification.

ANNEX 10

Reinforcing the parameters of observational studies for MDR-TB patients on treatment

A10.1 Background

The central role that data play in the monitoring and control of TB treatment was deeply rooted in global strategies developed since the early 1990s to address the re-emergent threat posed by this disease *(1,2)*. Monitoring and evaluation system, and impact measurement is one of the five pillars which underpinned the DOTS approach to the global epidemic that the World Health Organization and its partners adopted *(3)*. This focus was retained in the more comprehensive Stop TB strategy elaborated in later years *(4)*. Early guidance on running programmes for drug-resistant TB likewise had information systems and data management as one of its five core areas *(5)*. Drug regimens used to treat patients with multidrug-resistant TB (MDR-TB) are of longer duration, requiring a more protracted monitoring of bacteriological markers of disease than for the drug-susceptible forms. MDR-TB is also associated with more adverse events *(6)*. The routine measurement of these parameters, as well as the assignment of the final outcome to the patient at the end of treatment, requires the processing of many more data points. Monitoring treatment outcomes is of the utmost importance for the programme manager to assess patient well-being and risk to the community.

Prior to the studies which were set up to assess the effectiveness of new medicines like linezolid, bedaquiline and delamanid *(7–10)*, randomized controlled trials (RCTs) for treatment outcomes of MDR-TB patients using older "legacy" second-line drugs have been absent. The latest WHO recommendations on the composition and duration of second-line regimens are thus largely based on observational studies of MDR-TB patients treated in national programmes under field conditions *(11,12)*. Evidence based on observational studies is usually rated as "low" or "very low" quality, presenting challenges when used for policy making *(13)*. Despite the advent of RCTs in the field of MDR-TB therapeutics in recent years, it is very likely that to a substantial degree global policy and clinical practice will still depend for years to come on data other than those from properly conducted trials. Following the marketing authorization granted by stringent drug regulatory authorities for bedaquiline and delamanid for use in MDR-TB treatment *(14,15)*, ahead of results from phase 3 studies, a number of countries are expected to start using these new medicines to treat patients outside of a trial setting. During this period, valuable information on the effectiveness and safety of such a medicine could therefore accrue from experience of its use under programmatic conditions.

Another recent development is the introduction of MDR-TB regimens which are substantially shorter than those currently recommended by WHO *(16)*. Alongside a trial designed to test a nine-month standardized regimen as part of a RCT *(17)*, several African countries started to treat MDR-TB patients by early 2013 using such short regimens as part of a multicentre, observational study *(18)*.

While RCTs will remain indispensable to improve the quality of the evidence and the strength of future recommendations, the largest body of new evidence in the use of older and newer TB medicines in the near future is still expected to come from observational studies. Apart from the substantial expense needed to run them, RCTs may not be suitable to answer all questions about a given intervention. Observational studies may be more appropriate to detect rare or late adverse effects of treatments, and are more likely to provide an indication of what is achieved in daily medical practice *(19)*. To this end it is crucial that all practical measures are taken to ensure that data are of the best possible quality. In this section recent experience in using observational study data has been used to develop policy recommendations for the programmatic management of drug-resistant TB and make concrete suggestions on how to safeguard the quality of evidence that is gathered.

A10.2 Data on MDR-TB case management

Compared with other health conditions, the monitoring of MDR-TB has certain specificities that have an important bearing on the methodology needed for the collection of data. Prescribed treatment lasts long, typically 20 months or more. The dose and combination of the antibiotics vary depending on the ones available, the patient's clinical condition and response to treatment. Adverse drug reactions are common and frequently necessitate a change of regimen *(6)*. Comorbidity in the patient, particularly HIV-infection, may necessitate additional medicines to be taken concomitantly *(20)*. The quality of the medicines available on the market can differ substantially *(21)*. Repeat bacteriology – sputum smear microscopy, culture (and less frequently repeat drug susceptibility testing (DST)) – is the mainstay method for the assessment of response to treatment. While the definitions of final outcomes are fairly well standardized and widely known *(22)*, those defining cure, treatment failure and most cases of relapse require a bacteriology test result and may thus be influenced by the quality of testing in the laboratories. There is, however, a long-standing tradition in the standardized registration and reporting of outcomes in "cohorts" within TB programmes and a similar approach has also been widely used for MDR-TB *(23)*. These cohorts represent new enrolments on treatment during one year in one country or unit(s) specialized in treating MDR-TB patients. By 2013, over 100 countries were reporting aggregated outcome results to WHO for more than 34 000 MDR-TB patients started on treatment in national cohorts *(24)*. As a rule, the choice of treatment for these patients is determined by the medicines available to the health care provider and in the country, the national policy and patient factors, namely the resistance profile of the infecting strain, history of previous use of a particular medicine and response to treatment or adverse reactions. No randomization of patients to a particular regimen is used. Some of these cohorts have been monitored prospectively using standardized parameters for a number of years *(25),* and such studies allow more detailed and accurate observation of the determinants of patient outcome.

A10.3 On existing evidence and its quality

When developing recommendations for clinical and public health practice, WHO has adopted the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) to assess the quality of a given body of evidence *(26)*. GRADE uses internationally agreed standards for making recommendations in a transparent way. As part of this process, the quality of evidence is rated on a 4-point scale from "very low" to "high" (see table below *(13)*).

QUALITY	DEFINITION
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

Five factors are important for the quality of evidence:

1. Limitations in the study design and execution
2. Consistency: conformity in findings between different studies looking at the same question
3. Directness: whether the evidence directly answers the question
4. Precision: the degree to which repeated measurements show the same results
5. Publication bias: in terms of what is likely to get published out of what is available

Well-conducted RCTs usually generate data of "high quality". In contrast in well-conducted observational studies, the quality of evidence usually starts at "low". This implies that any effect observed from such studies is uncertain and that bias cannot be fully excluded. Upgrading the quality of evidence may be warranted if the magnitude of the effect is very large, if there is evidence of a dose–response gradient or if all plausible residual confounding may reduce the demonstrated effect or increase the effect if no effect was observed. However, quite often the opposite happens and flaws in design or in the conduct of the study lower the quality of evidence to "very low".

In the coming years, the biggest knowledge base on results of MDR-TB patient treatment using the standard second-line anti-TB medicines will still remain heavily reliant on observational studies. Pragmatic measures to safeguard the value of this body of evidence are therefore important.

A10.4 Profiling the main concerns of observational studies

In this section, the weaknesses in the knowledge base of studies employing older anti-TB medicines for the treatment of MDR-TB patients are identified and grouped under five areas. All of these have an important bearing on the quality of evidence and implications on its reliability as a basis for sound policy making.

1) Lack of randomization: The vast majority of existing information relating treatment outcomes to MDR-TB regimen composition and duration of treatment is based on observational studies without any randomization of patients to different treatment arms *(11)*. This may introduce bias in the way that patients are assigned to a given combination of drugs and the way that they are monitored in the course of treatment. In contrast the effectiveness of new anti-TB medicines, such as bedaquiline and delamanid, has been studied using randomized methods *(8,10)*.

2) Heterogeneity of study design: Observational studies vary in form and include longitudinal cohorts, case–control studies, case series, case reports, interrupted time-series and studies with quasi-experimental design. A number of them are operational research projects in which parameters were well defined ahead of starting and adhered to during conduction of the study. However, there is a large body of data, some of it published, which is based on the treatment of patients under the conditions that normally occur in the field *(27)*. The adherence of such cohorts to standardized methodology varies. Programmes usually have broad eligibility criteria as they need to cater to all their patients, while some special studies are more selective in their inclusion (e.g. shorter regimens *(16)*). The size of the studies also varies, and a number of published series are composed of less than 25 subjects. These small studies are likely to generate results that are not representative of the whole constituency of MDR-TB patients in a country. Indicators and definitions used are sometimes not aligned between studies because the data have not been uniformly collected and definitions not applied consistently.

3) Comparability of intervention: Most MDR-TB regimens in use today are composed of medicines that have been in use for several decades. However, MDR-TB regimens are commonly individualized with a composition, dosage and duration determined by the patient's condition and very often the availability of the medicines themselves. Matching patients to their treatment opens up to the risk of bias. For example, treatment with more medicines is more likely to be used for sicker patents. Some studies dating back more than a decade employed early generation fluoroquinolones, which have since been replaced by more effective ones. The evidence for certain aspects of management may be context-specific and difficult to extrapolate, such as the effectiveness of MDR-TB care in specialized centres as opposed to decentralized mainstreaming in primary care: this may be difficult to standardize in a way that can be generalized to different settings. Any recommendations derived on such findings would therefore require much deliberation by experts with a reduction in their reliability.

4) Completeness of data: There may be incomplete information on proxies of disease severity (such as bacterial load on direct sputum microscopy, radiograph images, clinical grading, and delay till start of treatment), HIV status, bacteriological endpoints (especially culture results on fixed dates), relapse, adverse drug reactions (including serious ones), and reasons for interruption of treatment and death.

5) Absence of information: A number of useful indices of care which are important to the patient (such as cost and quality of life), and to the programmes may be missing. Cost to the service – an important consideration when assessing resources for MDR-TB treatment – is often not reported in the same manner as other more conventional outcomes, such as cure, death, failure and relapse.

A10.5 Addressing potential weaknesses proactively

Measures to protect the quality of studies to the maximum possible must be instituted at different stages of a study: at design, during the collection of data, during recruitment of subjects and when results are reported. When designing observational studies – including cohort event monitoring (CEM) for active pharmacovigilance – the factors in Section A10.3 above require special attention to avoid evidence derived from these studies from getting downgraded to the "very low" quality category.

Different approaches are required to limit the factors that can lower the quality of evidence. Bias: a number of biases in selection, measurement, confounding and publication can occur. Patient and programme-related data need to be captured and reported in a standardized and exploitable manner. This can improve generalizability and decrease confounding. Losses and variations in the duration of follow-up to determine relapse should be reduced to a minimum. The rigour and completeness of crosschecks with vital statistics to trace deaths need to be upheld. Completeness of information (e.g. sputum smear results and DST of all fluoroquinolones and injectable drugs) needs to be ensured. When results are published it is important to express the magnitude of effect well, to indicate any dose–response relationship that may have been observed, and to discuss whether the direction of all plausible bias is more likely to reduce the effects observed. The publication of negative findings is important.

Consistency: Data have to be collected on covariates, which will be needed in order to adjust for heterogeneity at the analysis phase.

Directness: The primary and secondary outcomes, in alignment with the main research question/s, need to be defined.

Precision: Ensure the inclusion of maximum possible subjects and observations. The use of equipment, which gives reproducible and precise measurements, is important.

The systematic collection of data in a standardized manner is of paramount importance in observational studies. The patient Treatment card (Part 4, Form 01) provides the main data elements needed for most observational studies. However, if active pharmacovigilance for adverse events during treatment is to be mounted alongside the usual parameters monitored, particularly when new medicines or "shorter regimens" are introduced, additional data will be needed *(28,29).* Other facets of a programme's performance, including cost and the model of care, which are not usually measured systematically may also be captured.

A10.6 Data collection: the "what" and the "how"

This section focuses on practical measures to ensure that data are managed in the best possible way. The collection of patient-level data has already been described in other parts of this Handbook, particularly Part 4, Form 01. However, these data will not be sufficient for the purposes of observational studies designed to measure both indicators of effectiveness and adverse effects.

Programmes will need to develop **questionnaires** in paper or electronic format to capture patient data. These forms need to combine the variables that are necessary to assess response to treatment (effectiveness) as well as adverse events (harms), especially in an individual exposed to new medicines or novel regimens. They also need to have information, which will also be used to adjust observed effects by patient strata (e.g. by age, previous treatment history or disease severity). Well-designed forms will greatly facilitate the collection of reliable data. Tables A10.1 and A10.2 define the key data elements required for patient registration in observational studies of MDR-TB treatment (adapted from references *(5,30)*). A clear distinction is made between the two instances at which data are collected.

1. **Treatment initiation**: collection of the **baseline** dataset is completed when the patient is starting treatment and is enrolled within a "cohort" (Table A10.1). Adjustments may be made subsequently following further verification of patient status at initiation;
2. **Treatment review:** the **review** updates are registered at each follow-up encounter with the patient (Table A10.2).

Where paper-based records are in use this would require **two separate forms** for initiation and review encounters. Much of the same information may already be captured in the Second-line TB treatment card (Part 4, Form 01): in such instances the programme may adapt the forms in use to avoid repeated registration. Examples of forms which combine the data needed for TB case management, pharmacovigilance and observational studies and which can be adapted to specific programme needs are due to be published shortly *(31)*. In settings where electronic systems are used to manage patient data, adjustments can be made to the existing database in order to capture additional variables at the required frequency for the subset of patients who are included in CEM.

The indicators of effectiveness and adverse effects, and the frequency with which they are generated, need to be decided in advance. The standard indicators for treatment outcome as used in programmes have been described in this Handbook (Chapter 2). Other indicators, such as time to conversion, relapse and frequency of serious adverse events, would need to be defined and customized to the specific needs of the individual programme. Standard criteria of seriousness and severity for adverse events need to be defined by the programme (such as in page 106 of reference *(28)*).

Many observational studies of MDR-TB treatment do not report about the cost of the intervention to the service or to the patient. Adding a cost dimension will greatly aid in describing the resources needed with greater precision. It would also allow the derivation of composite outcomes that incorporate costs. Table A10.2 suggests some data elements that may be collected at the individual case level to better profile such expenditure. In order to enable comparisons between sites it is helpful to gather information on key activities, such as the average number of health care worker visits, and number of tests, supplies and medicines. However, these are not exhaustive as they fail to capture amongst others the capital costs to a programme and other running costs (e.g. training and technical assistance), and also the direct and indirect costs incurred by the patient as a result of the disease and the treatment given. Patients on treatment often suffer substantial losses as a result of the need to stop working, to travel or to move home *(32)*. More elaborate instructions on how to collect data for cost

description and cost-effectiveness analysis in TB control have been published and these can be adapted according to the needs of the programmatic component of drug-resistant TB *(33)*.

- The use of electronic systems is indispensable for the proper collection, storage, management, transfer and analysis of data *(30)*. A few key principles in the use of electronic systems are highlighted.
- While the potential advantages of electronic recording and reporting are considerable, so too are the possible pitfalls. Adopting electronic recording and reporting does not stop at the choice of computers and software. Much of it is about changing how people work. In addition to the data entry personnel, programmers and other staff who need to work in concert; the infrastructure required to support a system may be quite important (proper maintenance of equipment, electricity, internet and communication networks).
- When transferring data to an electronic system it is important that the records remain intact, standardized and comparable. Transcription of data between systems (e.g. from a paper treatment card to an electronic database) is an eminent source of error. Direct entry of data onto a computer interface, be it on a desktop, laptop, tablet or smartphone, may obviate this extra step. In an electronic system, a number of validation checks can be built in to alert the user when implausible or inconsistent values are entered, prompting checks and corrections as necessary.
- When paper-based systems are updated, newly printed materials such as forms, registers and reporting templates also need to be modified, printed and distributed, and older versions of printed materials removed from circulation. This is usually a slow process. In contrast, with careful planning and the right skills, well-designed electronic systems can be modified relatively quickly and consistency guaranteed throughout.
- If data from observational studies are to be exploited properly they need to be made available to the researcher in individual data format, for each treatment episode or unique patient. In routine TB surveillance such individual data are usually only available at the health facility or district level. When these data are registered in electronic format they can be shared more efficiently with the persons who need them. In this format they may also be merged in a multicentre dataset from other centres or countries thus making more in-depth hypothesis testing possible.
- The database architecture needs to allow for data from the reviews to link up with those for the baseline dataset. A unique key in an electronic dataset obviates the need to re-enter identifiers of the patient and health centre at each review: these data may be useful for validation purposes but can be removed when this process is completed in order to anonymize records ahead of their analysis. Otherwise the system should not be encumbered with data that will not be used for analysis (e.g. telephone numbers, details on daily administration of medicines and other non-specific commentary). Many different packages have been successfully employed for this purpose, including open-source ones that bear no license fees for the user.
- Aggregation of data is useful to assess progress in implementation. When data are stored electronically it is possible to automate the production of standard indicators and reports and modify these according to the need.

A10.7 Conclusion

Is it expected that any programme treating MDR-TB patients under normal field conditions will contribute to the global knowledge base on this aspect of care? The answer is "probably not". In contrast to routine monitoring and evaluation of patients, operational research is not expected of all programmes providing MDR-TB care. But more programmes could mount such studies by tightening up the parameters of their existing "cohorts" with a relatively small amount of additional investment. Better data, in greater quantity, and with a broader geographical span would present a valuable addition to what is available today. It would help cut down on the many unknowns and uncertainties, which still surround the treatment of MDR-TB patients. The patient series which are most likely to enrich the existing data will need the following features as a minimum:

- Treatment centres with reliable access to good quality medicines and monitoring facilities, run by staff with good proficiency in clinical care.
- A quality-assured methodology for the study parameters and organization of data, respecting ethical norms and standards for data management.
- Series with relatively large numbers of patients of a diverse age and sex profile, without very narrow eligibility criteria, and in whom an optimized second-line drug treatment regimen for MDR-TB was used throughout, making the intervention more straightforward to interpret and to apply to other settings.
- A sound analysis, reporting of indicators, listing of limitations and the results published or submitted to a peer-reviewed journal. Elaborate checklists on how to report the different types of observational studies are available as part of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement *(34)* (www.strobe-statement.org/index.php?id=available-checklists).

Table A10.1. Baseline data at MDR-TB patient treatment initiation (see also Annex 6 and reference *(28)*)

DOMAIN	DATA ELEMENT	ANSWER OPTIONS AND OTHER REMARKS
Location	Geographic area	Country, region, district, city or ward in which the patient is started on treatment; use unique codes for place names.
	Facility name	Unique code of reference of the health centre
	Facility type	Public/private; specialized or general; primary, secondary, tertiary

DOMAIN	DATA ELEMENT	ANSWER OPTIONS AND OTHER REMARKS
Identification and demographic	Unique patient number	Patient personal ID (e.g. social security number). In patient-based information systems this will be identical for all treatment episodes. Important for data linkages between different data sources, e.g. recovery of HIV testing results
	Unique registration number	The code for the specific MDR-TB treatment episode being registered. The same patient may have >1 code assigned over time for different treatment episodes. Important for data linkages between different data sources, e.g. recovery of DST results from laboratory databases
	Patient names	As generally used by the patient (e.g. first, middle and family names)
	Date of birth	If full date (i.e. dd/mm/yyyy) is not known provide the year of birth or age in completed months or years
	Sex at birth	Male, female
	Origin	By country of birth or, if not available, citizenship. Race or ethnicity is used in some countries.
	Civil status	Married, single, other union, widow/er, divorced/ separated [information can be updated at review]
	Employment	Employed, retired, student, unemployed
	Imprisonment	If yes, to identify if current/previous and duration of imprisonment
	Current homelessness	Yes, No
Baseline clinical assessment	Date of interview	dd/mm/yyyy; could be same as date of registration
	Date of diagnosis	The date (dd/mm/yyyy) when the patient was first diagnosed with the current episode of RR-/MDR-TB; usually based on clinical manifestations, or radiology plus bacteriology and DST
	Site of disease	Pulmonary, extrapulmonary (exact site)
	Previous TB	Yes, no, unknown If Yes, date of diagnosis of each episode, number of treatments, drug regimen composition and duration, and DST pattern Assign the *patient registration group* (as per the Treatment card [Part 4, Form 01] of this Handbook)
	Previous TB treatment outcome	If previously treated the outcome of the latest episode (cured, completed, failed, lost to follow up, unknown)
	Other medical history	Including at least HIV/AIDS, diabetes mellitus, malnutrition, renal insufficiency, hepatic insufficiency/ cirrhosis, cardiac dysrhythmias, chronic obstructive pulmonary disease, convulsions, psychiatric conditions, drug use, alcohol use, smoking

DOMAIN	DATA ELEMENT	ANSWER OPTIONS AND OTHER REMARKS
	History of allergy or adverse drug reactions	Indicate the medicine and classify the type of reaction according to MedDRA and parameters of severity and seriousness *(28)*
	New events	Include all new events or changes in pre-existing conditions that began in the 30 days prior to the baseline interview. Include date of onset, and if applicable, date resolved (dd/mm/yyyy), outcome, severity and seriousness *(28)*.
	Currently pregnant	Yes, no, uncertain (date of last menstruation may be recorded)
	Breastfeeding infant	Yes, no
	Contacts	Line list, for each close contact at home and elsewhere, the: relationship, age, history of TB and TB treatment, current clinical manifestations of TB and results for any testing done [information can be updated at each review]
	Patient symptoms	Fever, weight loss, cough, haemoptysis, dyspnoea, others (specify)
	Patient height	In centimetres
	Patient body weight	In kilogrammes and expressed as body mass index
	Abnormalities noted at examination	By functional system: head, ears, nose, and throat; vision; thyroid; lymphatic system nodes; cardiac; pulmonary; abdominal (including pancreas); skin; musculoskeletal; urogenital; neurological; extremities; other (specify)
	Functional status	Not ambulatory; ambulatory; able to work
Baseline bacteriology & drug susceptibility testing (DST)	Date sample collected	Standard notation (dd/mm/yyyy) for each test
	Date result issued	Standard notation (dd/mm/yyyy) for each test
	Microscopy	Use standard notation [see page 11 of reference *(22)*]
	Xpert MTB/RIF test	Use standard notation [see page 12 of reference *(22)*]
	Culture	Use standard notation [see page 12 of reference *(22)*]
	DST	Use standard notation [see page 12 of reference *(22)*]

DOMAIN	DATA ELEMENT	ANSWER OPTIONS AND OTHER REMARKS
Results of other baseline investigations	Date sample collected	Standard notation (dd/mm/yyyy) for each test
	HIV test	Positive, negative, indeterminate
	CD4 count	
	Glucose	
	Electrolytes	Levels of potassium, magnesium, calcium
	Renal function	Urea, creatinine, creatinine clearance
	Liver function	ALT (SGPT), AST (SGOT), bilirubin, albumin
	Blood indices	Haemoglobin, haematocrit, leukocytes, platelets
	Electrocardiogram (ECG)	Rate; rhythm; trace; QTc interval
	Chest radiography	Cavitary; extent of parenchymal disease; uni- or bilateral (useful in grading extent and severity of disease)
	Other	Specify (e.g., thyroid stimulating hormone)
Treatment given	Date of registration for treatment	Standard notation (dd/mm/yyyy) for date when the record was entered in the Second-line TB treatment register
	Date treatment starts	Standard notation (dd/mm/yyyy) for each medicine taken at any time in the previous 30 days
	Date treatment stops	Standard notation (dd/mm/yyyy) for each medicine taken at any time in the previous 30 days
	Anti-TB medicine	For each medicine give: name, dosage, frequency, route
	Other medicines and traditional medicines	For each medicine given in the past 30 days name, indication, dosage, frequency, route, and if it is currently being used

Table A10.2. Data collected at MDR-TB patient review (see also Annex 7 in reference *(28)*)

DOMAIN	DATA ELEMENT	ANSWER OPTIONS AND OTHER REMARKS
Identification	Unique patient number	See Table A10.1
	Unique registration number	See Table A10.1
	Patient names	See Table A10.1

Clinical assessment at review	Date of review	Standard notation (dd/mm/yyyy) for date of encounter
	New events	Include all new events or changes in pre-existing conditions that began since the last interview. Include date of onset and if applicable date resolved (dd/mm/yyyy), outcome, severity, seriousness and re-challenge *(28)*
	Pregnancy	Yes, no, uncertain (date of last menstruation may be recorded)
	Breastfeeding infant	Yes, no
	Patient symptoms	Fever, weight loss, cough, haemoptysis, dyspnoea, others (specify)
	Patient height/ length	In centimetres
	Patient body weight	In kilogrammes and expressed as body mass index
	Abnormalities noted at examination	By different functional system: head, ears, nose, throat; vision; thyroid; lymphatic system nodes; cardiac; pulmonary; abdominal (including pancreas); skin; musculoskeletal; urogenital; neurological; extremities; other (specify)
	Functional status	Not ambulatory; ambulatory; able to work
Bacteriology and drug susceptibility testing (DST)[a] at review	Date sample collected	Standard notation (dd/mm/yyyy) for each test
	Date result issued	Standard notation (dd/mm/yyyy) for each test
	Microscopy	Use standard notation [see page 11 of reference *(22)*]
	Culture	Use standard notation [see page 12 of reference *(22)*]
	DST	Use standard notation [see page 12 of reference *(22)*]
Results of other investigations at review	Date sample collected	Standard notation (dd/mm/yyyy) for each test
	HIV test	Positive, negative, indeterminate
	CD4 count	
	Glucose	
	Electrolytes	Levels of potassium, magnesium, calcium
	Renal function	Urea, creatinine, creatinine clearance
	Liver function	ALT (SGPT), AST (SGOT), bilirubin, albumin
	Blood indices	Haemoglobin, haematocrit, leukocytes, platelets
	Electrocardiogram (ECG)	Rate; rhythm; trace; QTc interval
	Chest radiography	Cavitary; extent of parenchymal disease; uni- or bilateral (useful in grading extent and severity of disease)
	Other	Specify (e.g., thyroid stimulating hormone, lipase)

[a] The frequency of the tests is determined by the monitoring and evaluation policy. However, monthly sputum smear and culture are generally recommended and DST may need to be repeated in the case of failure of conversion or to investigate the possibility of acquisition of additional resistance *(35,36)*. The capture of data on bacteriology is important; its absence in the past has limited the possibility to undertake analyses to determine the optimal duration of intensive and continuation phases.

Treatment given	Date treatment starts	Standard notation (dd/mm/yyyy) for each medicine taken at any time since the last interview
	Date treatment stops	Standard notation (dd/mm/yyyy) for each medicine taken at any time since the last interview
	Anti-TB medicine	For each medicine give: name, dosage, frequency, route, if it is currently being used, reason for stopping (if the case) and adherence (>80% of doses taken or <80% of doses taken)
	Other medicines and traditional medicines taken since last interview	For each medicine give: name, indication, dosage, frequency, route, if it is currently being used and reason for stopping (for recommended coding see page 101 in reference *28*)
	All new medicines prescribed at this encounter	For each medicine give: start and expected stop dates (dd/mm/yyyy), name, indication, dosage, frequency and route
	Surgery[b]	Type, extent, use of anaesthesia, hospital stay and complications
Outcome	Date of final outcome	Standard notation (dd/mm/yyyy) for date outcome met
	Final treatment outcome	Cured, treatment completed, treatment failed, died, lost to follow up, not evaluated (as defined in page 7 of reference *(22)*). ICD code for cause of death is recommended.
Cost	Medicines	Unit cost per medication given
	Tests	Cost of individual tests at diagnosis and monitoring; frequency (including screening of contacts)
	Hospitalization	Number of days hospitalized and unit cost per day
	Surgery	Individual cost of intervention/s
	Outpatient clinic visits[c]	Number of visits to a health centre or specialist consultations and unit cost per visit
	Home visits[c]	Number of visits to patient's home by treatment supporter and unit cost
	Incentives to patient	Overall cost
	Incentives to supporters	Overall cost

[b] Given that surgical interventions are often customized and not easy to standardize it may be useful to retain a copy of the individual patient notes, which can be consulted if additional details are needed during data analysis.

[c] If unit costs are not available in a particular setting they may need to be derived using duration of visits multiplied by the estimated cost of human and material resources consumed in each situation.

A10.8 References

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ANNEX 11

Sample forms for Core Package of aDSM

11.1 Clinical and laboratory testing schedule for aDSM

To be adapted to the treatment regimen and national policy[1]

	M0	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23	M24
Date																									
Clinical screen																									
Visual acuity																									
Simple hearing test																									
Audiogram																									
Neuro & psychiatric investigations																									
Serum creatinine																									
ALT (SGPT)																									
AST (SGOT)																									
Bilirubin																									
Alkaline phospatase																									
γGT																									
ECG																									
Lipase																									
Amylase																									
Potassium																									
Magnesium																									
Calcium																									
Albumin																									
CBC																									
Blood glucose																									
Thyroid tests: TSH																									

[1] *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* (WHO/HTM/TB/2014.11). Geneva, World Health Organization. 2014

Shade cells for the months when the test will not be done.

Notation for marking the cells: 0= screen/test not done 1=screen/test done; result pending 2=screen/test done; no SAE 3=screen/test done; SAE detected

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic-oxaloacetic transaminase);

CBC=complete blood count; ECG=electrocardiogram; γGT=gamma glutamyl transferase; TSH=thyroid stimulating hormone.

11.2 Alert for serious adverse events to the TB programme

CONFIDENTIAL – To be sent even upon suspicion of a serious adverse event

IS THIS REPORT A NEW EVENT? YES ☐ NO ☐

GIVE DATE WHEN PREVIOUS SAE FORM SENT: ☐☐ DD ☐☐☐ MMM ☐☐☐☐ YYYY

1. PATIENT DETAILS

LAST NAME _____ FIRST NAME _____

SEX MALE ☐ FEMALE ☐

DATE OF BIRTH ☐☐ DD ☐☐☐ MMM ☐☐☐☐ YYYY

age in yrs if DOB unknown

PREGNANCY YES ☐ NO ☐

ID NUMBER _____ PHONE NO. _____

ADDRESS

2. SUSPECTED and CONCOMITANT MEDICINE(S)

NAME (Brand name or Generic)	Total daily dose	Date started	Date stopped	Continues
				☐
				☐
				☐
				☐
				☐

3. DETAILS OF SERIOUS ADVERSE EVENT

DATE EVENT STARTED _____ DATE EVENT STOPPED _____

DESCRIPTION OF EVENT

WHY IS THE EVENT CONSIDERED SERIOUS?

- ☐ Death
- ☐ Life-threatening event (specify: _____)
- ☐ Hospitalization or prolongation of hospitalization
- ☐ Persistent or significant disability (specify: _____)
- ☐ Congenital anomaly
- ☐ Other (specify: _____)

4. ACTION TAKEN	5. OUTCOME OF SERIOUS ADVERSE EVENT
☐ Medicine withdrawn	☐ Recovered / resolved
☐ Dose increased	☐ Recovering / resolving
☐ Dose reduced	☐ Recovered with sequelae
☐ Dose not changed	☐ Not recovered / not resolved
☐ Unknown	☐ Died
	☐ Unknown

6. REPORTER

NAME _____ POSITION _____

FACILITY/CLINIC _____

ADDRESS

_____

E-MAIL _____ PHONE NO. _____

SIGNATURE

DATE SENT:

☐☐ DD ☐☐☐ MMM ☐☐☐☐ YYYY

Explanatory Note

TO BE ADAPTED ACCORDING TO THE LOCAL SITUATION

- This form is intended for the Core Package of active tuberculosis drug-safety monitoring and management (aDSM). For more details please refer to other documents on aDSM. The spontaneous reporting form in use by the national pharmacovigilance authorities may be adapted to provide for the purposes of alerting the TB programme of SAEs and avoiding parallel reporting structures.
- The completed form can be sent electronically, via email or fax to <address> and the responsible authority alerted by phone.
- The report should be sent within <number> hours after it is detected, even upon suspicion of seriousness.
- The report should be sent even if not all details are available and regardless of certainty of association with any particular medicine. The essential details are the identifiers of the patient and the reporter; the name of the suspected medicine(s); and basic details on the serious adverse event.
- If the report relates to a previously notified event indicate this under section 3; if more than one serious adverse event occur in the same individual, send separate forms for each event.
- All health care professionals are encouraged to report. Patients and relatives may also report.
- Upon receipt of the information the responsible authority will review the information and contact the reporter and/or facility for more details. All information, including identity of the patient and reporter, will be handled in strict confidence. Apart from action to protect public health, anonymised statistics from these reports will be used to improve drug-safety.
- When reporting please use DD MMM YYYY format to report dates. Under DESCRIPTION OF EVENT in section 3, provide a single diagnosis and include anatomical location if applicable. If diagnosis is unknown, describe clinical picture.

ANNEX 12

Adverse events of clinical significance or special interest for aDSM[5]

See section 11.4.1 for the definition of types of adverse events mentioned on this page.

i. All serious adverse events (SAEs)

ii. All adverse events of special interest (suggested list):[6]
   - Peripheral neuropathy (paraesthesia)
   - Psychiatric disorders and central nervous system toxicity (e.g. depression, psychosis, suicidal intention, seizures)
   - Optic nerve disorder (optic neuritis) or retinopathy
   - Ototoxicity (hearing impairment, hearing loss)
   - Myelosuppression (manifested as anaemia, thrombocytopenia, neutropenia or leukopenia)
   - Prolonged QT interval (Fridericia correction)
   - Lactic acidosis
   - Hepatitis (defined as increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥5x the upper limit of normal (ULN), or increases in ALT or AST ≥3x ULN with clinical manifestations, or increases in ALT or AST ≥3x ULN with concomitant increase in bilirubin ≥1.5 x ULN)
   - Hypothyroidism
   - Hypokalaemia
   - Pancreatitis
   - Phospholipidosis
   - Acute kidney injury (acute renal failure).

iii. Adverse events leading to treatment discontinuation or change in drug dosage.

iv. Adverse events not listed above but judged as otherwise clinically significant by the clinician.

[5] Adapted from UNITAID, Partners in Health, Médecins sans Frontières, Interactive Research & Development. Pharmacovigilance guideline for endTB Projects outside Interventional Clinical Trial. Version 0.7. 2015.

[6] The list shown here is provisional and may be modified according to the regimen composition or the patient cohort.

ANNEX 13.1

Sample schedule of routine tests to monitor patients on regimens containing bedaquiline or delamanid

(in addition to standard PMDT assessments)

Laboratory evaluation	Baseline	Week two	Monthly for first six months	Quarterly for remainder of therapy	Symptom directed
Liver function tests	X		X	X	Nausea, vomiting, jaundice, abdominal pain
Lipase	X[a]				Nausea, vomiting, jaundice, abdominal pain
Potassium	X		X	X	QTc prolongation, cramps, palpitation
Magnesium	X[a]				QTc prolongation, cramps, palpitation
Calcium	X[a]				QTc prolongation, cramps, palpitation
Albumin	X[b]			X	
Complete blood count (CBC)	X		X	X	Fatigue, nose bleeds, gum bleeds, easy bruising
12-lead ECG (for follow up, digital measures of QTc can be done instead of full 12-lead ECG)	X	X	X[c]	X[c]	Dizziness, syncope, palpitations

a If available.

b For regimen containing delamanid.

c At a minimum ECGs should be checked at week two then quarterly, but some programs check them on a monthly basis.

ANNEX 13.2

Sample schedule of examinations during intensive, continuation, and follow-up phases for a shorter MDR-TB regimen[a]

(example from an existing protocol)

	Intensive phase, four months (can be extended by one or two months)					Continuation phase, five months					Follow up phase, 12 months after end of treatment	
Examination	**M0**	**M1**	**M2**	**M3**	**M4i**	**M5**	**M6**	**M7**	**M8**	**M9**	**6M**	**12M**
Written informed consent	X											
Clinical evaluation	X	X	X	X	X	X	X	X	X	X	X	X
Sputum smear	XX	X	X	X	XX	X	X	X	X	XX	X	X
Sputum culture	X[h]	X	X	X	X	X	X	X	X	X	X	X
Drug-susceptibility testing[b]	X				X					X	X[j]	X[j]
Xpert MTB/RIF	X										X	X
Line probe assay (GenoType MTBDRsl® assay)	X										X[k]	X[k]
Audiometry[c]	X		X		X							
Simple hearing test[c]	X	X	X	X	X							
Chest X-ray	X									X	X	X
CBC[d]	X				X					X		
Serum creatinine[e]	X	X	X	X	X							
Serum potassium[e]	X	X	X	X	X							
Blood glucose	X											
Thyroid tests: TSH	X						X					
Liver function tests[f]	X	X	X	X	X		X					
ECG[g]	XX	X		X			X			X		
Pregnancy test (for women)	X											
HIV test	X											

	Intensive phase, four months (can be extended by one or two months)					**Continuation phase, five months**					**Follow up phase, 12 months after end of treatment**	
Examination	**M0**	**M1**	**M2**	**M3**	**M4i**	**M5**	**M6**	**M7**	**M8**	**M9**	**6M**	**12M**
If HIV-positive, CD4 count	X											
Hepatitis B (HepBs antigen) and hepatitis C (HCV antibodies)	X											
Visual acuity	X											

Notes:

AM: Amikacin; CFZ: Clofazamine; E: Ethambutol; GFX: Gatifloxacin; H: Isoniazid; KM: Kanamycin; MFX: Moxifloxacin; PTO: Prothionamide; R: Rifampicin; Z: Pyrazinamide.

a 4 KM(AM) CFZ MFX(GFX) E H Z PTO / 5 CFZ MFX(GFX) E Z (schedule adapted from : http://fieldresearch.msf.org/msf/handle/10144/322296)

b If culture-positive. DST will be done for H, R, KM, fluoroquinolones.

c If injectable drug is given for more than four months, examinations should be continued every two months until injections are stopped.

d RBC count, WBC count, haemoglobin, haematocrit, WBC differential count, platelet count.

e If injectable drug is given for more than four months, continue monthly examination of tests that should be done on the fourth month of treatment till injections are stopped.

f Bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, gamma glutamyl transpeptidase (γGT).

g ECG should be obtained at the baseline and repeated at least 2, 12, 24 and 36 weeks after starting treatment. ECG should be repeated as necessary in case of clinical suspicion of heart rhythm and conduction disturbances.

h If culture-positive, drug susceptibility testing for H, R, KM, fluoroquinolones, and genotyping of positive follow up isolate as well as stored baseline isolate from this patient would be performed.

i If the intensive phase is extended by one or two months, the month-four examinations should be repeated in each additional month.

j If smear-positive or Xpert-positive.

k Initial *M. tuberculosis* isolate stored at -80°C.

ISBN 978 92 4 154880 9

WHO

Handbook for Guideline Development

World Health Organization

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Handbook for Guideline Development

World Health Organization

WHO Library Cataloguing-in-Publication Data

WHO handbook for guideline development.

1.Guidelines as a topic – standards. 2.Review literature. 3.Meta-analysis. 4.Peer review. 5.Evidence-based medicine. 6.World Health Organization. I.World Health Organization.

ISBN 978 92 4 154844 1 (NLM classification: WA 39)

Contents

1. Introduction

What is a WHO guideline?

A WHO guideline is any document containing recommendations about health interventions, whether these are clinical, public health or policy recommendations. A recommendation provides information about what policy-makers, health-care providers or patients should do. It implies a choice between different interventions that have an impact on health and that have implications for the use of resources. Guidelines are recommendations intended to assist providers and recipients of health care and other stakeholders to make informed decisions. WHO has adopted internationally recognized standards and methods for guideline development to ensure that guidelines are free from bias, meet a public health need and are consistent with the following principles.

- Recommendations are based on a comprehensive and objective assessment of the available evidence.
- The process used to develop the recommendations is clear. That is, the reader will be able to see how a recommendation has been developed, by whom, and on what basis.

What is the aim of this handbook?

This handbook provides stepwise advice on the technical aspects of developing a WHO guideline and the methods used. It aims to provide a clear path through the process and seeks to ensure that the resulting guidelines have credibility and meet WHO's criteria for content, methods and presentation, while remaining accessible and useful.

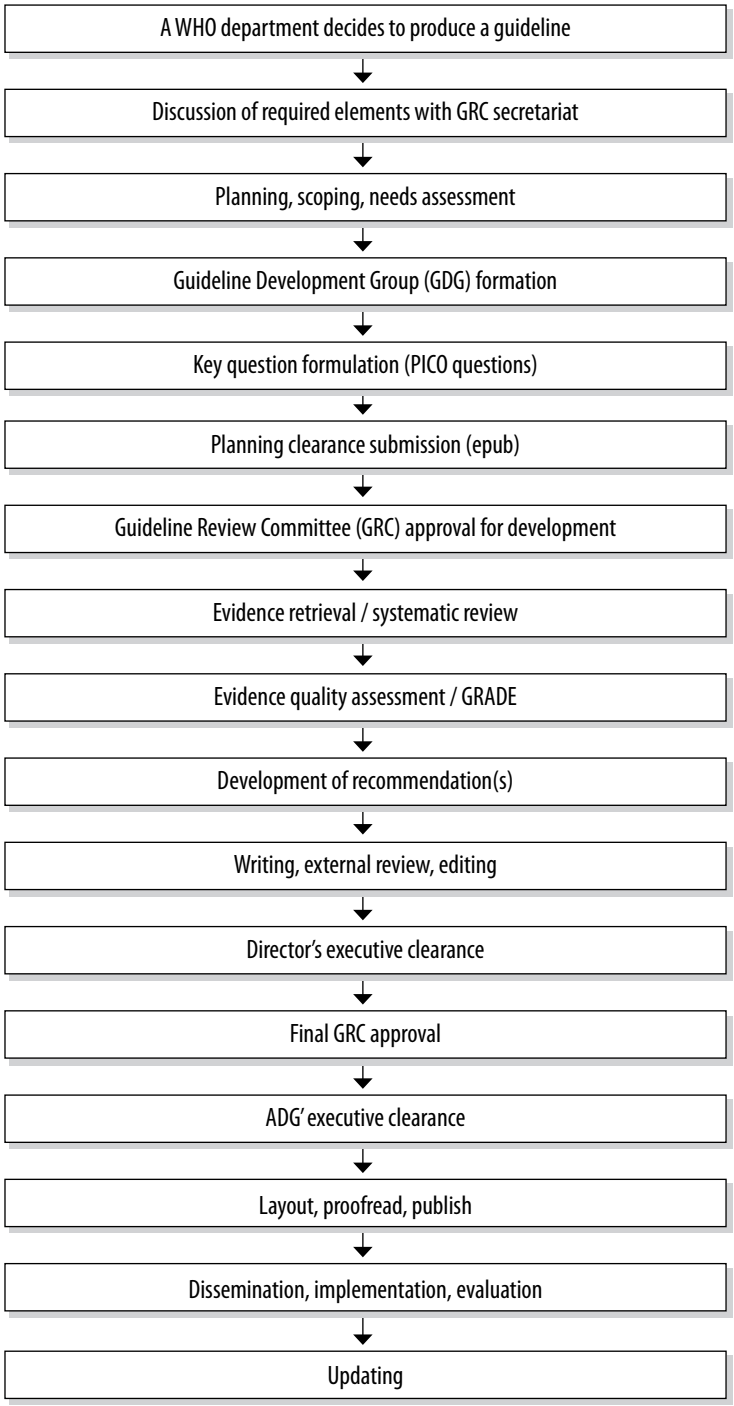
Who is the handbook for?

- Any WHO department who decides to produce a guideline.
- Members of the WHO steering group.
- Members of the guideline development groups (GDGs).
- Members of the external review group.
- Anyone interested in understanding how WHO develops guidelines.

How to use this handbook?

The structure follows the development of a WHO guideline from start through to publication. The guideline development process is summarized in Figure 1.1.

Figure 1.1 Overview of guidelines development process



Types of guidelines

If you are planning to produce a guideline, consider which of the following types of product best fits your purpose. The type of product will determine the methods and timeframe for development.

Rapid advice guidelines

A rapid advice guideline is produced in response to a public health emergency (such as pandemic influenza) in which WHO is required to provide rapid global leadership and guidance. This type of document needs to be produced within 1–3 months and will be evidence-informed, but it may not be supported by full reviews of the evidence. It will be prepared mainly by the responsible WHO staff members with external consultation and peer review. It must be published with a review-by date that indicates when the guidance will become invalid, or when it will be updated or converted to a standard guideline.

Standard guidelines

A standard guideline is produced in response to a request for guidance in relation to a change in practice or controversy in a single clinical or policy area – such as treatment of postpartum haemorrhage or minimum requirements for safe delivery of HIV care. A standard guideline is not expected to cover the full scope of the condition or public health problem. This guideline will usually take 9–12 months to complete and should be prepared after consultation on the scope of the guideline and the issue that it covers. It should be supported by systematic reviews of the evidence and one or two meetings of the guideline development group for consultation. A standard guideline may have a specified review-by date depending on the expected rate of change of evidence in the topic area. Most WHO guidelines fall into this category.

Full guidelines

A full guideline is one that provides complete coverage of a health topic or disease, such as dengue fever. It would be expected to include recommendations in relation to all aspects of the topic (e.g. surveillance, diagnosis, public health and clinical interventions) and to be fully based on systematic reviews of the evidence for each aspect. These are likely to take 2–3 years to complete, and will require several meetings of a guideline development group. Given the time and expense of producing full guidelines, the need for doing these in WHO needs to be carefully justified.

Compilations of guidelines

A compilation of guidelines contains current recommendations from WHO and other sources, but does not include any new recommendations. Compilations of guidelines are subject to Guidelines Review Committee (GRC) approval. All recommendations included must be current and should be referenced thoroughly and accurately. Producing a compilation of guidelines can be complex and updating may be difficult since individual recommendations may go out of date at different times.

In principle, all recommendations used in a compilation should be updated by WHO. However, recognizing that WHO resources are limited, this may not be realistic. Members of the guideline development group should discuss and agree on an acceptable level of quality and document their decisions carefully. The GRC recommends using the Appraisal of Guidelines for Research and Evaluation (AGREE) tool (available at http://www.agreetrust.org/) to do this.

It is also important that recommendations used in a compilation are of adequate quality. WHO recommendations are considered of adequate quality for use in a compilation if they were cleared by the GRC from 2009 onwards. If compiled recommendations have not been cleared by the GRC, an explicit and systematic process must be in place to ensure the quality of the compiled guidance. Production times for compilations of guidelines vary widely.

Some guideline compilations do not require GRC review. These are:

- documents in which all the recommendations have previously been cleared by the GRC under its full (not transitional) requirements;
- documents that are clearly limited to operational guides for such guidelines.

Guideline compilations that require GRC review are documents in which any of the recommendations were initially published without GRC review.

Adaptations of guidelines

Guidelines originally intended for one setting may be adapted for use in another, such as routine obstetric care in emergency settings. Adaptations of guidelines must follow standard GRC procedures.

Guidelines prepared in collaboration with other organizations

Health-care guidelines are produced by many organizations, including national agencies, intergovernmental organizations and specialist medical societies. From time to time, it may be appropriate for WHO to collaborate with these groups to produce a joint guideline. However, national agency guidelines usually have a much narrower focus than those produced by WHO, and international society guidelines may have inherent problems owing to conflicts of interest in the funding of their development. The GRC will make case-by-case assessments of these types of proposals. However, joint guidelines must follow current WHO guideline development standards as outlined in this handbook. In addition to being aware of potential problems with regard to copyright, it is important to note that:

- adaptation or endorsement of another organization's guideline should be initiated by the WHO department concerned and not by the external group;
- adaptation or endorsement of another organization's guideline can be considered when no WHO guideline exists or an existing WHO guideline is outdated;
- minimum standards for WHO guidelines should be met (no funding from commercial sources, evidence systematically reviewed, conflicts of interest declared and reported, and methods of developing the guideline reported);

- the approach to reviewing and summarizing evidence should be consistent with that recommended for WHO guidelines;
- WHO should ensure global representation of experts in the development of the recommendations;
- the recommendations should be appropriate for a global audience.

Information products that are NOT considered guidelines

- Documents containing standards for manufacturing health technologies, such as pharmaceuticals and vaccines.
- 'How to' documents, or operational manuals (e.g. how to set up a research project or how to implement a service).
- Documents that describe standard operating procedures for organizations or systems.
- Documents that state established principles (e.g. ethics, human rights, WHO constitutional issues).
- Documents that provide information on different options for interventions without recommending any particular intervention.

If you are not sure whether your proposed document is a guideline, please submit it to the GRC for review.

The Guidelines Review Committee

Why was the GRC set up?

The Guidelines Review Committee (GRC) was established by the Director-General in 2007 to ensure that WHO guidelines are of high quality and are developed through a transparent, evidence-based decision-making process.

Since this date, all WHO publications containing recommendations must be approved by the GRC. Such publications are required to meet an unmet need, to be developed using internationally accepted best practices, including the appropriate use of evidence. This handbook provides guidance on the development of documents or publications containing WHO recommendations, and sets out the procedures to follow when such a document is submitted to the GRC for approval. To facilitate ease of reading, the term 'guideline' is used to refer to any document containing WHO recommendations.

The GRC reviews every WHO guideline twice during its development – once after the scope of the guideline has been defined at the initial planning stage, and again after the recommendations have been developed and the guideline document has been edited. The GRC meets on a monthly basis to review both initial proposals for guideline development and final versions of guidelines prior to their publication. The review of the initial proposals includes an assessment of whether the proposed guideline development process is consistent with the steps described in this handbook. The review of final submissions is done to ensure that the approved process has been followed and that the final guideline

document meets all reporting requirements and contains clear and actionable recommendations. The GRC also offers suggestions and advice on how to improve the quality of the guidelines at any stage of the process.

To allow adequate time for review, all relevant documents must be submitted to the GRC, through the publication clearance system no later than two weeks before the date of the next meeting.

The GRC can be contacted at grcinfo@who.int.

The GRC Secretariat

The principal aims of the Secretariat are to:

- coordinate and provide technical support on guidelines development to WHO departments, headquarters and regional offices;
- organize training on guideline production for WHO staff;
- provide administrative support for the work of the GRC;
- collaborate with other organizations and international networks that provide methodological expertise in relation to guideline development, adaptation and implementation;
- maintain the database of the GRC submissions.

2. **Planning guidelines**

Good planning will yield good guidelines

The first and most important step when planning is to ask a single question: *is this guideline really needed?*

WHO guidelines should meet a defined global need, have a public health perspective and not duplicate existing advice. Consult other departments at the beginning and decide, as early as possible, who should have primary responsibility for developing the guideline and who should be involved.

Who wants it? Is it a request from one or more WHO Member States? WHO guidelines generally should meet a global need, have a public health perspective and not duplicate existing resources. If an existing guideline meets the need, a new one is not required.

Why now? Is it required by WHO's governing bodies? Are there already guidelines on the same topic from other organizations or other WHO departments? Is the best advice on this topic available only from WHO?

Is it part of a departmental programme of work? Implementation of a guideline by WHO headquarters or by countries will be much easier if it fits with a programme or project. If no programme or project exists, is it really necessary to prepare the guideline?

Implementation? Who is likely to implement it? If you cannot identify a process for implementation, then you should not start.

What will it achieve? Will the guideline address poor practice or to try to change clinical programme approaches, or health policy? This should be the focus of most guidelines, and it is what differentiates guidelines from textbooks or reference works.

When is it needed? Is the guideline a response to a situation where need for advice is urgent? If so, consider producing rapid advice guidelines. These guidelines usually need to be produced and published as quickly as possible, ideally in 1–3 months and therefore the requirements and processes are different from those of other guidelines.

Agreement? Do you have agreement from your director? You will need to have formal approval from your director before your proposal can be considered by the GRC and your Assistant Director-General (ADG) will need to approve the proposal and final product.

Collaboration? Are there other departments that should be involved, or that might be producing similar products? The answer to this is nearly always yes. Avoid duplicating earlier or current work by consulting other relevant WHO

departments, the GRC secretariat and the WHO library. Make a preliminary search of published work relevant to your planned guideline. Once you have identified the relevant departments, decide which department should have primary responsibility for the guideline and who will be involved in developing it.

If you cannot answer all these questions, it is probably best not to start.

Practical planning

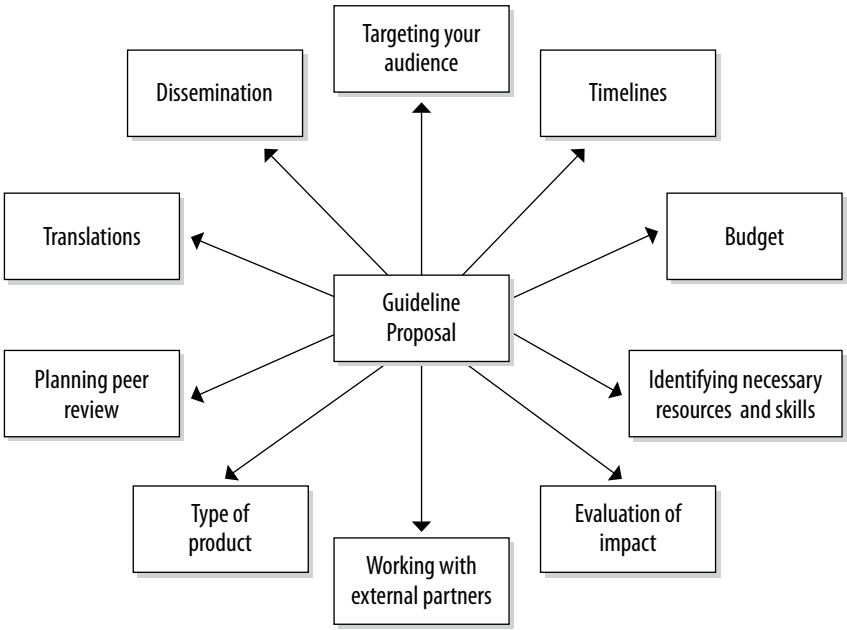
Having established that there is good reason to develop a guideline the next step is to answer some practical questions (Figure 2.1).

a. **Setting objectives.** Why are you doing this? What is the need you are responding to and why does WHO need to be producing this document? Set clear, achievable objectives that will govern development of your guideline.

b. **Targeting your audience.** Who is your target audience? Most WHO guidelines need to speak to multiple audiences, which makes them challenging to produce. If you can identify the key target audience, your task will be easier. Writing documents to meet the needs of policy-makers, health-care managers and clinicians simultaneously is not straightforward and should be avoided wherever possible.

c. **Timelines.** When does it need to be completed? Realistically, a good quality guideline will take at least 9–12 months to produce if all the evidence has already been synthesized and you have someone to write it. If the guideline is going to cover a large number of questions, it may take up to 2–3 years to produce.

Figure 2.1 Planning your guideline



d. **Funding.** Do you have adequate funds? For a standard WHO guideline, assuming that you will need to commission systematic reviews, an evidence synthesis and assessment, hold at least one consultation meeting, pay for writing, editing and layout of your document, please allow at least US$ 300 000. Note that WHO may not accept money from commercial bodies for guideline development and sources of funding for guidelines may need to be approved by the legal department.

e. **Existing guidance and resources.** Are there existing guideline documents that cover the same issue? If so, what is the added value and justification for the proposed document? If a WHO version is needed to build on an area covered by an existing guideline from a recognized national developer (e.g. the UK's National Institute for Health and Clinical Excellence), the existing guidelines can be used as a starting point. To be considered for adaptation, third-party guidelines should have been developed using standards equivalent to those described in this Handbook to ensure transparency and freedom from bias. Consider updating existing WHO recommendations if they are out of date or of low quality. When examining existing guidelines, do a quality assessment using a tool such as the Appraisal of Guidelines for Research and Evaluation (AGREE) tool available at http://www.agreetrust.org/

f. **The evidence base.** What existing scientific evidence can guide the recommendations? Do you know of existing systematic reviews? If not, it is worth doing a preliminary literature search at this stage to get a sense of what information is available. For standard and full WHO guidelines, a systematic search for evidence should be completed before developing the recommendations. If there is no evidence, what will be the basis of your guideline?

g. **Who should be involved?** It is worth spending some time at the beginning of the process to draw up a list of key external organizations, experts and stakeholders who will need to be consulted or involved in the process.

- **First,** identify your WHO guideline steering group (WHO staff members responsible for guideline development).
- **Second,** identify members of your guideline development group who will be actively involved in the development of the guidelines (usually 10–20 persons).
- **Third,** you should establish an external review group made up of experts and stakeholders whom you may wish to consult on the scope of the document, the questions it covers and the choice of important outcomes for decision-making. Members of this group should also review the completed draft guideline. The external review group may include groups likely to oppose or criticize the output on the basis of scientific or philosophical differences. While it may not be possible to reach agreement with them, it is important to consider their input.

In addition, many of these groups and experts will play a key role in the implementation of the recommendations in the guideline; they are more likely to help implement the recommendations if they are involved from the beginning.

h. **Type of publication.** Consider what format will be most useful for your guideline users. Electronic versions may be more practical and cheaper, perhaps accompanied by short paper publications, wall charts, pamphlets, etc.

i. **Translations.** Are you planning translations? Which languages are spoken by those most in need of the advice in your guideline? Consider the implications for your budget and time frame and choose your guideline language carefully.

Having established all this, you are ready to move to the next stage, scoping your guideline.

Scoping the guideline

Scoping the guideline is the process of defining what the guideline will include and what it will not include. The scope should describe:

- the area of practice or policy to which the guideline applies
- those whom the recommendations are intended to affect
- the actions and interventions of interest
- the outcomes that may result – both positive and negative.

The scope should yield questions that will govern the data search, and help frame likely recommendations. It should ensure that the guideline is of manageable size and adequately focused.

Scoping is considered one of the most difficult but important aspects of guideline development. If you get the scope right, the guideline should be manageable.

How to scope the guideline

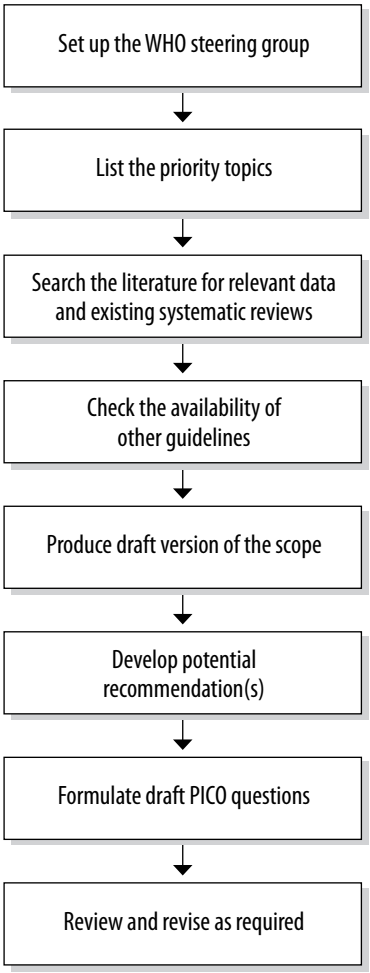
Set up a steering group. Convene a small group of WHO staff to define the scope of the guideline, including representatives of all relevant departments and ask this group to provide feedback on your assessment of priority topics, reference documents, questions and potential recommendations, as follows (Figure 2.2 Scoping procedure).

1. **List the priority topics.** What must be included? Identifying the key issues is crucial because this determines the breadth and depth of the work. Do not try to include everything; resist the temptation to write a textbook. Concentrate on the interventions or policies where change in practice is desired, and areas where there is controversy. Also consider the feasibility of implementing potential

recommendations. Although some background information may be useful, try to avoid repeating standard information (e.g. epidemiology, pathology, pharmacology) on the topic unless this is the area of controversy you wish to resolve in the guideline.

2. **Search the literature.** Do a preliminary search of the literature to identify relevant sources. This includes existing guidelines and systematic reviews, health technology assessment reports and economic evaluations relevant to the guideline topic. At this stage the search should not be exhaustive; once questions and draft recommendations have been formulated, rigorous systematic reviews will be done to retrieve the appropriate evidence.

Figure 2.2 Scoping procedure



3. **Draft potential recommendations.** Considering the potential final form of the guideline makes it easier to focus the development work.
4. **Sharpen the focus.** Take a step back and ask if you need to include all of these topics, questions and recommendations. The group should try to restrict the final list to the minimum at this stage, as it tends to expand during the development of the guideline.
5. **Formulate questions**. Use the topic list and possible recommendations to formulate the key questions to be answered in the guideline. These questions will guide the evidence synthesis and are best developed using the questions using the population, intervention, comparison, outcome (PICO) format (see section on formulating questions below).
6. **Review**. Once your group has finalized the scope, it should be circulated to the external review group for comments. (They should be reminded that WHO is producing a guideline, not a textbook, as the responses will almost always tend to expand the planned scope.)
7. **Reconsider**. Once you have the external feedback, check again. Is what you are trying to do feasible? Is your time frame reasonable? Do you have sufficient financial and human resources?

Further reading

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3. **Setting up guideline groups**

When developing WHO guidelines, three groups need to be set up:

- the WHO steering group
- the external review group
- the guideline development group.

Each group has different roles but the membership of each needs to be balanced so that members' technical interests, skills, expertise, values and knowledge of regional considerations complement one another and, ideally, negate potential biases.

The WHO steering group

The first group that needs to be set up is the WHO steering group. This should include members from any department or regional office that works directly on the topic of your guideline, though it is wise to keep it small (less than 10 members) to maximize efficiency. The steering group will assist with:

- scoping the guideline (described in Chapter 2);
- developing potential recommendations;
- drafting the PICO questions and overseeing evidence retrieval;
- selecting members of the guideline development group and external review groups;
- organizing guideline development meetings;
- overseeing the writing and finalization of the guidelines.

The external review group

This group is composed of people with an interest in the subject of the guideline. Members can be asked to review different stages of the development process. They may review the scope, the draft recommendations, and the PICO questions during the earlier stages. They will also be asked to review the guideline document when recommendations have been finalized. This group should be geographically and gender-balanced and include stakeholders and content experts.

The guideline development group

The guideline development group (GDG) is made up of external experts whose central task is to come up with evidence-based recommendations. The group can hold online or teleconference meetings but will usually need to have at least one face-to-face meeting. The group should be small enough for

effective group interaction but large enough to ensure adequate representation of relevant views. A group of 10–20 is usually feasible and affordable.

The role of this group is to:

- determine the PICO questions that the guideline addresses;
- choose and rank outcomes;
- provide advice, as required, on any modifications of the scope as established by the WHO steering group;
- appraise the evidence used to inform the guideline;
- advise on the interpretation of this evidence, with explicit consideration of the overall balance of benefits and harms;
- formulate the final recommendations, taking into account diverse values and preferences.

Composition of the guideline development group

The guideline development group should be multidisciplinary, gender and geographically- balanced - members should come from regions likely to use the guideline. There are different ways of finding, nominating and selecting members of guideline development groups. In addition to drawing members from established technical networks, collaborating centres and formally appointed expert advisory panels, you may wish to consider publishing an open call for nominees. Established guideline development groups within WHO have nomination procedures that you may wish to consider. Whichever mix of methods is used, the decision-making process should be documented. The aim is to have a balanced group (Figure 3.1) that includes:

- relevant technical expertise;
- implementers of the guideline such as programme managers and health professionals;
- representatives of groups most affected by the guideline, such as patients;
- methodologists (experts in assessing evidence and developing guidelines, health economists, statisticians, as required).

The group needs to identify a writer for the guideline – this person may need to be appointed in addition to the other members. A clearly written guideline and a well-documented process is critical to final clearance and subsequent use, so the writer needs to be involved throughout all the planning and development stages. Inclusion of end-users, either in the guideline group and/or in the external review group, increases the likelihood of producing a guideline that is appropriate to their needs and that will be implemented effectively.

The chair

The selection of the chair of the group is a key decision. Look for a chair who is expert in facilitating groups and interpreting evidence. While content knowledge is important, content experts with strong views about particular interventions should not chair the group. Where the best choice is a content expert, options for reducing risk of bias include ensuring that the chair does not have a veto within the group.

Technical experts

Technical content experts are selected for their expertise in the subject of the guideline. A balanced group includes a range of expertise and affiliations, with representatives from professional groups who will be implementing the guideline in each region.

End-users

These members represent groups affected by the likely recommendations (e.g. people with diabetes if the guidelines are about the management of diabetes, labour union representatives if the guidelines are about human resources for health) and/or groups likely to implement the guidelines (e.g. palliative care nurses for guidelines about pain management). Although it can be challenging to find such representatives for global guidelines, an increasing number of consumer groups are operating at international level. Many countries have nongovernmental organizations with members who may be able to participate, either as observers on behalf of their organizations, or in their individual capacity, as full members.

Involving consumers in guideline groups helps to ensure that:

- the questions addressed are relevant to consumers
- relevant aspects of the experience of illness are considered
- critical outcomes are identified and prioritized
- the final guideline can be understood by those it affects.

Barriers to consumer participation include:

- the lack of suitable consumer groups
- time constraints
- the complexity of scientific terminology used by committees.

Experience from organizations such as the United Kingdom's National Institute for Health and Clinical Excellence shows that consumers, provided with training and support, make critical contributions to guideline development.

Methodologist

Many WHO guideline groups include a methodologist, an expert in guideline development processes, to complement the technical expertise of the subject-matter experts. Methodologists should be consulted during the planning stage, before the guideline development group has been formed, as they can often provide valuable advice on group composition.

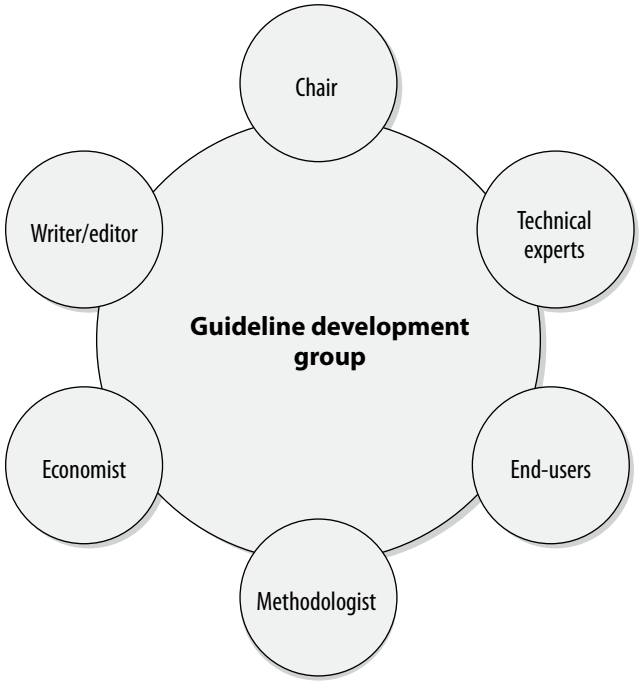
Economist

An economist should be able to advise on the potential economic benefits and drawbacks of the recommendations the group is considering making. The economist should also advise on how to best search the evidence on resource use and costs associated with likely recommendations and interpret that evidence for the group.

Designated writer/editor

It is strongly recommended that one person should be responsible for writing the guideline, while the rest of the group reviews and endorses the document. Later, when external review comments are received, this same person should finalize the document. This will help to ensure coherence, clarity and accuracy.

Figure 3.1 Guideline development group composition



Running an effective guideline development group

The chair

During meetings, the chair should ensure that each member is able to present their views, that assumptions can be debated and that the discussions are open and constructive. The chair should keep the group focused on the agenda and the timescale of the project.

Managing conflicts of interests

Chapter 4 explains how to manage and report conflicts of interest. The basic principles are that declarations are collected and reviewed before appointments are made and any changes need to be reported to the secretariat. At the meeting, each participant should verbally report potential conflicts of interests. Any changes to a member's declaration of interests should be recorded in the minutes of the meeting.

Planning for effective meetings

The guideline development group meeting needs to cover a lot of material in a short time. Ensure that everyone understands his or her role and the expected outputs by providing clear information about the how the meetings will run, including scope, roles, tasks and processes.

Scope of the meeting

- What is expected from meeting participants in terms of advance preparation?
- What needs to be achieved during the meeting?
- What can be done afterwards?
- What follow-up will take place with meeting participants?

Roles and process

- How the guideline will be developed.
- The roles of all guideline development group members, methodologists and observers.
- Declarations and management of conflicts of interest.
- How evidence will be retrieved and assessed.

Achieving meeting objectives

If the purpose of the meeting is to sign off on questions for guideline development.

- Prepare a draft set of questions as formulated by the steering group.
- Circulate the questions ahead of time to all meeting participants.

If the purpose of the meeting is to formulate recommendations.

- Distribute the evidence profiles at least a week prior to the meeting.
- At the meeting, present draft recommendations that have been prepared by the WHO steering group, so that participants can review and revise as necessary.

Further reading

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4. **Declaration and management of interests**

A conflict of interest occurs when a set of conditions in which professional judgement concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain). The declaration of a secondary interest does not automatically mean the presence of a conflict of interest that precludes participation in a guideline development group or expert review group.

In WHO, a 'conflict of interest' can be defined as any interest held by an expert that may affect or reasonably be perceived to affect the expert's objectivity and independence in providing advice to WHO. The conflict of interest rules are designed to avoid potentially compromising situations that could undermine or otherwise affect the work done by WHO. Consequently, the scope of the inquiry is any interest that could reasonably be perceived to affect the function that the expert is performing.

This chapter describes the main principles of how interests should be managed during a guideline development process. More detailed information can be obtained from the GRC secretariat and the office of the legal counsel.

Who should declare interests?

According to the rules in the WHO guidelines for declaration of interests, all experts participating in WHO meetings must declare any interest relevant to the meeting before their participation. In the case of guideline development this means that all members of the guideline development group and the expert review panel, as well as any other experts or advisers invited to guideline development meetings, should fill in a declaration of interests (DOI) form.

In addition, anyone invited to participate in a substantive way in the development of a guideline must also complete a DOI form, and must agree to the publication of the declaration in the guideline. Preparation of systematic reviews specifically for the guideline panel and evidence profiles, or contributing to the formulation of recommendations and writing the guideline are considered substantial contributions.

How to manage interests?

The WHO process of managing interests is as follows:

1. Experts and advisers complete the DOI forms before the guideline meeting.

2. The WHO steering group assesses the declared interests prior to the person participating in the meeting to determine whether a conflict exists that may preclude or limit the participation of the person in the guideline group.
3. At each meeting of the guideline group, the declaration of interest forms are summarized and presented to the entire group, so that the group can be aware of any interests that exist among the members. Each member is offered the opportunity to update and/or amend their declaration. The management strategy for each member is also presented to the entire panel.
4. All declared interests are reported in the final guideline document.

What needs to be declared?

WHO collects and reports interests in three categories: financial, academic and public positions.

A financial conflict of interest arises when the expert receives income or support that is related to, or could be affected by, the outcome of the WHO meeting or activity in which they are involved. This includes both personal interests and interests of immediate family members of the expert. Financial interests include:

- personal financial gain (paid work, consulting income or honoraria) or research, proprietary interests and patents;
- grants or fellowships from a commercial entity that has an interest in the topic or the outcomes of the guideline group's work;
- shares or bonds in a related commercial entity;
- employment or consultancies.

Academic conflicts and public positions may be more difficult to recognize but the principle is to include any interest that could be reasonably perceived to affect an individual's objectivity and independence while working with WHO.

Assessing declarations of interest

Declarations of interests are required for potential members of both the external review group and the guideline development group before these groups are finalized and invitations issued. The WHO technical officer needs to collect and review these declarations, in collaboration with the WHO guideline steering group. Further advice can be sought from legal counsel as required.

The aim is to have a chair and a majority of guideline group members with no conflicts of interest.

The first question is whether any declared interests constitute a conflict of interest. What constitutes a potentially significant conflict of interest is a matter of judgement. Some examples of interests that are clearly a conflict and that should preclude participation in developing recommendations include:

- owning shares in a company that manufactures a product or technology that may be recommended for use in the guideline (note that there is a financial threshold specified in the reporting form);
- holding a patent on a product or technology that may be recommended for use in the guideline;
- having a family member who works for a company that manufactures a product or technology that may be recommended for use in the guideline;
- current or past involvement in a major academic programme of work that concerns a product or technology likely to be considered in a recommendation, including conducting trials or systematic reviews that recommend a particular product or technology;
- receiving funding from, being or have recently been employed by, consulting for, or acting as an adviser, paid speaker, or opinion leader for a company or organization with an interest in a specific product related to the guideline – this involves receiving any support for travel, professional training or similar.

If members declare interests that are relevant to the meeting, the WHO technical officer and steering group, assisted by legal counsel, decides whether and to what extent they can participate in the guideline development. These decisions are made on a case-by-case basis, but in general, participants should not participate at all if they declare significant personal financial interests in a single company with a commercial interest in the outcome of the guideline.

Participants can participate in the discussion, but are recused during the development of recommendations if:

- they have links with multiple companies that have commercial interests in the outcome of the guideline;
- they have received research funding from companies that have commercial interests in the outcome of the guideline.

A person with a conflict of interest should not chair a guideline group meeting. Guideline group members who are involved in either primary research or conducting systematic reviews relating to the recommendations in question, should declare these activities as academic interests. All decisions on how to manage declared interests need to be documented prior to the meeting and included in the final guideline. Legal counsel will provide advice on how to handle individual cases.

Management decisions may be:

- the conflict of interest requires no action beyond declaration at the meeting and reporting in the final guideline;
- the conflict of interest is significant but related to only some areas of the guideline development group's work in which case the participant cannot participate when the group considers these areas, and will not have access to the relevant documents;
- the conflict of interest is such as to preclude participation;
- the conflict of interest is such that participation in the discussion is

appropriate, but the member will be recused for development and ratification of recommendations.

Open declaration at the meeting

All declarations of interest made by guideline development group members should be provided to all participants at the meeting as one of the first items on the agenda. If there are any changes to previously declared interests, WHO staff will then need to make a judgement as to whether the revised declarations of interests are of potential importance with respect to likely recommendations and if so, how to manage the declared conflicts. All decisions made should be clearly documented and shared with the entire guideline group (i.e. everyone should know how the conflicts of interest will be managed for the individual members).

Reporting DOIs in the guideline

A summary of how conflicts of interest declarations were collected, any declared conflicts and a brief description of how they were managed must be included in the actual guideline document. If no conflict was declared, this information needs to be provided as well. The GRC will not clear a guideline document that does not contain this information.

Declared conflicts of interest should be reported in the guideline according to the following examples. The wording of this part of the guideline document must be approved by legal counsel before final review by the GRC.

> *Dr N.C. reported being an investigator on trials for GlaxoSmithKline, Quintiles, Uriach and Biomarin but not for any products or products related to those being considered at the meeting, and also holding shares in Biota. She therefore was excluded from discussion of the late item on antivirals.*
>
> *Dr M.R. reported having been a consultant for Roche on drug research and development. He is currently a member of a data safety and monitoring board for Roche; receives royalties through the US National Institutes of Health from the use of gossypol for cancer; and is a consultant to several start-up companies, none of which have products on the market. As there were no products related to any of these items on the agenda, no action was required.*
>
> *Dr A.F. reported having a family member who is an employee of Merck, Sharpe and Dohme, Brazil. He therefore excluded himself from review or discussion of the product applications from Merck on this agenda.*

What to do when there are too many conflicts?

WHO has traditionally relied on experts to develop its recommendations, on the assumption that experts' advice is objective and free from bias. Unfortunately, research has shown that there is an association between the

financial interest of guideline group members and decisions that support those interests. If you need to consider input from experts who have conflicts, the GRC secretariat can advise on how to use an evidence jury. To do this, you need at least two thirds of your group to have no conflicts of interest. They become your jury. The experts present their evidence and views to the jury. The jury then develops the recommendations in the absence of the experts. This requires dividing the meeting into two parts: a first session with all members present for the presentation of the evidence and a second closed session, with only the jury, to develop and ratify recommendations.

Further reading

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Steinbrook R. Controlling conflict of interest: proposals from the Institute of Medicine. *NEJM,* 2009, 360:2160–2163 (http://content.nejm.org/cgi/content/full/360/21/2160, accessed 8 June 2012).

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5. **Formulating questions and choosing outcomes**

The choice of questions that need to be addressed by the guideline strongly influences the final recommendations – so getting this stage right is crucial. The questions should be used to systematically search the evidence for answers to controversial areas the guideline is trying to address. When the scope of the document has been developed and potential recommendations identified, the questions that need to be asked should become clear. Because these questions drive the evidence search and form the basis of your recommendations, they should be clear and well defined.

When developing these questions it helps to look at the type of information needed. Usually the information leads to two types of questions: background and foreground questions.

Background questions. These relate to the subject of the guideline and provide important background information on the issues under consideration. However, they do not provide direct evidence informing recommendations. They include questions on definitions, the prevalence of the problem or disease and mechanisms underlying possible interventions (i.e. how the intervention might work).

> *e.g. How is human papilloma virus infection associated with cervical cancer?*

Questions about mechanisms may be answered with a wide range of information ranging from basic scientific data to theoretical frameworks such as behavioural change theories underpinning public health interventions. A full review is not usually required for background information referred to in the guideline, such as a section on the epidemiology or pathology of a disease.

Foreground questions. These address the effectiveness of an intervention that the guideline development group is considering recommending. They usually include questions about the efficacy of the intervention but can also provide information on negative consequences, social acceptability, or the cost-effectiveness of an intervention under consideration, helping provide an evidence base for values, preferences and economic implications that should be considered when making a recommendation.

> *e.g. What impact does human papilloma virus vaccination have on the incidence of cervical cancer?*

The foreground questions are the most important ones for a guideline. They are used to inform the recommendations and they will require a systematic

review and quality assessment of the evidence using the GRADE (grading of recommendations, assessment, development and evaluation) approach. Because the answers to foreground questions will form the evidence base upon which the recommendations will be made, these questions should be framed in a way that enables a systematic search of the literature. The PICO format is an effective way to do this.

Formulating PICO questions

PICO refers to four elements that should be in a question governing a systematic search of the evidence: Population, Intervention, Comparator and Outcomes (see Box 5.1 PICO question components).

Population

Who is targeted by the action being recommended?

- How can they be best described? What are the relevant demographic factors? Please consider age groups, sex, ethnicity, social identities, behavioural characteristics, etc.
- What is the setting? For example, hospitals, communities, schools.
- Are there any subgroups that might need to be considered?
- Are there groups or subgroups that should be excluded?

Intervention

What action is being considered?

- Which treatment, procedure, diagnostic test, prognostic factor, risk factor, lifestyle change, social activity, screening test, preventive measure, or approach is being evaluated?
- Are there variations you might want to consider? (dosage, frequency, delivery or administration, personnel and delivery channels, timing and duration, etc.).
- Where interventions are complex, consider which components are of most interest to your guideline group and how they might best be described.

Comparator

What are the alternative choices of action?

- This may be what is currently being done – including no specific treatment – or another measure the guideline panel may be considering in comparison.
- Comparisons may be made to placebo, no intervention, standard care, current standard diagnostic, variations of the intervention or a different one.

Outcomes

What is the purpose of the recommendation?

- What will it achieve?
- What harms could it lead to?

- Possible outcomes both positive and negative need to be selected carefully with input from experts, implementers and those most affected by the recommendations.

Box 5.1 PICO question components	
Population	(Who is targeted by the action being recommended?)
In girls aged 9–13 years	
Intervention	(What action is being considered?)
does HPV vaccine	
Comparator	(What are the alternative choices of action?)
compared with no vaccination	
Outcome	(What is the purpose of the recommendation?)
reduce the incidence of cervical carcinoma?	

Examples of PICO questions

In a rural population in a low-income country (Population), does paying higher salaries to health workers (Intervention), compared with paying standard salaries (Comparator), increase the number of health workers in rural areas (Outcome)?

This format can also be used for questions on diagnosis, prevention, aetiology and resource use. For example:

- In babies born to HIV-positive women (P), does screening with a new rapid diagnostic test (I), compared with standard diagnostic methods (C) accurately detect disease (O)?
- In an urban population (P), is exposure to an environmental chemical (I), compared to no exposure (C) associated with an increased risk of cancer (O)?
- Is intervention A (I) as cost-effective in preventing mortality (O) compared to intervention B (C)?
- In a national population (P), how does one intervention (I), compared to another (C), perform in terms of costs per quality-adjusted life year gained (O)?

PICO questions may be broad or narrow in scope. While a broad question will lead to a comprehensive summary of a larger body of evidence and more generalizable findings, it may also require more resources to answer. A broad question may also yield greater heterogeneous evidence, making interpretation difficult. A narrow question may be easier to manage, but the evidence might

be sparse and findings less generalizable. Depending on the scope of the guideline and the availability of information the steering group may decide to split a broad question into a number of narrow questions.

Example of a broad PICO question:

> *Do financial incentives (I) compared to no financial incentives (C) improve the retention (O) of health workers (P) in rural areas?*

Example of a narrow PICO question:

> *Does a housing allowance (I) compared to no housing allowance (C) improve the retention (O) of health workers (P) in rural areas?*

Choosing and rating outcomes

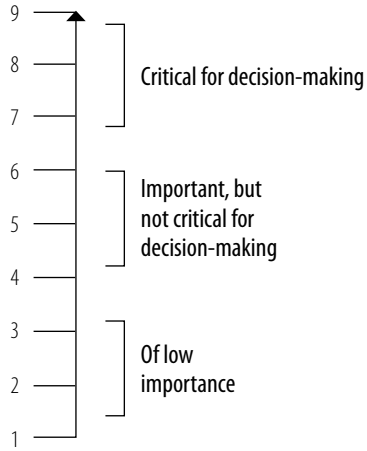
The purpose of any recommendation is to achieve a desirable effect or outcome. Choosing the most important outcome is therefore critical to producing a useful guideline but different groups value outcomes differently. For this reason it is essential that the external review group (which should contain end-users, implementers and policymakers, as well as technical experts) be asked to identify the key outcomes that need to be considered when the recommendations are made.

Rating outcomes

The WHO steering group should make an initial list of relevant outcomes, including desirable and undesirable effects and ask both the guideline development group and the external review group to identify any other outcomes that have not been listed.

Once a workable list of outcomes has been collected, an effective means of prioritizing these is to ask group members (this can be both the guideline development group and the external review group) to rate them. Group members are asked to give outcomes a score from 1–9, where 7–9 rates the outcome as critical for a decision, 4–6 indicates that it is important and 1–3 indicates that it is not important (Figure 5.1). The average score for each outcome can then be used to determine the relative importance of each outcome, although it is helpful to provide the range of results as well.

Figure 5.1 Scale for rating outcomes



If necessary, the final rating of outcomes can be reviewed and confirmed at a later stage when the guideline group meets.

Finalizing the questions

Questions should be finalized by the WHO steering group after input from all the relevant experts, including end-users (e.g. programme managers, partner agencies, and consumer and patient groups), who should, ideally, be members of either the guidelines development group or the external review group. Because the number of questions that need systematic reviews will be a major determinant of the time and resources needed to complete the guideline, the steering group should aim to reduce the number of questions to those dealing with the most controversial and least understood areas.

Step 1: Generate initial list of questions

The WHO steering group develops an initial list of questions based on the scope of the guideline. It helps to divide these into background and foreground questions.

Step 2: Draft PICO questions

The WHO steering group, with input from the guideline development group, applies the PICO framework to the foreground questions.

Step 3: List relevant outcomes

The WHO steering group should list relevant outcomes, including both desirable and undesirable effects. The guideline development group reviews this and may add additional important outcomes.

Step 4: Comment and revise

The list of questions and outcomes of interest should be sent to the external review group for review and revision and inclusion of any omissions.

Step 5: Rate outcomes

Selecting relevant outcomes is critical to producing an effective guideline. Outcomes should be rated in order of importance by a wide group comprising the guideline development group, the external review group and relevant stakeholders. To make this workable, a formal rating process, such as that described above, should be used.

Step 6: Prioritize questions

Prioritize questions and determine which questions need systematic reviews. This is done by the WHO steering group using input from the guideline development group and the external review group.

Further reading

Question formulation for clinical practice guidelines. In: *Handbook for the preparation of explicit evidence-based clinical practice guidelines.* Wellington, New Zealand Guidelines Group, 2001:15–21 (http://www.nzgg.org.nz/download/files/nzgg_guideline_handbook.pdf, accessed 8 June 2012).

Kaifeng AK. Principles of evidence based medicine. *Archives of Disease in Childhood,* 2005, 90:837–840.

O'Connor D, Green S, Higgins JPT, eds. Defining the review question and developing criteria for including studies. In: Higgins JPT, Green S, eds. *Cochrane handbook of systematic reviews of intervention. Version 5.0.1* (updated September 2008). The Cochrane Collaboration, 2008 (http://www.cochrane-handbook.org, accessed 8 June 2012).

Murphy MK et al. Consensus development methods and their use in clinical guideline development. *Health Technology Assessment,* 1998, 2(3) (http://www.ncchta.org/fullmono/mon203.pdf, accessed 8 June 2012).

6. **Evidence retrieval and synthesis**

Systematic reviews

WHO recommendations need to be based on the best evidence available. Ensuring that all the relevant evidence has been sought and presented is not always easy. An effective approach is to perform a systematic review using specific questions about the intervention(s) likely to be recommended in the guideline. Systematic reviews, if conducted properly, reduce the risk of selective citation and improve the reliability and accuracy of decisions.

The key characteristics of a systematic review are:

- a specific and clearly focused question (in PICO format)
- an explicit, reproducible method including pre-defined eligibility criteria
- a comprehensive, exhaustive and systematic search for primary studies
- a selection of studies using clear and reproducible eligibility criteria
- critical appraisal of included studies for quality
- systematic presentation and synthesis of the characteristics and findings of the included studies.

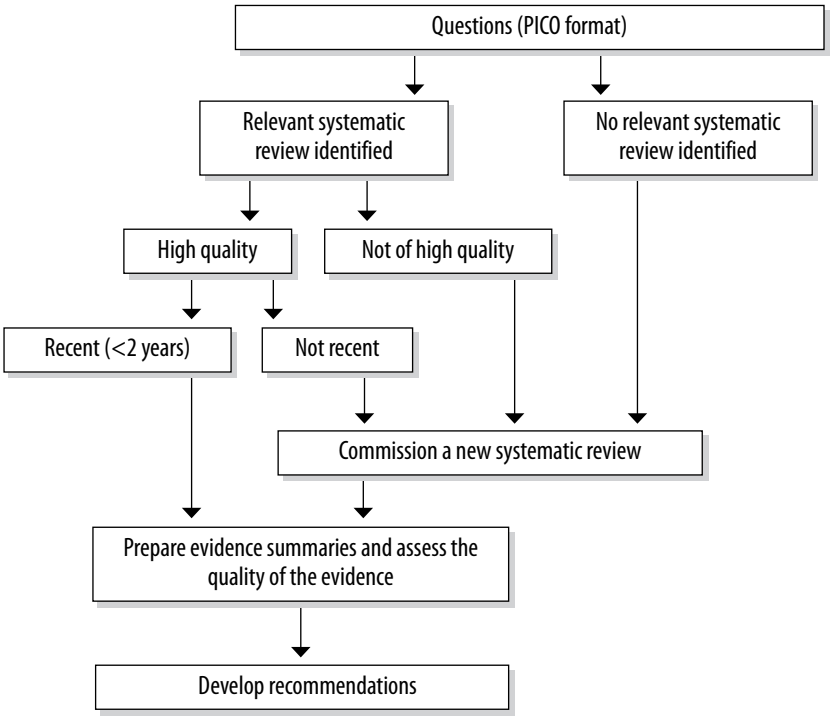
Is a new review needed?

While systematic reviews should be used to assemble all the evidence, it is not always necessary to commission new ones (see Figure 6.1 Evidence retrieval decision diagram). If current, relevant and high quality systematic reviews exist, these should be used. Updates, if needed, are less expensive and time-consuming than new reviews. The search for existing systematic reviews can be done by the WHO steering group, or can be sub-contracted to a group preparing the evidence summaries.

The Cochrane Collaboration – a large global network that produces systematic reviews – is a nongovernmental organization in official relations with WHO. The Cochrane Collaboration may be able to identify existing or forthcoming systematic reviews on the guideline topic. The GRC secretariat can refer you to WHO's Cochrane Collaboration focal point who will liaise with relevant Cochrane groups. For reviews on complex interventions such as behavioural change, these groups include:

- The Cochrane Qualitative Research Methods Group
  http://cqrmg.cochrane.org/
- The Cochrane Consumers and Communication Review Group
  http://www.latrobe.edu.au/chcp/cochrane/
- The Cochrane Effective Practice and Organisation of Care Group
  http://epoc.cochrane.org/

Figure 6.1 Evidence retrieval decision diagram



The Campbell Collaboration http://www.campbellcollaboration.org/ has a database of reviews of effectiveness of social and educational policies and practices.

The search for existing systematic reviews should be done in a systematic way and documented in a protocol. The protocol should describe the databases used and the search strategy applied to each. Please have your protocol reviewed by a WHO librarian or other expert in information retrieval to ensure that you have included all the necessary databases and search terms.

Your protocol may start by reviewing the reference lists of existing guidelines on the topic, before moving on to the major biomedical databases, such as PubMed. PubMed's clinical queries or special queries options permit specific searches to identify systematic reviews of different types of studies. You can also now use the publication limits in PubMed to limit your search to all reviews or only to meta-analyses. Systematic reviews of policy interventions may be difficult to find, and other search strategies will be needed. You will need to include a brief description of how and when this search was actually done, as well as the results, in the final guideline.

Evaluating the quality of systematic reviews

Once the systematic reviews are retrieved, the WHO steering group will need to assess the relevance, timeliness and quality of these reviews before making a decision as to whether new reviews will need to be commissioned. To assess relevance, compare the PICO question of the systematic review to the PICO questions for the guideline that were developed during the scoping. If a relevant systematic review is less than two years old, and is judged to be of sufficient quality, it can be used. If it is older than two years it needs to be updated to include more recent evidence. If it is a Cochrane Review, the relevant review group could be contacted to determine if an update is planned. If there are several systematic reviews, use the most recent one of high quality.

The following checklists may be used in assessing quality:

- Systematic review critical appraisal sheet
  http://www.cebm.net/index.aspx?o=1157
- Assessment of multiple systematic reviews (AMSTAR)

Please note that a checklist merely provides a list of items that should be appraised and that the final decision on whether a systematic review is of high quality is a judgement based on a combination of all items. The following five aspects are important quality indicators of a systematic review.

1. PICO question and eligibility criteria

The review question should specify the types of population, interventions, comparisons and outcomes of interest and the types of study that will be included in the review. Together, these form the basis of the pre-specified eligibility criteria.

Is the question being addressed clearly and explicitly stated with reference to participants, interventions, comparisons and outcomes? Does the review identify which study designs are included? Are inclusion and exclusion criteria clearly defined?

2. Information sources and search for original articles

A comprehensive search includes major bibliographic databases (e.g. Medline, EMBASE), but also a search of reference lists from relevant studies, conference abstracts and other grey literature and contact with experts to identify additional studies. Searches limited to the English language only are likely to miss relevant papers. Both text words and subject headings (e.g. Medical Subject Headings – MeSH terms) should be used.

Is the search strategy, including search terms used, clearly described? Is it comprehensive? Was a thorough search of appropriate databases done and are other sources of information used? Are there language limitations?

3. Study selection and data extraction

Assessment of eligibility of studies, and extraction of data from study reports, should have been done by at least two people, independently.

Were the title and abstracts scanned for eligibility by two independent researchers? Is the total number of titles and abstracts reviewed indicated? Is the number of excluded articles reported and are reasons for exclusion given? Were data extracted in duplicate?

4. Study quality and risk of bias

The risk of bias in included studies depend on the type of studies included. Examples of criteria for assessing risk of bias include randomization, blinding, completeness of follow-up.

Does the review describe how the risk of bias for each study was assessed? Were predetermined criteria used?

5. Synthesis and reporting of results

The review should describe how data were handled and the results of studies combined. A test for heterogeneity should be done if meta-analyses are presented. An assessment of risk of bias across studies – due to publication or reporting bias – should be reported.

If a meta-analysis was done, was a test for heterogeneity reported? If there was significant heterogeneity between studies, were possible reasons explored? Are the conclusions supported by the data?

If the identified systematic reviews are all of low quality, you will need to commission a new one.

How to commission a systematic review

A new systematic review is needed if relevant existing systematic reviews could not be identified, or when existing systematic reviews are of low quality. If you find a high-quality review that is more than two years old, you may be able to commission an update to include more recent evidence.

Systematic reviews take time, expertise and resources to do well, and are best commissioned from external suppliers by the WHO steering group. Members of the Cochrane Collaboration may be able to do or update the systematic reviews required. Regardless of supplier, you should estimate a minimum of US$ 20 000 per review, although this amount will vary depending on the complexity of the review needed.

In commissioning the reviews, the WHO Steering Group will need to:

- disseminate a request for proposals to established suppliers of systematic reviews;
- provide clear terms of reference to the suppliers selected;
- review and approve the suppliers' protocol before the evidence search is started; and
- request regular updates from the suppliers on the progress of the review.

Search strategies

Regardless of the supplier chosen, systematic reviews used to inform WHO recommendations must be developed according to the standards outlined by the Cochrane Collaboration in the Cochrane handbook. The handbook has a specific chapter dealing with reviews in public health and health promotion.

For a WHO guideline, it is important to search for studies from low- and middle-income countries in all regions as well as from more standard literature sources. Some journals are not well represented in PubMed and commercial databases such as EMBASE and CAB Abstracts. Regional databases grouped under the general heading of the Global Health Index contain unique citations and full-text articles. WHO's regional offices have supported the development of these indices to highlight the health research of developing countries. Most journals indexed by regional databases are not indexed in PubMed. Please ensure that the supplier of your systematic review consults a WHO librarian to ensure that the search strategy includes these databases. Your supplier is also likely to need a way of searching for and assessing evidence in WHO's six official languages and should specify how the relevant grey literature will be identified.

Including qualitative research

Systematic reviews on the effect of an intervention can be complemented by qualitative evidence. Qualitative evidence can help explain, interpret and apply the quantitative results of a systematic review. A synthesis of qualitative research can be done as part of the scoping of the guideline and can also help to define and refine the questions. The relevant chapter in the Cochrane handbook explains in detail how to include qualitative research and provides additional reading and relevant web sites.

A mixed methods synthesis brings together a meta-analysis of quantitative data and a qualitative analysis. In this case, systematic reviewers will search for qualitative research imbedded in original studies evaluating health interventions. This is most appropriate if the intent is to identify why the intervention might or might not work.

A qualitative evidence synthesis uses specific searches for – and synthesis of – evidence from qualitative studies. This type of synthesis can address questions on effectiveness of the intervention, such as contextual barriers and facilitators, or values and preferences of those receiving the intervention.

Evidence synthesis

The results of the systematic reviews will be presented to the guideline development group in a meeting in which the total body of evidence is assessed and recommendations are developed. The two most common ways of presenting the evidence are briefly described here, but for more details, please consult the Cochrane handbook.

Meta-analysis

If the data extracted from the systematic review meet certain requirements (the most important one being a high level of homogeneity of effect measures across studies), then the data can be combined using meta-analyses. A meta-analysis is the use of statistical methods to summarize the results of independent studies. By combining information from all relevant studies, meta-analyses can provide more precise estimates of the effects of health care than those derived from the individual studies included within a review. The results of a meta-analysis are usually displayed in a figure called a forest plot.

Narrative synthesis

If a meta-analysis is not feasible – due to heterogeneity – or not sensible because different types of interventions are covered, the evidence can be presented in a narrative synthesis. The method used to produce this synthesis needs to be specified before starting and followed rigorously to avoid introducing bias. The results of each individual study can be presented in a table. Irrespective of the way in which the results are presented, it is important that the same elements of information are included in the same order. Grouping the studies can help if a large number have been included in the review.

Further reading

Grimshaw J et al. Systematic reviews of the effectiveness of quality improvement strategies and programmes. *Quality and Safety in Health Care,* 2003, 12:298–303.

Harden A et al. Applying systematic review methods to studies of people's views: an example from public health research. *Journal of Epidemiology and Community Health,* 2004, 58:794–800.

Jackson N, Waters E for the Guidelines for Systematic Reviews in Health Promotion and Public Health Taskforce. Criteria for the systematic review of health promotion and public health interventions. *Health Promotion International,* 2005, 20:367–374.

Moher D et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine,* 2009, 6(7): e1000097

Liberati A et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine,* 2009, 6(7): e1000100

Ogilvie D et al. Systematic reviews of health effects of social interventions: 1. Finding the evidence: how far should you go? *Journal of Epidemiology and Community Health,* 2005, 59:804–808.

Ogilvie D et al. Systematic reviews of health effects of social interventions: 2. Best available evidence: how low should you go? *Journal of Epidemiology and Community Health,* 2005, 59:886–892.

Shepperd S et al. Can we systematically review studies that evaluate complex interventions? *PLoS Medicine,* 2009, 6(8): e1000086

Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011 (http://www.cochrane.org/training/cochrane-handbook, accessed 8 June 2012).

7. **Evidence assessment**

GRADE

The evidence that has been retrieved and synthesized in a systematic review needs to be assessed for quality. Quality of evidence is defined as the "extent to which one can be confident that an estimate of the effect or association is correct."

WHO uses the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because these represent internationally agreed standards for making transparent recommendations. Detailed information on GRADE is available through the GRC secretariat and on the following sites:

- GRADE working group: http://www.gradeworkingroup.org
- GRADE online training modules: http://cebgrade.mcmaster.ca/
- GRADE profile software: http://ims.cochrane.org/revman/gradepro

The GRC secretariat offers GRADE workshops throughout the year. Please contact the secretariat, or check the GRC intranet web page for training dates.

Assessing the evidence and developing evidence summaries is a specialized task that is best done by a methodological expert. WHO guideline development groups usually include, or work with, a methodologist. The GRC secretariat can recommend GRADE experts and methodologists from the Cochrane Collaboration. The methodologist is contracted to do the evidence assessment, prepare the evidence summaries, and present them at the guideline development group meeting. The guideline development group uses these summaries as the basis for their discussions and recommendations.

Guideline development group members that have no previous experience of working with GRADE should be briefed on the process by WHO prior to the guideline meeting. This can be done with a combination of the online training modules, publications and presentations listed above. Additionally, many guideline groups find it useful to start their meetings with an introduction to GRADE presented by the methodologist or the GRC secretariat.

Evidence profiles

The methodologist will present GRADE evidence profiles for each PICO question for which a systematic review was done (Table 7.1). Evidence profiles are tables that contain the quality assessment and the summary of findings.

Table 7.1 Components of a GRADE evidence profile

Question (PICO format)										
Quality assessment							**Summary of findings**			
							Study event rates (%)		Effects	
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	Overall quality of evidence	Intervention	Control	Relative effect (95% CI)	Absolute effect
Outcome A (evidence from randomized trials)										
Outcome A (evidence from observational studies)										
Outcome B (evidence from randomized trials)										

The quality assessment

GRADE categorizes the quality of evidence as high, moderate, low or very low (Table 7.2). These quality ratings apply to the body of evidence assessed for the PICO question, not to individual studies.

Table 7.2 Significance of the four levels of evidence

Quality	Definition	Implications
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The guideline development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

The starting point for rating the quality of evidence is always the study design, broadly classified into two types:

- randomized controlled trials (RCTs);
- observational studies, including interrupted time-series (or quasi-experimental design), cohort studies and case-control studies, and other types of design such as case series and case reports.

The design is the baseline for rating the quality of evidence. If you have studies of more than one design reporting the outcome, you should have a separate row in your table for each type. Although randomized controlled trials are the preferred source of evidence for measures of effectiveness, in many instances guideline developers rely on information from observational studies. This situation arises when RCTs are not ethical, appropriate or feasible, when few RCTs are available and observational studies are needed to estimate the effect size, or when information on the feasibility of the intervention in different settings is needed.

Evidence based on randomized controlled trials is given a high-quality rating and evidence from observational studies is given a low-quality rating. These initial ratings can be adjusted by the following factors.

Five factors that can lower the quality of evidence

1. Study limitations

For randomized controlled trials, the main criteria for assessing limitations are:

- whether concealment of allocation to treatment group is adequate;
- whether participants and investigators were blinded, especially if the outcomes are measured subjectively and subject to bias;
- whether an intention-to-treat analysis is reported;
- whether all withdrawals and patients lost to follow-up are accounted for;
- whether the trial was stopped early for benefit.

For studies of diagnostic accuracy, additional limitations include:

- whether patients were consecutively recruited and not classified by disease state;
- whether both the new test and the reference standard were done in all patients;
- whether evaluators were blinded to the results of the alternative test and reference standard.

For observational studies, the main criteria depend on the design (i.e. case-control or cohort studies). For both designs, the methods used to select the population in the study and the comparability of the two groups are important. For case-control studies the method of determining exposure to the factor of interest also needs to be evaluated. For cohort studies the method of measuring outcomes should be evaluated.

The evidence summaries should categorize the limitations as follows.

a. ***"No limitations"*** generally means that the majority of studies meet all the minimum quality criteria for the design. The implication of this is that the rating of quality of evidence remains the same as the initial assessment.

b. ***"Minor limitations"*** applies when minor flaws are found when analyzing how the available studies were designed and performed. If you decide there are minor limitations, these should be noted in a footnote in the evidence profile but they would not usually downgrade the quality.

c. ***"Serious limitations"*** means that one of the minimum criteria for quality is not met by the majority of studies in the review. This results in a -1 score for the overall quality rating (e.g. "high" becomes "moderate").

d. ***"Very serious limitations"*** means that at least two of the criteria proposed as potential study limitations are present in the majority of studies in the review. This results in a -2 score for quality.

2. Consistency

Consistency relates to whether the results are similar across studies. Differences in the direction, the size, and the significance of the differences in effect, guide the decision about whether important inconsistency exists. If all the results of the studies for one outcome are in the same direction with overlapping confidence intervals, there is unlikely to be significant consistency. To evaluate the degree of consistency of the results of the available studies, the direction and size of the effect for each outcome should be evaluated. If a formal meta-analysis was conducted, the result of the test for heterogeneity can be used to help assess consistency. Variability or inconsistency in results may arise from differences in the populations in the studies, in the interventions or in outcomes.

If there is inconsistency in the results, such as the largest trial showing results that contradict smaller trials, then a -1 score should be applied. If the results are very heterogeneous, "very serious" should be chosen, which will downgrade the evidence for this outcome by two levels. If only one study is present, consistency is not applicable as a criterion.

3. Directness

Directness, generalizability, external validity of study results and applicability are all synonyms. There are two types of indirectness.

- Indirect comparison occurs when a comparison of intervention A versus B is not available, but A was compared with C and B was also compared with C. Such trials allow indirect comparisons of the magnitude of effect of A versus B. Such evidence is of lower quality than direct comparisons of A and B would provide.
- Indirect population, intervention, comparator or outcome arise when the question being addressed by the guideline development group or by the authors of a systematic review is different from the available evidence regarding the population, intervention, comparator or outcome.

4. Imprecision

Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. In this case the quality of the evidence is lower than it otherwise would be because of uncertainty in the results.

When event rates are very low, 95 per cent confidence intervals around relative effects can be very wide, but 95 per cent confidence intervals around absolute effects may be narrow. In the latter case, the quality should not be downgraded for imprecision.

5. Reporting bias

Reporting bias (also called publication bias) is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies or selective reporting of outcomes. Reporting bias arises when investigators fail to report studies they have done (typically those that show no effect) or neglect to report outcomes that they have measured (typically those for which they observed no effect).

Despite methods to detect the possibility of publication bias, the authors of systematic reviews and guideline panels must often make assumptions about the extent of this bias. Reporting bias should be considered when published evidence is limited to a small number of trials, all of which were funded by a for-profit organization. In such a situation, consider the extent to which evidence about the magnitude of the effect is uncertain due to selective publication of studies or reporting of outcomes. If this is likely, downgrade the quality rating by one or even two levels.

The criteria that are used for downgrading the quality of evidence and the reason for the assessment should be explained in a footnote to the table.

Three factors that can increase the quality of evidence

1. Dose-response gradient

The presence of a dose-response gradient may increase confidence in the findings of observational studies and thereby increase the quality of evidence. However, this applies only to studies that are not downgraded for any reason. To rate the presence of a dose-response gradient:

- if there is no evidence of a dose-response gradient, there is no change;
- if there is evidence of a dose-response gradient, upgrade the evidence for this outcome by 1 level.

2. Direction of plausible bias

On occasion, all plausible biases from observational studies may tend to underestimate the true treatment effect. For instance, if only sicker patients receive an experimental intervention or exposure, yet they still improve, it is likely that the actual intervention or exposure effect is larger than the data suggest. Only studies with no threats to validity (not downgraded for any reason) can be upgraded. To rate the effect of all plausible residual confounding:

- if there is no evidence that the influence of all plausible residual confounding would reduce the observed effect, there is no change;
- if there is evidence that the influence of all plausible residual confounding would reduce the observed effect, upgrade the evidence for this outcome by 1 level.

3. Magnitude of the effect

When methodologically strong observational studies yield large or very large and consistent estimates of the magnitude of a treatment or exposure effect, we may have confidence in the results. In such situations, the weak study design is

unlikely to explain all the apparent benefit or harm, even though observational studies are likely to provide an overestimate of the true effect. The larger the magnitude of effect, the stronger the evidence becomes. Only studies with no threats to validity (not downgraded for any reason) can be upgraded.

The final category for the quality of evidence is determined by adding the additional ratings to the original baseline category (Table 7.3).

Table 7.3 How to upgrade or downgrade the quality of evidence

Downgrade in presence of	Upgrade in presence of
Study limitations -1 Serious limitations -2 Very serious limitations	Dose-response gradient +1 Evidence of a dose-response gradient
Consistency -1 Important inconsistency	Direction of plausible bias +1 All plausible confounders would have reduced the effect
Directness -1 Some uncertainty -2 Major uncertainty	Magnitude of the effect +1 Strong, no plausible confounders, consistent and direct evidence
Precision -1 Imprecise data	+2 Very strong, no major threats to validity and direct evidence
Reporting bias -1 High probability of reporting bias	

The summary of findings

In the summary of findings, the following information is presented.

- The number of patients (or, in the case of a policy intervention, units) studied: for the intervention and the control group the total number of patients and the number of patients who experienced the outcome are reported.
- The effect size: both absolute and relative effects are reported – these are obtained from the systematic reviews (e.g. from the meta-analysis).
- The quality of the evidence: this is the result of the quality assessment and is reported as one of the four categories of evidence (high, moderate, low or very low).
- The importance of the outcome: this is the result of the rating of the importance of the outcome that was done during the scoping process.

Statistical methods for combining results of observational studies are more complex than the methods used for combining randomized controlled trials. If it is possible to pool data, they can be reported in a standard GRADE evidence profile. If the results cannot be combined, the results can be presented in a narrative synthesis as described in Chapter 6.

Further reading

Barbui C et al. Challenges in developing evidence-based recommendations using the GRADE approach: the case of mental, neurological, and substance use disorders. *PLoS Medicine,* 2010, 7(8): e1000322

Bruce N et al. Enhancement to GRADE (termed GRADE+) for environmental health interventions. A proposal with special consideration of application to the development of WHO indoor air quality guidelines: household fuel combustion [manuscript in preparation].

Guyatt GH et al. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *Journal of Clinical Epidemiology,* 2010, 64:380–382.

Guyatt GH et al. Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations**.** *BMJ,* 2008, 336:924–926.

Schünemann HJ et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ,* 2008, 336:1106–1110.

8. **Developing recommendations**

Factors that condition recommendations

Once the evidence is retrieved, synthesized and assessed, this evidence must now be used to develop recommendations. In the GRADE approach the quality of the evidence and the balance between benefits and harms determine whether the recommendation is for or against the recommendation. The strength of the recommendation is determined by a consideration of values and preferences, and resource implications.

The quality of the evidence – the degree of confidence in estimates of effects – is the first factor considered. The higher the quality of evidence, the more likely a strong recommendation is warranted. If the quality of the evidence is lower, it will create greater uncertainty about the size of the relative effects. This uncertainty can concern both beneficial and harmful effects and therefore makes a conditional recommendation more likely.

When considering the balance between benefits and harm, one should look at the magnitude of the effect as well as the importance of the outcomes. If the benefits clearly outweigh the harms, a strong recommendation is more likely. A conditional recommendation is more likely if there is uncertainty about the balance of benefits versus harms or when there are only marginal net benefits, that is, when the anticipated net benefits are small.

Values and preferences are based either on collected qualitative evidence or by the experience and opinion of various stakeholders present in the guideline development group. The greater the variability in values and preferences, or uncertainty in values and preferences the more likely a conditional recommendation is warranted. There might be uncertainty about the relative importance of the benefits and harms to those affected, or differences in how these benefits and harms are perceived.

The guideline group's consideration of resource implications can be informed either by a full formal economic evaluation or by estimates collected during the evidence retrieval. The more resources the intervention consumes, the less likely a strong recommendation is warranted. Uncertainty about resource use – whether the net benefits are worth the costs, lack of information about the cost, or questions about whether the resource expenditure is justified by the anticipated benefit – make a conditional recommendation more likely.

Decision tables

Decision tables can be used to record the guideline's group judgements about these factors and how they contributed to the development of the recommendation, as shown in Table 8.1.

Table 8.1 Decision table to support the development of recommendations

Recommendation:		
Population:		
Intervention:		
Factor	Decision	Explanation
Quality of the evidence (The higher the quality of the evidence, the more likely a strong recommendation is warranted.)	High Moderate Low Very low	
Balance of benefits versus harms and burdens (The larger the difference between the benefits and harms, the more likely a strong recommendation is warranted. The smaller the net benefit and the lower the certainty for that benefit, the more likely a conditional recommendation is warranted.)	Benefits clearly outweigh harms Benefits and harms are balanced Potential harms clearly outweigh potential benefits	
Values and preferences (The greater the variability or uncertainty in values and preferences, the more likely a conditional recommendation is warranted.)	No major variability Major variability	
Resource use (The higher the costs of an intervention, that is, the more resources consumed, the more likely a conditional recommendation is warranted.)	Less resource-intensive More resource-intensive	
Overall strength of the recommendation: (strong or conditional)		
Research gaps:		

The strength of the recommendation

The strength of a recommendation communicates the importance of adherence to the recommendation.

Strong recommendations

With strong recommendations, the guideline communicates the message that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted as policy.

Conditional recommendations

These are made when there is greater uncertainty about the four factors above or if local adaptation has to account for a greater variety in values and preferences, or when resource use makes the intervention suitable for some, but not for other locations. This means that there is a need for substantial debate and involvement of stakeholders before this recommendation can be adopted as policy.

When not to make recommendations

When there is lack of evidence on the effectiveness of an intervention, it may be appropriate not to make a recommendation. The lack of evidence can be highlighted by stating: "No recommendation can be made because of insufficient evidence". Instead of providing a recommendation, the findings of the systematic review or an overview of interventions may be published. By doing so, a range of optional interventions can be presented without indicating a preference for one over the other. In other situations guidance from WHO might be needed, despite there being little or no evidence. In these instances the absence of evidence should be highlighted and the basis of the options presented such as case reports, national experience or opinion, should be clearly indicated.

Research recommendations

When there is a lack of evidence, or the available evidence is insufficient, research recommendations should be specified, and prioritized if appropriate. In formulating research needs, guideline groups should be as specific as possible about what is needed and why. Research recommendations can be structured as shown in Table 8.2.

Table 8.2 Suggested format for research recommendations

Core elements		
E	Evidence	What is the current state of the evidence?
P	Population	What is the population of interest?
I	Intervention	What are the interventions of interest?
C	Comparison	What are the comparisons of interest?
O	Outcome	What are the outcomes of interest?
T	Time stamp	Date of literature search or recommendation

continues

Optional elements		
d	Disease burden	Disease burden or relevance
t	Time	Time aspect of core elements of EPICOT
s	Study design	Appropriate study type according to local need

Reaching agreement on recommendations

The WHO steering group usually prepares the draft recommendations, including a justification and a reference to the relevant evidence profile for each recommendation.

The guideline development group reviews and discusses the evidence profiles presented by the methodologist. The guideline development group considers values and preferences and resource implications of the intervention. If evidence on these was collected, this is reviewed and discussed.

The guideline development group agrees on the direction and the strength of the initial recommendation. Ideally the group should take decisions about recommendations by consensus, but guideline development groups need to decide how they will reach a decision if consensus cannot be reached. Voting rules should be agreed on before the meeting.

Writing recommendations

Recommendations needs to be clear and actionable, reflect the PICO format, and indicate the strength of the recommendation and the quality of the evidence. Wherever possible, the language should be consistent across all recommendations made in a guideline.

Further reading

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9. **Producing and publishing your guideline**

Peer review

WHO guidelines should undergo peer review during development and before the draft is finalized for publication. There are several stages when peer review and external comment are sought.

- Drafts of the questions formulated for the guideline should be circulated for comments to experts and end-users at WHO headquarters, regional offices and externally.
- If systematic reviews are commissioned, the systematic review protocol (outlining search strategy and eligibility criteria) and included studies may be circulated to experts for comments on the methods and evidence identified.
- Draft evidence profiles can be circulated to experts for identification of any missing evidence and are reviewed at the guideline development group meeting.
- A final draft guideline with recommendations may be circulated for review before clearance.

The process of reviewing comments and responding to them should be recorded. It is not necessary to respond to every single comment individually. However, it is important to document how comments were handled, either as a version of the document with the changes, or as a separate summary.

If the guideline is circulated for comments after recommendations are finalized, be clear about what changes can be made. It is suggested that changes after finalization should be restricted to major errors of fact.

Different types of guidelines have a slightly different peer review requirements.

- Rapid advice guidelines: peer review can be limited to review of the complete draft only, immediately before final clearance, perhaps by 3–6 experts.
- Standard guidelines: a more complete peer review process is expected, including:
  - review of questions;
  - review of evidence tables and completed draft recommendations (after the guideline meeting);
  - a record of the response to the comments and any changes that are made.
- Full guidelines: peer review would be expected to be as above, with an optional additional review after a second draft.

Guideline format

All guidelines should have an executive summary, a main body and appendices. A general recommendation for the length of these sections is the 1–3–25 rule – i.e. an executive summary of 1 page, the main guideline of 3 pages, and appendices of 25 pages.

The executive summary should contain the key recommendations of the guideline. As executive summaries are often read as stand-alone documents, the quality of evidence for each recommendation should be specified in the executive summary as well in the main body of the guideline.

Summary of finding tables and descriptive evidence tables should be made publicly available but do not have to be included in the main guideline document. They can be published electronically as background documents, as long as they are cited in the guideline itself.

Prior to submission for clearance, the WHO steering group may wish to use the AGREE 2 appraisal instrument (http://www.agreetrust.org) to check whether the guideline meets international reporting criteria.

The production process

Production of WHO guidelines should follow the same process as other WHO publications. Detailed information on each step is available on the Intranet, a brief overview is provided here.

Writing

Identify a writer early in the process. This can be a WHO staff member or an external writer contracted on a freelance basis. If the writing will be done by a staff member, it is important to accurately estimate the demands that will be made on the person's time. Once you have an idea of the approximate length of your document, you can make a rough calculation of the time needed and can begin negotiations with an external writer if necessary. WHO does not have a standard writing pay scale but WHO Press usually advises a minimum of US$ 0.50 per word for writers, or a negotiated daily rate from current daily pay rates for consultants (available from the Human Resources Department). When negotiating fees and schedules, calculate a minimum of one week of full time work to produce 5000 words.

It is strongly recommended to avoid the 'committee' approach to writing a guideline. Asking experts to draft chapters for free may seem to be a cheap and efficient way of getting the job done, but unless you can guarantee quality, consistency and timely delivery, it will inevitably create more work than it eliminates.

Legal advice on proprietary products

Proprietary products should not be named. Devices and diagnostics used in interventions should be described generically avoiding identification

of specific products and trademarks. If in doubt, please contact WHO's legal counsel.

Editing and proofreading

You will also need an editor and a proof reader. WHO press maintains lists of approved freelance editors and proof readers, and provides sample terms of reference and standard rates of pay for these tasks. The best editors and proof readers are often booked up many months in advance, so plan production schedules as early as possible, and reserve their time accordingly.

Executive clearance and GRC approval

GRC review of final guideline documents occurs as part of the final executive clearance. Documents should be in a final edited form ready for layout and printing when they are submitted for final clearance.

Layout

Once you have an edited, proofed and cleared text, you will need to send it for layout. Again, WHO Press can advise on external typesetters and the specifications that you should include when contracting for this work. The WHO graphics team also provides an internal layout service. As many design decisions have major implications for the cost of production, printing, dissemination and subsequent translations, it is worth discussing the possibility of using an existing publication template with WHO Press before engaging an external designer. You will need a cover design, an ISBN (international standard book number) and a barcode, the latter two are issued by WHO Press.

Printing

Internal print will provide printing quotes and arrange for your files to be sent to the printer. You must have the printers' proofs checked again by your proof reader, so be sure to include this step in the initial proofreading contract. Once the print copies are delivered, you can focus on distribution and implementation.

Disseminating guidelines

Dissemination involves making guidelines accessible, advertising their availability and distributing them widely. Guideline developers should consult with WHO Press on priced and mandatory free distribution. When thinking about the dissemination of your guideline, consider the following options:

Online publication

There are different formats in which your guideline can appear on the Internet. At a minimum, you should contract your designer or typesetter to produce a web-ready PDF (portable document format) – a smaller file size than the PDFs produced for print – that is easier to download and navigate. Depending on the length of the guideline and its intended audience, you may

also wish to consider providing full-text HTML (hypertext mark-up language) and additional materials, both electronic and printed. The WHO web team is a good source of advice.

Translations

Because WHO guidelines target a global audience it might be appropriate to provide translations of the guideline in one or several languages, particularly the six official languages Arabic, Chinese, English, French, Russian and Spanish. To ensure accurate translation of technical content, experts should be involved in checking the translations. Translations must be planned in advance and the timing of the translations discussed with the translation suppliers or regional office involved. Do not forget to budget for translation costs. To reduce translation costs, translations may be limited to the executive summaries. Special care should be taken in the translation of the recommendations themselves: the meaning of the recommendation, or its strength should not change in translation.

Journals

The systematic reviews commissioned for the guideline may be submitted for publication in the Bulletin of the World Health Organization or other journals. Cochrane reviews are published in the Cochrane database. In order to increase awareness of the guideline, the process and/or recommendations may also be published in peer-reviewed journals.

Other forms of dissemination

Mobile phone applications for guideline dissemination and decision support are being developed. You may also wish to consider planning an official launch, a press release or press conference, an announcement on the WHO web site, distribution through regional offices or at meetings, or endorsement by stakeholders and interest groups.

Updating guidelines

Review-by date

WHO guidelines should be issued with a 'review-by' date to indicate how long the recommendations are expected to remain valid. There is no absolute rule about the length of validity. In deciding on the date by which a guideline should be reviewed, take account of the pace of change of research on the topic, areas where no evidence has been found, and the potential need for new advice. For standard and full guidelines a minimum of two years and a maximum of five years are suggested. The department that will be responsible for initiating the review should be named in the document.

Updating recommendations

All WHO recommendations that are not based on rigorous evidence review (particularly those published before the GRC was in established in 2007), should be updated as described in this handbook. Updating guidelines can be challenging if evidence has to be retrieved to support a large number of existing recommendations. In this situation it is important to give priority to controversial areas, or those in which new evidence has emerged.

Interim updates

Occasionally guideline developers may want to update guidelines before the 'review-by' date. For example, if new evidence supporting or contradicting the current recommendations is published. This new evidence should always be seen in the context of the total body of evidence supporting the recommendations. Therefore, it should be part of a new or updated systematic review. Any interim update that involves changing recommendations, needs to be reviewed by the guidelines review committee. Updates that add new evidence without changing the recommendations do not require review, although under certain circumstances, if the topic or new evidence is highly controversial, GRC review may be advisable.

10. **Implementation and evaluation**

Implementation

Implementation of a guideline should be taken into account right from the beginning of its development. A guideline project should ideally be in a departmental or other programme of work on the particular topic since that is more likely to lead to an effective plan for implementation.

Implementation will generally be the responsibility of regions and national or subnational groups, which is why they need to be involved in the development of the guideline. WHO headquarters and regional offices can support implementation activities by providing tools, support and coordination of efforts.

Implementation strategies need to be tailored to specific local circumstances. The basic steps for implementing a guideline are:

- analyse local needs and priorities (look for additional data on actual practice);
- identify all potential barriers and facilitating factors;
- determine available resources;
- design an implementation strategy (consider how to encourage the adoption of the recommendations and how to make the overall context favourable to the proposed changes).

There is a range of derivative documents or tools that can be developed to facilitate implementation. These can be distributed with the guideline, or they can be developed by local guideline implementers. Such documents or tools may include a slide set reflecting the guideline content; a 'how to' manual or handbook; a flow chart, decision aid or algorithm; fact sheets; quality indicators; checklists; application tools; templates, etc.

Implementation or operational research can help inform field testing and rollout strategies to promote the uptake of recommendations.

Evaluation and monitoring

An evaluation should be done to measure the impact of the guideline. The guideline should include outcome or performance measures that can be monitored for the main recommendations. Performance measures might be related to:

- guideline dissemination
- change in practice performance
- change in health outcomes
- change in end-user knowledge and understanding
- economic consequences.

Ideally, there should be baseline measures against which to assess performance in relation to the change induced by the guideline. Impact assessment of guidelines will need to be done in the places that they are implemented. WHO should work with Member States to evaluate the impact of the guidelines by coordinating efforts and providing advice and practical support.

Further reading

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Guidelines for the programmatic management of drug-resistant tuberculosis

2011 update

World Health Organization

This guideline was developed in compliance with the process for evidence gathering, assessment and formulation of recommendations, as outlined in the WHO Handbook for Guideline Development (version March 2010; available at www.who.int/hiv/topics/mtct/grc_handbook_mar2010_1.pdf).

First edition, 2006
Emergency update, 2008
2011 update

WHO Library Cataloguing-in-Publication Data

Guidelines for the programmatic management of drug-resistant tuberculosis – 2011 update.

1.Tuberculosis, Multidrug-resistant – drug therapy. 2.Tuberculosis, Multidrug-resistant – prevention and control. 3.Antitubercular agents – administration and dosage. 4.HIV infections – drug therapy. 5.Antiretroviral therapy, Highly active. 6.Guidelines.I.World Health Organization.

ISBN 978 92 4 150158 3 (NLM classification: WF 310)

Printed by the WHO Document Production Services, Geneva, Switzerland.

WHO/HTM/TB/2011.6

Design by Inís Communication – www.iniscommunication.com

Guidelines for the programmatic management of drug-resistant tuberculosis

2011 update

World Health Organization

Contents

Abbreviations

ART	antiretroviral therapy
DALY	disability-adjusted life year
CDC	United States Centers for Disease Control and Prevention
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
MDR-TB	multidrug-resistant tuberculosis
NTP	national tuberculosis control programme
PMDT	programmatic management of drug-resistant tuberculosis
SAE	serious adverse event
TB	tuberculosis
UNION	International Union Against Tuberculosis and Lung Disease
USAID	United States Agency for International Development
WHA	World Health Assembly
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Acknowledgements

This 2011 update of *Guidelines for the programmatic management of drug-resistant tuberculosis* was coordinated by Dennis Falzon under the guidance of Ernesto Jaramillo and Léopold Blanc of the World Health Organization's Stop TB Department. The contribution of the following experts and technical groups is gratefully acknowledged.

Guideline Development Group (area of expertise shown in parentheses)

Jaime Bayona, Socios En Salud Sucursal, Peru (programme management, public health)

José A. Caminero, University General Hospital of Gran Canaria, Spain and The UNION, Paris, France (clinical practice)

Charles L. Daley, National Jewish Health, United States (clinical practice)

Agnes Gebhard, KNCV Tuberculosis Foundation, Netherlands (programme management)

Myriam Henkens, Médecins Sans Frontières, France (programme management)

Timothy H. Holtz, HIV/STD Research Program, United States Centers for Disease Control and Prevention–CDC, Asia Regional Office, Thailand (epidemiology, surveillance, programme evaluation)

Joël Keravec, Management Sciences for Health, Brazil (drug management)

Salmaan Keshavjee, Harvard Medical School, United States (programme management, public health)

Aamir J. Khan, Indus Hospital TB Program, Pakistan (epidemiology, programme management)

Vaira Leimane, State Infectology Center, Clinic of Tuberculosis and Lung Diseases, Latvia (programme management, clinical practice)

Andrey Mariandyshev, Northern State Medical University, Archangelsk, Russian Federation (clinical practice)

Carole D. Mitnick, Harvard Medical School, United States (epidemiology, programme support)

Gloria Nwagboniwe, Alliance for Hope, Nigeria (civil society)

Domingo Palmero, Pulmonology Division, Hospital Muñiz, Argentina (clinical practice)

Ma. Imelda Quelapio, Tropical Disease Foundation, Philippines (programme management)

Michael L. Rich, Partners In Health, United States (clinical practice)

Sarah Royce, PATH, United States (surveillance, public health)

Sabine Rüsch-Gerdes, National Reference Centre for Mycobacteria, Germany (laboratory specialist)

Archil Salakaia, Management Sciences for Health, United States (programme management)

Rohit Sarin, LRS Institute of TB and Allied Diseases, India (clinical practice)

Holger Schünemann, McMaster University, Canada (Chairman of the Guideline Development Group; epidemiology, guideline methodology)

Elena Skachkova, Federal Centre of TB Monitoring, Russian Federation (surveillance)

Francis Varaine, Médecins Sans Frontières, France (clinical and programme management)

WHO headquarters, Geneva, Switzerland (members of the Guideline Development Group shown in italics)

Stop TB Department: Léopold Blanc, *Dennis Falzon*[a], Christopher Fitzpatrick, Katherine Floyd, *Haileyesus Getahun*[a], Malgorzata Grzemska[a], Christian Gunneberg[a], *Ernesto Jaramillo*[a], *Christian Lienhardt*, *Fuad Mirzayev*, Paul Nunn, Mario C. Raviglione, *Delphine Sculier*[a], *Fraser Wares*, *Karin Weyer*, *Matteo Zignol*[a]

HIV Department: *Chris Duncombe, Marco Antonio de Avila Vitoria*[a]

[a] Member of the WHO Guideline Steering Group.

External Review Group (area of expertise shown in parentheses for non-WHO staff)

Samiha Baghdadi, WHO Regional Office for the Eastern Mediterranean, Egypt

Mercedes Becerra, Harvard Medical School, United States (academia)

Vineet Bhatia, WHO Regional Office for South-East Asia, India

Masoud Dara, WHO Regional Office for Europe, Denmark

Mirtha del Granado, WHO Regional Office for the Americas, United States

Reuben Granich, WHO HIV Department, Switzerland

Lindiwe Mvusi, Department of Health, South Africa (programme management)

Nani Nair, WHO Regional Office for South-East Asia, India

Norbert Ndjeka, Department of Health, South Africa (programme management, clinical practice)

Wilfred A.C Nkhoma, WHO Regional Office for Africa, Zimbabwe

Katsunori Osuga, WHO Regional Office for the Western Pacific, Philippines

Hendrik Simon Schaaf, Department of Paediatrics and Child Health, Stellenbosch University and Tygerberg Children's Hospital, South Africa (clinical practice, paediatric MDR-TB, surveillance)

Catharina van Weezenbeek, WHO Regional Office for the Western Pacific, Philippines

Irina Vasilyeva, Central TB Research Institute of RAMS, Russian Federation (research, clinical practice)

Wang Xie Xiu, Tianjin Centers for Disease Control and Prevention, China (surveillance)

Richard Zaleskis, WHO Regional Office for Europe, Denmark

Evidence review teams

Chunling Lu, Carole D. Mitnick–Harvard Medical School, Boston, Massachusetts, United States and Richard A. White–Harvard School of Public Health, Boston, Massachusetts, United States

Gail Kennedy, George Rutherford, Karen Steingart–University of California (San Francisco), California, United States

Matthew Arentz, David Horne, Patricia Pavlinac, Judd L. Walson–University of Washington, Seattle, Washington, United States

Melissa Bauer, Richard (Dick) Menzies, Olivia Oxlade–McGill University, Montreal, Quebec, Canada

Consultant: Patricia Whyte, Griffith University, Queensland, Australia (guideline development)

The development and publication of the 2011 update of these guidelines was supported by the generous financial contribution of the United States Agency For International Development (USAID)

Executive summary

This 2011 update of *Guidelines for the programmatic management of drug-resistant tuberculosis* is intended as a tool for use by public health professionals working in response to the Sixty-second World Health Assembly's resolution on prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. Resolution WHA62.15, adopted in 2009, calls on Member States to develop a comprehensive framework for the management and care of patients with drug-resistant TB.

The recommendations contained in these guidelines address the most topical questions concerning the programmatic management of drug-resistant TB: case-finding, multidrug resistance, treatment regimens, monitoring the response to treatment, and selecting models of care. The guidelines primarily target staff and medical practitioners working in TB treatment and control, and partners and organizations providing technical and financial support for care of drug-resistant TB in settings where resources are limited.

The first two editions of the guidelines were published by WHO in 2006 and 2008 through writing committees of international experts. The current 2011 update was undertaken in accordance with the requirements of the Handbook for Guideline Development (2010) of WHO's Guidelines Review Committee. The process began in 2009 with an exercise to determine the scope of the Guidelines ("scoping"), followed by systematic reviews to summarize the evidence. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) method was used to review the evidence and formulate recommendations. The process involved three groups: a WHO Guidelines Steering Group of staff with technical expertise in different aspects of TB and in the development of evidence-based guidelines; a Guideline Development Group comprising a multi-disciplinary panel of external experts including clinicians; and an External Review Group of experts who peer-reviewed the process and the final draft.

The recommendations encourage the wider use of rapid drug-susceptibility testing with molecular techniques to detect TB patients with rifampicin resistance and provide adequate treatment. The use of culture remains important for the early detection of failure during treatment. The best available information at the time the reviews were conducted was used to help decide the most effective composition and duration of treatment for MDR-TB patients. Early use of antiretroviral agents is recommended for TB patients with HIV infection who also receive medication with second-line anti-tuberculosis regimens. Systems that primarily employ ambulatory models of care to manage patients with drug-resistant TB are recommended over others based mainly on hospitalization.

National TB control programmes, public health decision-makers and technical and implementing partners involved in the control of MDR-TB are encouraged to use the recommendations to guide their work, and to adapt national guidelines accordingly. These practices are expected to encourage more collection of evidence and initiate new research, particularly on the composition of regimens, and the duration of treatment for patients with extensively drug-resistant TB.

Funding and declarations of interest

Funding for the meetings and reviews involved in the updating of the guidelines came entirely from the United States Agency for International Development (USAID). The experts on the Guidelines Development Group and the institutions where they work contributed time for the various discussions and other activities involved in the update process.

The Declaration of Interest forms were completed by all non-WHO members of the Guideline Development Group and the External Review Group, as well as the members of the academic centres who were involved in the reviews. Four members of the Guideline Development Group declared interests that were judged to represent a potential conflict and were excused from the sessions of the meeting on 25–27 October 2010 during which recommendations relating to the drug regimens were discussed. Jaime Bayona was a consultant for the development of clinical trial design for studies of an anti-tuberculosis drug manufactured by Otsuka Pharmaceutical Co Ltd (OPC-67683). Charles L. Daley was chairperson of drug safety monitoring for two trials conducted by Otsuka Pharmaceutical Co Ltd. Carole D. Mitnick served as a member of the Scientific Advisory Board of Otsuka Pharmaceutical Co Ltd and had an advisory role on drug OPC-67683. Ma. Imelda Quelapio received support (monetary and non-monetary) for research from Otsuka Pharmaceutical Co Ltd.

The following members of the academic centres who performed the reviews of evidence from which the recommendations contained in these guidelines are derived presented their findings at the meeting: Matthew Arentz, Melissa Bauer, Richard Menzies, Carole D. Mitnick, Olivia Oxlade, Patricia Pavlinac and Judd L. Walson. They did not participate in the formulation of recommendations related to the respective reviews of evidence that they performed.

Objectives of the guidelines and target audience

Effective management of drug-resistant tuberculosis requires input from different components or units of the national TB control programme. These components include case detection, treatment, prevention, surveillance, and monitoring and evaluation of the programme's performance. Collectively, such activities are referred to as the "programmatic management of drug-resistant tuberculosis" (PMDT).

This 2011 update is intended as a tool for use by health professionals in response to the sixty-second World Health Assembly's call for Member States to develop a comprehensive framework for the management and care of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) (*1*). The recommendations aim to:

- address the most topical questions in MDR-TB control requiring guidance for which the best available evidence has been summarized through appropriate review of data;
- provide a reference for countries developing national guidelines and policies to scale up detection and treatment of MDR-TB as an integral part of their national programmes.

The target audience of the guidelines is staff and medical practitioners working in treatment and control of TB, partners implementing programmatic management of drug-resistant TB, and organizations providing technical and financial support for care of drug-resistant TB. Although primarily intended for use in resource-limited countries, the recommendations are also applicable in other settings.

Background and methods

The first two editions of these guidelines were published in 2006 (*2*) and 2008 (*3*) as a collaborative effort of many partners, most of whom were members of the Green Light Committee (*4*). This 2011 update follows WHO requirements for developing guidelines as specified in the Handbook for Guideline Development (2010), which involve an initial scoping exercise, use of systematic reviews to summarize evidence and application of the GRADE approach to develop recommendations (*5*).

The updated guidelines focus on the detection and treatment of drug-resistant TB in settings where resources are limited. Priority topics identified by WHO in this field and by its external experts were:

- case-finding (use of rapid molecular tests; investigation of contacts and other high-risk groups);
- regimens for MDR-TB and their duration in HIV-positive and HIV-negative patients;
- monitoring during treatment;
- models of care.

The guidelines are limited to topics not covered by other WHO policy documents published recently, including treatment of drug-susceptible TB and use of antiretroviral agents, treatment of patients with isoniazid-resistant TB and TB infection control. The 2011 update was produced through a systematic process starting in early 2009. Priority areas to be included in the update had been identified from those listed as outstanding areas for future direction following publication of the emergency update (2008). The previous PMDT guidelines were evaluated via a user questionnaire (*6*). Various experts, including TB practitioners, public health professionals, national TB control programme staff, guideline methodologists, members of civil society and nongovernmental organizations providing technical support, and WHO staff, were invited to form a Guideline Development Group to inform the update process. A second group, comprising national TB control programme staff, WHO regional TB advisors, and clinical and public health experts, was appointed to serve as an External Review Group (the composition of both groups is listed in the Acknowledgements).

The Guideline Development Group provided input on the selection of questions to address outstanding topics of controversy or areas where changes in policy or practice were warranted. It also selected and scored outcomes to determine those that were critical or important for making decisions on recommendations and to identify the data which were to be sought during retrieval and synthesis of evidence. By September 2009, the scope of the guidelines had been agreed, the questions formulated, and the selection and scoring of the main outcomes had been completed. Between October 2009 and May 2010, teams from leading academic centres were commissioned to review and compile the evidence. The early results of the reviews were made available to members of the Guideline Development Group before and during a meeting to develop the recommendations held at WHO headquarters in Geneva, Switzerland, on 25–27 October 2010.

Questions and outcomes

Table 1 lists the seven priority questions identified by the Guideline Development Group, worded in the PICO (Population, Intervention, Comparator, Outcome) or similar format.

Table 1. PICO questions for the 2011 update of the guidelines

1.	At what prevalence of MDR-TB in any group of TB patients is rapid drug-susceptibility testing warranted to detect resistance to rifampicin and isoniazid or rifampicin alone on all patients in the group at the time of TB diagnosis, in order to prescribe appropriate treatment at the outset?
2.	Among patients with MDR-TB receiving appropriate treatment in settings with reliable direct microscopy, is monitoring using sputum smear microscopy alone rather than sputum smear and culture, more or less likely to lead to the outcomes listed in Table 2 below?
3.	When designing regimens for patients with MDR-TB, is the inclusion of specific drugs (with or without documented susceptibility) more or less likely to lead to the outcomes listed in Table 2?
4.	When designing regimens for patients with MDR-TB, is the inclusion of fewer drugs in the regimen (depending on the drug used, the patient's history of its use and isolate susceptibility) more or less likely to lead to the outcomes listed in Table 2?
5.	In patients with MDR-TB, is shorter treatment, compared with the duration currently recommended by WHO, more or less likely to lead to the outcomes listed in Table 2?
6.	In patients with HIV infection and drug-resistant TB receiving antiretroviral therapy, is the use of drugs with overlapping and potentially additive toxicities, compared with their avoidance, more or less likely to lead to the outcomes listed in Table 2?
7.	Among patients with MDR-TB, is ambulatory therapy, compared with inpatient treatment, more or less likely to lead to the outcomes listed in Table 2?

Table 2 summarizes the scored outcomes that were selected by the Guideline Development Group. Fourteen members submitted scores for outcomes they considered to be the most critical when making decisions on choice of testing and treatment strategies. Members were asked to take a societal perspective in rating the outcomes. Relative importance was rated on an incremental scale:

1–3 points Not important for making recommendations on choice of testing and treatment strategies for drug-resistant TB*
4–6 points Important but not critical for making recommendations on choice of testing and treatment strategies
7–9 points Critical for making recommendations on choice of testing and treatment strategies

* None of the outcomes was scored in this category.

Table 2. Most important possible outcomes when making decisions on choice of testing and treatment strategies for drug-resistant-TB

Outcomes (text in parentheses shows the same outcome rephrased in the negative)	Average score	Relative importance
1. Cure (treatment failure)	8.7	Critical
2. Prompt initiation of appropriate treatment	8.3	Critical
3. Avoiding the acquisition or amplification of drug resistance	8.1	Critical
4. Survival (death from TB)	7.9	Critical
5. Staying disease-free after treatment; sustaining a cure (relapse)	7.6	Critical
6. Case holding so the TB patient remains adherent to treatment (default or treatment interruption due to non-adherence)	7.6	Critical
7. Population coverage or access to appropriate treatment of drug-resistant TB	7.5	Critical
8. Smear or culture conversion during treatment	7.4	Critical
9. Accelerated detection of drug resistance	7.4	Critical
10. Avoid unnecessary MDR-TB treatment	7.2	Critical
11. Population coverage or access to diagnosis of drug-resistant TB	7.1	Critical
12. Prevention or interruption of transmission of drug-resistant TB to other people, including other patients and health-care workers	6.9	Important but not critical
13. Shortest possible duration of treatment	6.7	Important but not critical
14. Avoiding toxicity and adverse reactions from anti-tuberculosis drugs	6.5	Important but not critical
15. Cost to patient, including direct medical costs and other costs such as transportation and lost wages due to disability	6.4	Important but not critical
16. Resolution of TB signs and symptoms; ability to resume usual life activities	6.3	Important but not critical
17. Interaction of anti-tuberculosis drugs with non-TB medications	5.6	Important but not critical
18. Cost to the TB control programme	5.4	Important but not critical

For the scope of question 1 (Table 1), the discussion leading to the recommendations the term rapid tests to those providing a diagnosis within two days of specimen testing, thereby including only tests using molecular techniques (line probe assay and Xpert MDR/RIF[1]). The different groups of drugs referred to in the text are composed of the agents shown in Table 3. In the analyses of data for questions 3–5, streptomycin was found to be used but it is generally considered a first-line drug. Later-generation fluoroquinolones included levofloxacin (750mg/day or more), moxifloxacin, gatifloxacin and sparfloxacin. Ciprofloxacin, ofloxacin and levofloxacin (up to 600mg/day) were considered earlier-generation fluoroquinolones for this analysis.

Table 3. Groups of second-line anti-tuberculosis agents referred to in these guidelines

Group name	Anti-tuberculosis agent	Abbreviation
Second-line parenteral agent (injectable anti-tuberculosis drugs)	kanamycin amikacin capreomycin	Km Amk Cm
Fluoroquinolones	levofloxacin moxifloxacin gatifloxacin ofloxacin	Lfx Mfx Gfx Ofx
Oral bacteriostatic second-line anti-tuberculosis drugs	ethionamide prothionamide cycloserine terizidone *p*-aminosalicylic acid	Eto Pto Cs Trd PAS
Group 5 drugs	clofazimine linezolid amoxicillin/clavulanate thioacetazone clarithromycin imipenem	Cfz Lzd Amx/Clv Thz Clr Ipm

NB. Other drugs not generally considered as second-line anti-tuberculosis agents were also used to treat drug-resistant TB in some of the cohorts included in this analysis. These included the parenteral agent *viomycin,* the fluoroquinolones *ciprofloxacin* and *sparfloxacin,* as well as *azithromycin, roxithromycin, high-dose isoniazid* and *thioridazine,* which were included under the Group 5.

Assessment of evidence and its grading

The evidence review teams assessed the evidence for the questions and their outcomes through a series of systematic literature reviews following an approved methodology that was documented (Annex 1). Titles, abstracts and full text of potentially relevant literature were screened using key subject words and text words. The search was not limited by study type or time period. Authors in the field and members of the Guideline Development Group were contacted to identify missing studies or studies in progress. Case-based data

[1] Xpert MTB/RIF refers to the currently available methodology that employs an automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance.

were collected from authors of published studies to analyse the effects relating to the questions dealing with bacteriology and treatment regimen (questions 2–6 in Table 1). Modelling work was done in the context of questions 1 and 2. The question on models of care (question 7) was addressed by a review of published and unpublished studies containing a full economic evaluation of patients on MDR-TB treatment.

Where possible, relative effects (hazard ratios, relative risks or odds ratios of an event) were calculated from pooled data of included studies. In two of the analyses, outcome was expressed as the cost per disability-adjusted life year (DALY) averted. The DALY is a summary indicator that expresses the burden of mortality and morbidity into a single value: perfect health is valued at 1 and death at 0 (a year with TB disease is valued at 0.729) (*7*). For the modelling of rapid drug-susceptibility testing (DST), estimated cost outcomes included total costs for each DST strategy, cost per MDR-TB case prevented, cost per TB-related death avoided and cost per DALY averted. Transmission of resistant strains and subsequent secondary cases were not estimated. For the analysis of models of care (question 7), costs considered for inclusion could be from any of the following perspectives: cost from the health service provider's perspective, cost from the patient's perspective (including direct medical costs as well as indirect costs related to transportation) and total societal cost. Whenever possible, the following outcomes were included in the outcome: proportion of treatment success, default or long-term deaths (including secondary, default and relapse cases) and case reproduction rate (transmission from primary cases).

GRADE evidence profiles based on the results of the systematic reviews were prepared for each question using a standard approach. These summaries present the effect of the intervention on each outcome (for example, the number of patients with MDR-TB), as well as the quality of the evidence for each outcome. The quality of evidence was assessed using the following criteria: study design, limitations in the studies (risk of bias), imprecision, inconsistency, indirectness, publication bias, magnitude of effect, dose–effect relations and residual confounding. Quality of evidence was categorized into four levels (Table 4).

Table 4. Quality of evidence and definitions *(8)*

Quality of evidence	Definition
High (⊕⊕⊕⊕)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate (⊕⊕⊕○)	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low (⊕⊕○○)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low (⊕○○○)	Any estimate of effect is very uncertain.

The Guideline Development Group held teleconferences to discuss the available evidence, the presentation of the results and their impact on making recommendations. One discussant was chosen from among the group's members to assess the evidence for each of the questions and to complement the presentation of the evidence by the evidence review teams. A preparatory meeting was held in September 2010 to review the interim results of the work relating to the questions on treatment regimens and duration, and use of rapid DST. The group met at WHO headquarters in Geneva, Switzerland, between 25 and 27 October to develop the revised recommendations. A week before the meeting, members were able to review the evidence profiles for each question via a password-protected electronic website (EZ Collab site). During the meeting and in the following months, additional files and successive versions of the guidelines were shared with the group on the same site.

At the meeting, the GRADE evidence profiles were assessed by the members of the Guideline Development Group when preparing the recommendations. The group used standard decision tables to move from evidence to recommendations. One table was prepared for each recommendation to record decisions and ensure that the group uniformly considered the quality of the evidence, the certainty about the balance of benefits versus harms, the similarity in values and the costs of an intervention compared with the alternative. The profiles allowed members to base their judgments when making recommendations on evidence summarized in a concise and uniform manner. Agreement on the recommendations was reached following discussions. In their deliberations, members of the group assessed the level of evidence and judged the strength of the recommendations according to the criteria shown in Table 5 (see web Annex 2 for a glossary of GRADE terms).

Table 5. Assessment of the strength of a recommendation

Strength	Definition
Strong	The Guideline Development Group is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.
Conditional	The Guideline Development Group concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects.

Apart from the quality of evidence, the strength of a recommendation was determined by the balance between desirable and undesirable effects, values and preferences, and costs or resource allocation (*5*). The higher the quality of evidence, the more likely that it leads to a strong recommendation. However, a strong recommendation may be made in the presence of very low quality evidence given variability in values and preferences between the experts, the balance between desirable and undesirable consequences of an intervention, and resource implications. For instance, evidence from observational studies without randomization is always of low quality, but if the studies are methodologically sound (not downgraded for concerns about the validity)

and the estimates of effect are consistent, a strong recommendation may still be possible. It is important to note that when making a conditional recommendation, the group considered its application only to a specific group, population or setting, or that new evidence might change the balance of risk to benefit or that the benefits might not warrant the cost or resource requirements in all settings (see also Table 6).

The recommendations in these guidelines are to be read along with the accompanying remarks on available evidence, which are relevant to their proper interpretation and implementation.

Table 6. Implications of the strength of a recommendation for different users (5)

Perspective	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients, and that patients must be helped to arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
For policy-makers	The recommendation can be adapted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

External review

The External Review Group commented on the questions during their formulation (in mid-2009) and on a draft text of the guidelines, including recommendations, following comments from the Guideline Development Group (in early 2011). For the initial discussion, eight of the peer reviewers submitted comments that were used for the revised set of priority questions submitted to the evidence review centres for the systematic reviews. Six reviewers made comments on the draft guidelines in early 2011.

Publication, implementation, evaluation and expiry

The guidelines will be published in English on the WHO web site as well as in a peer-reviewed publication. WHO's Stop TB Department will work closely with regional and country offices, the Stop TB Partnership and other implementing partners to ensure their wide dissemination through electronic and paper format.

A companion manual is planned for 2011 to provide practical information on implementing programmatic management of drug-resistant TB. The manual will update previous guidance on this subject.

An evaluation of how users have implemented the guidelines will be developed to measure different dimensions of uptake of the recommendations, including the time until adaptation (if any) and barriers to effective implementation.

It is expected that the Stop TB Department, in collaboration with its partners, will review and update these guidelines about four years after their publication or earlier if new evidence, regimens or diagnostic tests become available.

1. Rapid drug susceptibility testing for early start of appropriate treatment

Recommendation

Rapid drug susceptibility testing (DST) of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis of TB, subject to available resources (conditional recommendation, ⊕◯◯◯/very low quality evidence).

Evidence

The evidence used to determine the optimal timing of DST and the method of testing to be used relied on simulations from modelling work (*9*). There are inherent limitations when using models, which are linked to the underlying assumptions. Sensitivity analyses, however, showed fairly consistent results when epidemiological conditions and costs were varied.

For the purposes of the recommendation, the group considered a rapid test as one providing a diagnosis of resistance to isoniazid and rifampicin or rifampicin alone within two days of specimen testing. Only molecular tests can detect resistance so fast, of which two technologies – line probe assay and Xpert MTB/RIF – are currently recommended for use by WHO. Conventional DST of cultured mycobacteria typically provides results within 1–3 months.

Outcomes of interest were reduced mortality, increased likelihood of cure, decreased development of additional resistance, and reduced likelihood of failure and relapse, expressed as the cost per DALY averted. The model did not take into consideration ongoing transmission that may occur if diagnosis of resistance is delayed.

Summary of findings

Performing DST in all patients before treatment using a rapid test that detects resistance to isoniazid and rifampicin was the best strategy for averting deaths and preventing acquired MDR-TB. The modelling work showed that rapid testing of both isoniazid and rifampicin at the time of diagnosis was the most cost effective testing strategy for any patient group or setting, even at very low levels of resistance among TB patients (MDR-TB in >1% and isoniazid resistance (other than MDR-TB) in >2%). For previously untreated patients, DST at the start of treatment was a better strategy than waiting to

test only those patients who remained sputum-smear positive later in the course of their first-line treatment.

Rapid DST of rifampicin alone did not have the same benefit as rapid testing of both isoniazid and rifampicin resistance. This is because DST of rifampicin alone could not prevent the acquisition of additional resistance in patients resistant to isoniazid only.

Benefits

A short time to diagnosis may influence the composition of a patient's initial treatment and increase the likelihood of starting appropriate treatment early. The likely benefits of rapid DST therefore include increased cure rates, decreased mortality, reduced development of additional drug resistance, and a reduced likelihood of failure and relapse.

The detection of rifampicin resistance by Xpert MTB/RIF usually suffices to start a patient on a second-line TB regimen (*10*), subject to confirmatory testing in situations with low rifampicin resistance (see also under Risks).

Use of rapid tests to detect resistance to both rifampicin and isoniazid would have better outcomes than tests to detect resistance to rifampicin alone. The detection of patients with isoniazid resistance alone may provide an opportunity to initiate effective treatment before additional acquisition of resistance to rifampicin develops. The model assumptions included appropriate treatment for non-MDR-TB isoniazid-resistant TB. The optimal regimen for the treatment of isoniazid-resistant strains has not been determined, and benefits may be less if suboptimal regimens are used.

The influence on secondary transmission of resistant strains was not included in the model and therefore estimates of reduction in mortality and morbidity from early detection and treatment are likely to be conservative. The increased costs of using the diagnostic test may be offset by a reduction in the requirement of conventional TB laboratory capacity which may be substantial.

Risks

The harms of rapid DST include false-positive results leading to wasted resources, and increased toxicity to the patient from unnecessary administration of second-line medications. Awareness of these potential harms is particularly important in patient groups in which rifampicin resistance is rare. Rifampicin resistance detected by Xpert MTB/RIF in such a situation will have a low predictive value and results need to be confirmed by phenotypic DST or line probe assay (*10*). Another potential harm from placing all rifampicin-resistant patients on an MDR-TB regimen is the exclusion of isoniazid from their treatment, thus depriving them of a safe and useful bactericidal drug.

Values and preferences

A high value was placed on outcomes such as preventing death and transmission of MDR-TB as a result of delayed diagnosis, as well as lowered costs. Such costs to the TB control programme were considered important but not critical. The recommendation is conditional, in part because of the resources required for its implementation. Programmes that cannot adhere to the recommendation for rapid testing at the time of TB diagnosis in all patient groups according to the thresholds mentioned above may still decide to perform rapid testing in previously treated patients (*11*) and other groups at higher risk of MDR-TB ideally based on surveillance data.

2. Monitoring the response to MDR-TB treatment

Recommendation

The use of sputum smear microscopy and culture rather than sputum smear microscopy alone is recommended for the monitoring of patients with MDR-TB during treatment (conditional recommendation, ⊕◯◯◯/very low quality evidence).

Evidence

The evidence used to assess how best to monitor treatment in MDR-TB patients using sputum smear microscopy and culture in settings with reliable direct microscopy was based on data pooled from 10 published observational studies (*12–19*). Monthly monitoring by culture was used as the reference in all the analyses. Random-effects Cox proportional hazards models were used to estimate the hazard ratio of failure, comparing monthly culture to alternative monitoring strategies.

Summary of findings

Performing monthly sputum smear microscopy and culture was the best strategy in identifying failures earlier. Sputum smear microscopy alone resulted in delayed detection of failure: when done at monthly rather than two monthly intervals it increased the detection of failure slightly (not significantly). In patients who were smear-negative at the start of treatment, monthly smear monitoring (compared with culture) resulted in a statistically significantly greater risk of delayed detection of failure compared with smear-positive patients. Stratified estimates by HIV serostatus, body mass index, and extent of disease on chest radiograph, were not significantly different ($P>0.05$).

The related end-points of drug resistance, initiation of appropriate treatment and the acquisition of resistance were not measured. There was no information about reversion or reinfection and no data were available to assess the quality of culture and smear testing. Other methods of evaluating response to treatment such as clinical indicators or chest radiography were not evaluated.

Benefits

Concomitant use of sputum smear microscopy and culture test results helps identify patients whose bacteriology remains positive or reverts to positive following initial

conversion to negative. This is of use to clinicians in identifying patients likely to fail their treatment and instituting infection control measures in a timely manner. There was overall certainty about the risk of missing or delaying the detection of failure if smear alone was used instead of culture. Additional benefits would be expected from reduced transmission and development of resistance as well as appropriate changes to treatment regimens, but these were not explicitly addressed by the analysis.

Risks

Delayed detection of failure is expected to increase transmission and increase the probability of acquisition of resistance. Up to now, a minimum of monthly sputum smear microscopy and culture examination prior to culture conversion to negative[2] and quarterly culture with monthly smear examination after conversion has been recommended for the monitoring of patients on treatment for MDR-TB (*3*).

Even if monthly culture performed throughout treatment showed the highest benefit to detect failures, resource implications are important. Cost for sputum smear testing alone ranged between one-fourth to a half of the combined cost of culture and smear testing (based on information from nine studies reviewed for these guidelines) (*20–26*). It is likely that this difference may be higher where culture diagnosis is not readily available. More laboratory resources (staff, equipment, utilities) are required to perform culture, and fewer culture laboratories exist in the low-resource conditions of most high-burden countries. In settings where the risk of failure is low, selected patients can be prioritized for monthly culture.

The quality of culture performance differs importantly. False-positive cultures could lead to changes in regimen that may entail more potentially toxic medication. A false-negative culture result may influence a treatment decision based on clinical and direct microscopy findings.

Values and preferences

A high value was placed on outcomes such as preventing death, decreasing the transmission of MDR-TB that could result from its delayed diagnosis, and avoiding increased use of resources. The recommendation is conditional in part because of the resources required for implementing it.

As direct microscopy of sputum smear can identify the most infectious cases within a very short time, it has added value alongside culture for infection control purposes.

[2] Defined as two consecutive sets of negative results of sputum smear microscopy and culture from samples collected at least 30 days apart.

3. Composition of second-line anti-tuberculosis regimens

Recommendations

3.1 In the treatment of patients with MDR-TB, a fluoroquinolone should be used (strong recommendation, ⊕◯◯◯/very low quality evidence).

3.2 In the treatment of patients with MDR-TB, a later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (conditional recommendation, ⊕◯◯◯/very low quality evidence).

3.3 In the treatment of patients with MDR-TB, ethionamide (or prothionamide) should be used (strong recommendation, ⊕◯◯◯/very low quality evidence).

3.4 In the treatment of patients with MDR-TB, four second-line anti-tuberculosis drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase[3] (conditional recommendation,⊕◯◯◯/very low quality evidence).

3.5 In the treatment of patients with MDR-TB, regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or PAS (*p*-aminosalicylic acid) if cycloserine cannot be used (conditional recommendation, ⊕◯◯◯/very low quality evidence).

Evidence

The evidence used to address the questions on which drugs to include (with or without information on their DST patterns) and the number of drugs to be used in regimens for MDR-TB patients was based on studies published in three major systematic reviews (*27–29*). All three reviews searched EMBASE and MEDLINE databases as well as the Cochrane Library and the ISI Web of Science. Studies published before 1970 and those including only XDR-TB cases were excluded. The reviewers then pooled individual patient data from studies which had featured in the systematic reviews for a meta-analysis.

The meta-analysis included 32 studies with more than 9000 treatment episodes for which the authors could be contacted and were willing to share their data (*30*). Patients

[3] The intensive phase is the initial part of a course of treatment during which a parenteral (injectable) agent is used.

with XDR-TB (N=410) were excluded, as their treatment regimens were considered not to be comparable with those of other MDR-TB patients. Cohorts included had to have had at least 25 subjects treated for MDR-TB, and one or more of the treatment outcomes meeting the standard definitions (*31*). Missing values for age, sex, past TB, extent of disease, HIV infection and DST were imputed (>50% of cohort members having an observed value for these variables), but not those for treatment modality or outcome. None of the cohorts was part of randomized controlled trials and thus the quality of evidence was judged to be low or very low. While the odds ratios in the analysis were adjusted for age, sex, HIV-serostatus, past TB treatment, past MDR-TB treatment and extent of disease, there remains a risk of substantial bias (certain drugs may have only been used for sicker patients). Other limitations included incomplete ascertainment of relapse, the under-representation of certain geographical regions, and missing data for some of the variables examined.

Findings from this analysis may not necessarily be generalizeable to all populations in settings with high or low prevalences of drug resistance or different levels of resources. Nonetheless, the results of this analysis represented the best available evidence to date for the group to make recommendations on the composition of treatment regimens.

Summary of findings

Use of drugs to which the strain was reportedly susceptible showed a marginal benefit when compared with their use regardless of susceptibility patterns. Choice of drug would thus depend on the DST of the strain isolated from the patient or close contacts with MDR-TB, previous use of the drug in the patient, and the frequency of its use or documented background drug resistance in the setting. In applying this observation to clinical practice, it is important to underline the uncertainties around the reproducibility and reliability of DST of pyrazinamide (and ethambutol) (*32*), as well as the second-line drugs other than the parenteral agents and the fluoroquinolones (*33*).

The analysis showed that in the intensive phase, a regimen with at least four drugs likely to be effective, when adjusted for clinical covariates, all other drugs used concomitantly as well as the total number of susceptible drugs used throughout treatment, was associated with a statistically significant peak in cure with a plateau thereafter.

Data from this analysis did not reveal any second-line parenteral agent – kanamycin, amikacin or capreomycin – to be superior in effect to any other. Given its lower cost, kanamycin would be preferred. Amikacin can be used instead of kanamycin. In an analysis comparing patients who were cured or completed treatment with those who failed or relapsed, capreomycin was shown to be effective if the case was resistant to kanamycin. The use of streptomycin in MDR-TB patients is not recommended.

Fluoroquinolones were significantly associated with cure and this effect was more pronounced in later-generation fluoroquinolones (see Background and methodology for definition). It was highest when used against strains known to be susceptible.

Fluoroquinolones should therefore always be used unless there is an important contraindication. Ciprofloxacin, even if it may have some anti-tuberculosis activity, should not be used (*34*).

Among the oral bacteriostatic drugs, the association with cure was higher with ethionamide than with cycloserine, which was higher than with PAS. Ethionamide or prothionamide should therefore always be included in a regimen unless there is a particular contraindication. Ethionamide showed little effect in patients who had taken prior treatment for MDR-TB. PAS performed the worst, showing no significant effectiveness in the main analysis. Its use would thus be recommended only if an additional drug is needed to achieve a five-drug regimen or if ethionamide or cycloserine cannot be used or are unlikely to be effective. The data did not allow comparison of outcomes between once daily PAS and divided doses, or the formulation of PAS: decisions on how to administer PAS should thus rely on a balance between its tolerance in the patient and the resources available to observe doses.

Patients on Group 5 drugs were observed to have worse outcomes, an effect largely attributed to confounding. When the individual effect of amoxicillin/clavulanate, clofazimine, macrolides[4] and thioacetazone was analysed, no significant association with cure could be discerned. No separate analysis was possible for linezolid and high-dose isoniazid given the small number of cases treated with these agents.

Pyrazinamide showed a slightly added benefit in one of the analyses in which adjustment was made for other medication used concomitantly. Ethambutol was associated with a marginal but statistically significant reduction in likelihood of cure among patients not previously treated for MDR-TB. As in the case of Group 5 drugs this effect was attributed to confounding rather than a detrimental effect of ethambutol.

The analysis of data from this review bore inconclusive results about the contribution of ethambutol and Group 5 drugs in the treatment of MDR-TB patients and as a result they have not been included among the drugs making up the recommended standard MDR-TB regimen.

The principle of using additional drugs for extensive disease could not be supported by the data used for this review.

As patients with XDR-TB were excluded from the analysis, the current recommendations do not necessarily apply to this subgroup of patients. Until better evidence is available to determine the optimal regimens for treatment of these patients, the same principles used to design MDR-TB regimens should be used, based where possible on the DST pattern of the individual patient, particularly for later-generation fluoroquinolones and second-line parenteral agents. All MDR-TB patients should thus be tested for susceptibility to these two classes of drugs.

[4] Azithromycin, clarithromycin and roxithromycin were included in this analysis.

The recommended composition of second-line regimens for MDR-TB patients has changed from those in the 2008 emergency update (*3*) (Table 7). The previous guidelines had likewise recommended designing regimens based on known drug resistance patterns in the country or patient, the history of previous treatment by the patient, and the drugs commonly used in the country. The inclusion of at least four drugs with either certain, or almost certain, effectiveness was previously recommended. The previous recommended regimen was composed of pyrazinamide and/or ethambutol, one fluoroquinolone, one parenteral agent and second-line oral bacteriostatic drugs. Resort to antibiotics from Group 5 was only recommended if additional drugs were needed to bring the total to four. More drugs were recommended in the case of extensive disease or uncertain effectiveness.

Table 7. Changes to the recommendations on regimen composition between the 2008 and 2011 updates of the guidelines

2008 emergency update (*3*)	2011 update
Include at least four anti-tuberculosis drugs with either certain, or almost certain, effectiveness during the intensive phase of treatment.	Include at least four second-line anti-tuberculosis drugs likely to be effective as well as pyrazinamide during the intensive phase of treatment.
Consider adding more drugs in patients with extensive disease or uncertain effectiveness.	No evidence found to support the use of more than four second-line anti-tuberculosis drugs in patients with extensive disease. Increasing the number of second-line drugs in a regimen is permissible if the effectiveness of some of the drugs is uncertain.
The regimen should include pyrazinamide and/or ethambutol, one fluoroquinolone, one parenteral agent and second-line oral bacteriostatic anti-tuberculosis drugs (no preference of oral bacteriostatic second-line anti-tuberculosis drug was made).	The regimen should include pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and cycloserine, or else PAS if cycloserine cannot be used.
Ethambutol may be considered effective and included in the regimen if DST shows susceptibility.	Ethambutol may be used but is not included among the drugs making up the standard regimen.
Treatment with Group 5 drugs is recommended only if additional drugs are needed to bring the total to four.	Group 5 drugs may be used but are not included among the drugs making up the standard regimen.

Benefits

The recommendations contained in this section aim to increase the likelihood of cure and reduce the risk of failure, relapse and death. The decision to recommend an additional drug to the regimen during the intensive phase of treatment – from the minimum of four inferred from the analysis – was based on expert opinion. It is intended

to safeguard against the acquisition of additional resistance, particularly in the case of undetected primary resistance to the four drugs considered to be effective given the unreliable nature of DST for drugs other than parenteral agents and fluoroquinolones. Estimates of effects for fluoroquinolones were probably conservative given that patients treated with ciprofloxacin were included in the control group. Studies of the *inhA* promoter region mutation, although not assessed in this review, may guide treatment by identifying strains that are resistant to ethionamide (*35*) although the additional costs need to be considered.

Risks

A slight incremental trend in serious adverse events (SAE) was discerned as the number of drugs in the continuation phase increased from two to five. About 14% of patients on oral bacteriostatic drugs had SAE, while for the other drugs evaluated this was much lower (1–6%). An association between the total number of drugs used and the risk of SAE was observed. This association was not observed during the intensive phase.

The risk of additional acquisition of resistance is a concern in cases of unrecognized resistance to some of the drugs used. The long-term potential for SAE, particularly in children and for the later-generation fluoroquinolones, remains unknown. However, a Cochrane review assessing fluoroquinolones as additional or substitute drugs in regimens for drug-sensitive and drug-resistant patients found that substituting or adding fluoroquinolones to a regimen had no demonstrable effect on the occurrence of SAE (*34*).

Values and preferences

A high value was placed on preventing death and transmission of MDR-TB and a lower value on the potential for SAE resulting from long-term treatment. As a result, the long-term use of fluoroquinolones was considered to outweigh the higher cost and any possible long-term SAE. The recommendation is thus strong. While the use of later-generation fluoroquinolones is generally preferred, a separate recommendation on their use was graded conditional rather than strong because there is uncertainty about the risk of SAE from the long-term use of these agents.

4. Duration of second-line anti-tuberculosis regimens

Recommendations

4.1 In the treatment of patients with MDR-TB, an intensive phase of 8 months is suggested for most patients, and the duration may be modified according to the patient's response to therapy (conditional recommendation, ⊕◯◯◯/very low quality evidence).

4.2 In the treatment of patients newly diagnosed with MDR-TB (i.e. not previously treated for MDR-TB), a total treatment duration of 20 months is suggested for most patients, and the duration may be modified according to the patient's response to therapy (conditional recommendation, ⊕◯◯◯/very low quality evidence).

Evidence

The evidence used to derive recommendations on the duration of treatment was based on an analysis of the same individual patient data collected and described in Section 3 above. All data were from observational studies, and the quality of evidence was classified as very low. Attempts to control for selection bias and confounding in this review are unlikely to have adjusted for all important factors, and patients who receive longer therapy may be those who are more sick. Patients with XDR-TB were also excluded from the analysis. The findings may not be generalizable to all populations in settings with high or low prevalence of drug resistance or with different levels of resources.

Summary of findings

The analysis provided evidence for an association between treatment success and the total length of treatment and the length of the intensive phase. The trend in relative risk for cure over successive months of treatment was studied to determine the optimal minimum duration for both total treatment and the intensive phase. The adjusted relative risk for cure peaked at an intensive phase lasting between 7.1 and 8.5 months (see also Table 8 and Annex 2). For total treatment duration, the peak occurred between 18.6 and 21.5 months for patients who had no previous MDR-TB treatment. The peak occurred later in patients who had been treated for MDR-TB (27.6–30.5 months), but no clear incremental trend was observed in these patients and the number of observations was far fewer than for those who had no previous MDR-TB treatment.

Table 8. Odds ratios of treatment success by duration of intensive phase and total treatment

Duration of intensive phase of treatment			Total duration of treatment[a]		
Duration (months)	Observations	Adjusted[b] odds ratio (95% CLs)	Duration (months)	Observations	Adjusted[b] odds ratio (95% CLs)
1–2.5	308	1.0 (ref)	6.0–12.5	743	1.0 (ref)
2.6–4.0	1406	1.2 (0.5–2.9)	12.6–15.5	384	2.4 (1.5–3.6)
4.1–5.5	481	2.4 (1.3–4.3)	15.6–18.5	1646	4.6 (2.0–10.4)
5.6–7.0	377	3.7 (1.9–7.1)	18.6–21.5	612	9.3 (5.8–15.0)
7.1–8.5	172	5.1 (2.1–12.7)	21.6–24.5	435	6.8 (4.2–11.1)
8.6–20	792	2.2 (1.2–3.9)	24.6–27.5	207	8.2 (4.2–15.9)
			27.6–30.5	106	2.4 (1.2–5.0)
			30.6–36	48	1.3 (0.6–2.7)

[a] Only in patients with no previous treatment for MDR-TB.

[b] Adjusted for age, sex, HIV status, previous TB treatment, previous MDR-TB treatment and extent of disease.

CLs = Confidence Limits

Most patients may be expected to receive this length of treatment but in some it may have to be modified depending on their bacteriological status and other indicators of treatment progress.

The recommendations have thus changed from those contained in the 2008 emergency update, which recommended a duration of treatment for MDR-TB patients based on the use of a parenteral agent for a minimum of 6 months and at least 4 months past culture conversion, and a minimum total length of treatment of 18 months after culture conversion. The new recommended duration of intensive phase is 2 months longer than the minimum previously recommended. There is, however, no substantial difference in the total length of treatment being recommended because conversion typically takes a few months to occur. The data used for this analysis could not inform whether a minimum duration of the intensive phase after conversion was a determinant of outcome.

Benefits

When selecting the duration of treatment, the analysis allowed a choice to be made within a narrow margin of a few consecutive months, thus reducing the likelihood of prolonging treatment unnecessarily. While shorter regimens would confer clear benefits and be preferred, evidence for the effectiveness of a 9-month regimen for MDR-TB patients has up to now been limited to data from one setting (included in this review) (*16*). The Guideline Development Group supports further investigation of

the safety and effectiveness of shorter regimens using the randomized controlled trial design in order to strengthen evidence for their potential use for the treatment of drug-resistant TB.

Risks

The risk of serious adverse events (SAE) was observed to increase beyond the first 12 months of treatment but was not correlated with the length of the intensive phase beyond the first 2 months. These trends should be interpreted with caution as they may be confounded by the number of drugs used (independently correlated with SAE) as well as features of the illness process not accounted for in the measure of extent of disease used in this analysis.

Values and preferences

A high value was placed on outcomes such as preventing death and transmission of MDR-TB as a result of failed treatment as well as avoiding harms and minimizing use of resources. The group placed a lower value on reducing the duration of treatment, while acknowledging that many patients may place a higher value on avoiding a long treatment course due to burden and inconvenience.

5. Use of antiretrovirals in patients on second-line anti-tuberculosis regimens

Recommendation

Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-tuberculosis drugs, irrespective of CD4 cell-count, as early as possible (within the first 8 weeks) following initiation of anti-tuberculosis treatment (strong recommendation, ⊕◯◯◯/very low quality evidence).

Evidence

Evidence was reviewed from 10 studies (*36–45*) to assess patient treatment outcomes when antiretroviral therapy (ART) and second-line anti-tuberculosis drugs were used together. None of the data were from randomized controlled trials. Individual patient data were available for 217 drug-resistant TB patients in total, of whom 127 received ART. The level of evidence in individual observational studies varied from low to very low quality.

Summary of findings

The pooled individual patient data from longitudinal cohort studies showed a lower risk of death and a higher likelihood of cure and resolution of TB signs and symptoms in patients using ART compared with those not using ART (low quality evidence). There is very low quality evidence for other outcomes which were considered critical or important for decision-making (for example, serious adverse events from second-line drugs for drug-resistant TB, occurrence of sputum smear or culture conversion, interactions of ART with anti-tuberculosis drugs and default from treatment). Available data did not allow assessment for a number of other outcomes of interest, namely avoiding the additional acquisition of drug resistance, preventing TB transmission, sustaining relapse-free cure, establishing the optimal duration of MDR-TB treatment, avoiding unnecessary MDR-TB treatment, and reducing cost and improving population access to appropriate care.

Benefits

The strong recommendation for use of ART is based in part on indirect evidence from its use in any patient with active TB, which shows large beneficial effects and a very high mortality when ART is not employed (*46)*, particularly in very immunocompromised patients (CD4 cell-count <50 cells/mm^3) (*47*, *48*). In the absence of other data specific to patients with drug-resistant TB receiving second-line anti-tuberculosis medication, the decision on when to start ART should be no different from the approach to the HIV-positive drug-susceptible TB patient. ART should thus be initiated regardless of CD4 cell-count and as soon as anti-tuberculosis treatment is tolerated, ideally as early as 2 weeks and no later than 8 weeks after initiation of anti-tuberculosis treatment (*46*, *49*).

Risks

The successful implemention of this recommendation will depend upon the availability of more providers trained specifically in the care of HIV and drug-resistant TB and drug–drug interactions. A substantial increase in the availability of and patient's access to treatment and additional support for ensuring adherence would likely be needed. The need for increased integration of HIV and TB care for effective patient management, prompt evaluation of adverse events and case-holding throughout treatment will necessitate more resources. For the benefit of the user, a table of adverse events for which both an antiretroviral agent and an anti-tuberculosis medicine have been implicated and could conceivably interact is included online (Annex 3).

Values and preferences

A high value was placed on outcomes such as prevention of early death and TB transmission, and a lower value was placed on the resources required to make ART available to all MDR-TB patients infected with HIV.

6. Models of care for managing MDR-TB

Recommendation

Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization (conditional recommendation, ⊕◯◯◯/very low quality evidence).

Evidence

Outcomes from models of MDR-TB care based mainly on clinic-based ambulatory treatment were compared with those using mainly hospital-based inpatient treatment. The data used came from published and unpublished cost-effectiveness studies in four countries (Estonia, Peru (*17*), the Philippines (*18*) and the Russian Federation [Tomsk oblast]). The design of these observational studies did not allow direct comparison of effects between models of care. Given that none of the studies were randomized controlled trials the evidence was considered very low. Cost-effectiveness was modelled for all possible WHO Member States in a probabilistic analysis of the data from the four countries (50).

Summary of findings

Cost varied widely across the modelled settings. The cost per DALY averted by an ambulatory model in one setting was sometimes higher than the cost per DALY averted by a hospitalization model in another setting. However, cost per DALY averted was lower under outpatient-based care than under inpatient-based care in the vast majority (at least 90%) of settings for which cost-effectiveness was modelled. The variation in cost-effectiveness among settings correlated most strongly with the variation in the cost of general health-care services and other non-drug costs. Despite the limitations in the data available, there was no evidence that was in conflict with the recommendation and which indicated that treatment in a hospital-based model of care leads to a more favourable treatment outcome.

Benefits

The overall cost-effectiveness of care for a patient receiving treatment for MDR-TB can be improved with an ambulatory model. The benefits include reduced resource use, and at least as many deaths avoided among primary and secondary cases, compared

with hospitalization models. This result is based on clinic-based ambulatory treatment (patients attend a health-care facility); in some settings, home-based ambulatory treatment (provided by a worker in the community) might improve cost-effectiveness even further. The benefit of reduced transmission can only be expected if proper infection control measures are in place in both the home and the clinic. Potential exposure to people who are infectious can be minimized by reducing or avoiding hospitalization where possible, reducing the number of outpatient visits, avoiding overcrowding in wards and waiting areas and prioritizing community-care approaches for TB management (*51*). The regimen used in one of the studies of ambulatory care was from a time when the combinations of medicines were not yet optimized, so outcomes achieved were probably inferior to those which can be accomplished with the regimens in use today. Admission to hospitals for patients who do not warrant it may also have important social and psychological consequences which need to be taken into account.

Risks

There may be some important barriers to accessing clinic-based ambulatory care, including distance to travel and other costs to individual patients. Shifting costs from the service provider to the patient has to be avoided, and implementation may need to be accompanied by appropriate enablers. While placing patients on adequate therapy would be expected to decrease the bacterial load and transmission of drug-resistant TB, infection control measures for home-based and clinic-based measures will need to be part of an ambulatory model of care to decrease the risk of transmission in households, the community and clinics. TB control programmes will have to consider whether they are capable of reallocating resources from hospital to ambulatory care support in order to undertake the necessary changes in patient management. The choice between these options will affect the feasibility of implementing the recommendation in a particular programme.

Values and preferences

A high value was placed on conserving resources and on patient outcomes such as preventing death and transmission of MDR-TB as a result of delayed diagnosis and inpatient treatment. There should always be provision for a back-up facility to manage patients who need inpatient treatment. This may be necessary in certain patient groups at particular risk, such as children during the intensive phase, among whom close monitoring may be required for a certain period of time.

Research gaps

The process of developing these guidelines revealed some important gaps in knowledge that are important to address in future research, particularly in the context of large-scale expansion of treatment for patients with drug-resistant TB. These include:

- lack of moderate or high quality evidence from randomized controlled trials for optimizing treatment regimens in patients with MDR-TB, including the best combination of drugs and treatment duration;
- lack of evidence for the best drug regimens for treating patients with isoniazid resistance, with XDR-TB and with non-MDR-TB polydrug-resistance;
- very limited information about treatment of paediatric MDR-TB;
- identification of the most effective chemoprophylaxis for contacts of MDR-TB cases;
- the therapy for symptomatic relief from adverse reactions linked to second-line anti-tuberculosis drugs.

A number of the gaps listed above had been identified in a review published in 2008 (*52*). It is expected that the current update of the guidelines will stimulate more support for studies on treatment and other aspects of programmatic management of patients with drug-resistant TB.

Available at www.who.int/tb/challenges/mdr/programmatic_guidelines_for_mdrtb/

Annex 1. Methods for evidence reviews and modelling

WHO/HTM/TB/2011.6a

Annex 2. GRADE glossary and summary of evidence tables

WHO/HTM/TB/2011.6b

Annex 3. Potentially overlapping toxicities of antiretrovirals and anti-tuberculosis agents (including first-line TB drugs)

WHO/HTM/TB/2011.6c

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ISBN 978 92 4 150158 3