The emergence in 2006 of extensively drug-resistant strains of tuberculosis, especially in countries with a high prevalence of human immunodeficiency virus, are serious threats to global public health and jeopardizes efforts to effectively control the disease. These important developments and the availability of new evidence related to the diagnosis and management of drug-resistant tuberculosis have mandated an urgent update of existing guidelines. ***Guidelines for the programmatic management of drug-resistant tuberculosis: emergency updated edition 2008*** replaces previous publications by the World Health Organization on this subject.

The guidelines offer updated recommendations for the diagnosis and management of drug-resistant tuberculosis in a variety of geographical, economic and social settings, and the recording of data that enables the monitoring and evaluation of programmes. Intended for use by both tuberculosis control programmes and medical practitioners in low- and middle-income countries, the guidelines take into account a number of recommendations, which will support the achievement by countries of the goals of the Global Plan to Stop TB 2006–2015 of the Stop TB Partnership.

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Guidelines for the programmatic management of drug-resistant tuberculosis

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Declaration of interests

All of the above contributors completed a WHO Declaration of Interest form. The following interests were declared:

Case Gordon declared that he is an unpaid advocate for patients with anti-TB drug resistance and for improved access to high-quality care. He declared that he has himself survived XDR-TB.

Tim Holtz declared that he is an unpaid technical adviser and member of the Scientific Advisory Board of a manufacturer of anti-TB products, to advise on the development of a new anti-TB compound that will be tested in clinical trials of MDR-TB regimens.

Salmaan Keshavjee declared that his employer received funding from a foundation associated with a manufacturer of anti-TB products to support the research and training unit that he is heading.

Carole Mitnick declared that she is serving as a paid member of the Scientific Advisory Board of a manufacturer of anti-TB products, to advise on the development of a new anti-TB compound that will be tested in clinical trials of MDR-TB regimens.

Michael Rich declared that his employer received funding from a manufacturer of anti-TB products, in support of his salary.

Abbreviations

ACSM	advocacy, communication and social mobilization
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
CDC	United States Centers for Disease Control and Prevention
CHW	community health worker
CMV	cytomegalovirus
CPT	co-trimoxazole preventive therapy
CXR	chest X-ray
DOT	directly observed therapy
DOTS	The internationally recommended strategy for TB control until 2005, and the foundation of the new Stop TB Strategy introduced in 2006
DRS	drug resistance surveillance
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
FDC	fixed-dose combination
FIND	Foundation for Innovative New Diagnostics
GLC	Green Light Committee
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
HPF	high-power field
HRD	human resource development
IHR	International Health Regulations
IRIS	immune reconstitution inflammatory syndrome
LFT	liver function test
MDR-TB	multidrug-resistant tuberculosis
MIC	minimum inhibitory concentration
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NTM	non-tuberculous mycobacteria
NTP	national TB control programme

PI	protease inhibitor
PIH	Partners In Health
PPD	purified protein derivative
PPM	public–private mix
R&R	recording and reporting
SCC	short-course chemotherapy
SMX	sulfamethoxazole
SRL	supranational reference laboratories
STB	WHO Stop TB Department
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
UVGI	ultraviolet germicidal irradiation
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Antituberculosis drug abbreviations

GROUP	DESCRIPTION	DRUG	ABBREVIATION
1	First-line oral antituberculosis drugs	isoniazid	H
		rifampicin	R
		ethambutol	E
		pyrazinamide	Z
		rifabutin	Rfb
2	Injectable antituberculosis drugs	kanamycin	Km
		amikacin	Amk
		capreomycin	Cm
		streptomycin	S
3	Fluoroquinolones	levofloxacin	Lfx
		moxifloxacin	Mfx
		ofloxacin	Ofx
4	Oral bacteriostatic second-line antituberculosis drugs	ethionamide	Eto
		protionamide	Pto
		cycloserine	Cs
		terizidone	Trd
		p-aminosalicylic acid	PAS
5	Antituberculosis drugs with unclear efficacy or unclear role in MDR-TB treatment (not recommended by WHO for routine use in MDR-TB patients)	clofazimine	Cfz
		linezolid	Lzd
		amoxicillin/clavulanate	Amx/Clv
		thioacetazone	Thz
		clarithromycin	Clr
		imipenem	Ipm

Antiretroviral drug abbreviations

DRUG CLASS	NAME	ABBREVIATION
Non-nucleoside reverse transcriptase inhibitors	efavirenz	EFV
	nevirapine	NVP
Nucleoside reverse transcriptase inhibitors	zidovudine	AZT
	lamivudine	3TC
	stavudine	D4T
	didanosine	ddI
	zalcitabine	ddC
	abacavir	ABC
	tenofovir	TDF[a]
Protease inhibitors	indinavir	IDV
	ritonavir	RTV
	saquinavir	SQV
	nelfinavir	NFV
	lopinavir/ritonavir	LPV/RTV

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

Executive summary

Multidrug-resistant tuberculosis (MDR-TB), defined as TB caused by organisms that are resistant to isoniazid and rifampicin, two first-line anti-TB drugs, continues to threaten the progress made in controlling the disease. The emergence of extensively drug-resistant TB (XDR-TB), defined as MDR-TB that is resistant as well to any one of the fluoroquinolones and to at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin), has heightened this threat. XDR-TB has been identified in all regions of the world since 2006. Treatment outcomes are significantly worse in XDR-TB patients than in MDR-TB patients. Outbreaks of XDR-TB in populations with high prevalence of HIV have caused alarmingly high mortality rates. The emergence of XDR-TB as a new threat to global public health demands that health officials and health-care providers respond with a coordinated strategy drawing on the Stop TB Strategy.[1]

Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008 provides updated guidelines and recommendations on how to manage drug-resistant TB (DR-TB) based on a rapid assessment of the best available evidence by a group of experts. A fully revised second edition will be published in 2010, following WHO guidance on retrieval, synthesis and grading of evidence. Until that time, the emergency update serves as interim guidance for TB control programmes and medical practitioners on all aspects of the management of DR-TB, including XDR-TB. It contains 19 chapters based on the original 18 chapters from the first edition published by the World Health Organization in 2006[2] plus an additional chapter on patient-centered care.

[1] The Stop TB Strategy launched by the World Health Organization in 2006 describes the recommended interventions that should be implemented to achieve the targets for global TB control that have been established within the context of the Millennium Development Goals. See Raviglione MC, Uplekar MW. WHO's new Stop TB Strategy. *Lancet*, 2006, 367:952–955.

[2] *Guidelines for the programmatic management of drug-resistant tuberculosis*. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.361).

The key changes for the emergency update 2008 are summarized below.

CHAPTER	KEY RECOMMENDATIONS (* indicates updated recommendation)	KEY CHANGES
Chapter 1 Background information on drug-resistant tuberculosis	Not applicable	• Target audience is defined. • Development of guidelines is described. • Stop TB Strategy is summarized. • New data are provided from the WHO/IUATLD Global Project on Antituberculosis Drug Resistance Surveillance. • Updated information is provided from a survey of the network of supranational reference laboratories to determine the prevalence of XDR-TB among strains sent for drug susceptibility testing (DST).
Chapter 4 Definitions: case registration, bacteriology and treatment outcomes	Not applicable	• Definition of XDR-TB is introduced. • Concise instructions for registration of new cases of XDR-TB are provided.
Chapter 5 Case-finding strategies	• All patients at increased risk for MDR-TB should be screened for drug resistance.* • Patients infected with HIV should receive DST at the start of anti-TB therapy to avoid mortality caused by unrecognized MDR-TB.* • Rapid DST should be used for the initial screening of MDR-TB whenever possible. • Patients at increased risk for XDR-TB should receive DST of isoniazid, rifampicin, second-line injectable agents and a fluoroquinolone.*	• Stronger emphasis is placed on the recommendation that all patients at increased risk for MDR-TB should receive DST, with the goal of universal access to DST for all that need it. • The use of rapid DST in all HIV-infected patients who are smear-positive is highly encouraged, and it is recommended that all HIV-infected patients at moderate to high risk be screened for resistance in order to avoid the high mortality associated with unrecognized MDR-TB. • An algorithm for the use of rapid drug-resistance testing is introduced. • The use of DST for second-line drugs in case-finding for XDR-TB is introduced, and risk factors for XDR-TB are described.

CHAPTER	KEY RECOMMENDATIONS (* indicates updated recommendation)	KEY CHANGES
Chapter 6 Laboratory aspects	• All patients with suspected MDR-TB or XDR-TB need access to laboratory services for adequate and timely diagnosis. • Laboratories should be tested for proficiency and quality assured externally to perform DST.* • Laboratories should perform DST for the fluoroquinolones and second-line injectable agents where adequate capacity and expertise exists.* • DR-TB strains can be transported safely across international borders if international procedures and guidelines are followed.* • Laboratories must follow all standardized protocols for infection control and biosafety. • Quality control and quality assurance should be in place for microscopy, culture and DST. Links with supranational reference laboratories are strongly encouraged.	• Definitions of common terms used in laboratory issues are provided at the start of the chapter. • New recommendations for DST to second-line drugs are proposed based on recent WHO policy guidance; • References for regulations on how to transport infectious specimens internationally are provided.
Chapter 7 Treatment strategies for MDR-TB	• Design regimens with a consistent approach based on the hierarchy of the five groups of anti-TB drugs. • Promptly diagnose MDR-TB and initiate appropriate therapy. • Use at least four drugs with either certain, or almost certain, effectiveness. • DST should generally be used to guide therapy; however, do not depend on DST of ethambutol or pyrazinamide in individual regimen design, pyrazinamide, Group 4 and 5 drugs. • Do not use ciprofloxacin as an anti-TB agent in management of DR-TB.** • Design a programme strategy that takes into consideration access to quality-assured DST, rates of DR-TB, HIV prevalence, technical capacity and financial resources.	• The five groups of anti-TB drugs are re-defined. Thioacetazone is placed in Group 5. High-dose isoniazid and imipenem are added to Group 5. • Ciprofloxacin is removed as an anti-TB agent because of its weak efficacy compared with other fluoroquinolones. • Strong caution is warranted for any programme that uses gatifloxacin given the rare but dangerous adverse effects of dysglycaemia associated with this drug. • A new review of DST of second-line drugs has resulted in strong caution against basing the design of individual regimens on results of DST of ethambutol, pyrazinamide, or Group 4 and 5 drugs.

CHAPTER	KEY RECOMMENDATIONS (* indicates updated recommendation)	KEY CHANGES
Chapter 7 (*continued*)	• Treat MDR-TB patients for 18 months past the date of culture conversion. • Use adjunct therapies including surgery and nutritional or social support. • Treat XDR-TB aggressively whenever possible. • Treat adverse effects immediately and adequately.	• Table 7.2 is new and summarizes programme strategies accepted by the Green Light Committee that take into consideration quality of DST, rates of DR-TB, technical capacity and financial resources. • The management of XDR-TB is introduced.
Chapter 10 HIV infection and MDR-TB	• Perform provider-initiated HIV testing and counselling in all TB suspects.* • Use standard algorithms to diagnose pulmonary and extra-pulmonary TB. • Use mycobacterial cultures and, where available, newer more rapid methods of diagnosis. • Determine the extent (or prevalence) of anti-TB drug resistance in patients with HIV. • Introduce antiretroviral therapy (ART) promptly in MDR-TB or XDR-TB /HIV patients. • Consider empirical therapy with second-line anti-TB drugs.* • Provide co-trimoxazole preventive therapy (CPT) as part of a comprehensive package of HIV care to patients with active TB and HIV.* • Arrange treatment follow-up by a specialized team. • Implement additional nutritional and socioeconomic support. • Ensure effective infection control. • Involve key stakeholders in MDR-TB/HIV activities. • Monitor overlying toxicity with ART and DR-TB therapy.	• Stronger emphasis is placed on performing DST of HIV-infected individuals at the start of anti-TB therapy in areas of moderate or high MDR-TB prevalence. This subject is also introduced in Chapter 5 as a key change. • Greater detail is provided on the concomitant treatment of HIV and MDR-TB, including discussion of immune reconstitution inflammatory syndrome. • Table 10.3 provides a list of potential overlapping and additive toxicities of ART and anti-TB therapy.

CHAPTER	KEY RECOMMENDATIONS (* indicates updated recommendation)	KEY CHANGES
Chapter 11 Initial evaluation, monitoring of treatment and management of adverse effects	• Standard monitoring should be implemented for all patients on MDR-TB treatment. • Results both of sputum smear and culture should be monitored monthly to evaluate treatment response.* • Increased monitoring is required in HIV cases and for patients on ART.* • Health-care workers in MDR-TB control programmes should be familiar with the management of common adverse effects of MDR-TB therapy. • Ancillary drugs for the management of adverse effects should be available to the patient.	• New recommendations for monitoring the response to treatment are described. • Laboratory monitoring for patients receiving both ART and MDR-TB therapy is added to Table 11.1.
Chapter 12 Treatment delivery and adherence	• Use disease education, DOT, socioeconomic support, emotional support, management of adverse effects and monitoring systems to improve adherence to treatment. • National TB control programmes (NTPs) are encouraged to incorporate community-based care and support into their national plans.*	• A section on community-based care and support is added to this chapter. NTPs are encouraged to add community-based care and support into their national strategies and plans.
Chapter 14 Management of contacts of MDR-TB patients	• MDR-TB contact investigation should be given high priority, and NTPs should consider contact investigation of XDR-TB as an emergency situation.*	• NTPs should consider contact investigation of XDR-TB as an emergency situation.
Chapter 15 Drug resistance and infection control	• Infection control, including administrative and engineering controls as well as personal protection, should be made a high priority in all MDR-TB control programmes. • XDR-TB patients should be placed isolated following a patient-centred approach and WHO ethical and legal guidance until no longer infectious.*	• Infection control measures are proposed, with special attention to XDR-TB and the high mortality of patients coinfected with HIV and DR-TB. • XDR-TB patients should be placed in ward isolation until no longer infectious. • MDR-TB patients should receive routine care outside of normal HIV care settings.

CHAPTER	KEY RECOMMENDATIONS (* indicates updated recommendation)	KEY CHANGES
Chapter 18 Category IV recording and reporting system	• A standardized method of recording and reporting should be implemented in DR-TB control programmes. • DR-TB treatment cards should have an expanded section for information on patients with HIV.* • The International Health Regulations (IHR2005) should be followed.*	• Chapter 18 has been rewritten to be simpler and more consistent with the DOTS recording and reporting system. • The treatment card described in Chapter 18 has an expanded section for information on patients with HIV. • Box 18.1 provides additional recording and reporting components, which are optional for programmes. • The International Health Regulations 2005 should be followed.
Chapter 19 Managing DR-TB through patient-centered care	Not applicable	• Chapter 19 is the only completely new chapter in this revision. Any patient in whom MDR-TB or XDR-TB is suspected or diagnosed should be provided with high-quality patient-centered care, as outlined in both the International Standards for Tuberculosis Care, the Patients' Charter for Tuberculosis Care and in the WHO Good Practice in Legislation and Regulations for TB Control.

Foreword to the 2008 emergency updated edition

The emergence of resistance to antituberculosis drugs, and particularly of multi-drug-resistant TB (MDR-TB),[1] has become a major public health problem in a number of countries and an obstacle to effective global TB control. Nearly half a million cases of MDR-TB emerge every year as a result of under-investment in basic activities to control TB, poor management of the supply and quality of antituberculosis drugs, improper treatment of TB patients and transmission of the disease in congregate settings. However, in many areas such as Africa, the extent of drug resistance is unknown and in most resource-constrained countries the treatment of patients with MDR-TB is absent or inadequate.

As with other infectious diseases, from staphylococcal infections to malaria, pathogens have almost invariably developed resistance to the drugs used to treat them. Tuberculosis is no exception: strains resistant to streptomycin were identified within months of the start of use, in the mid 1940s, of this first antituberculosis drug. Indeed, the emergence of drug resistance was the primary reason that therapy for TB evolved to include treatment with more than one drug for up to 18 to 24 months – the standard of care for over two decades. The advent of rifampicin in the early 1970s permitted a drastic reduction in the duration of therapy to six months while the efficacy of treatment improved. But those familiar with drug resistance in general would have predicted the emergence of resistance to what are now termed these "first-line" drugs, and by the mid-1990s, most countries participating in a global survey of anti-TB drug resistance registered cases of MDR-TB. The worse was yet to come: in 2006, extensively drug-resistant TB (XDR-TB) emerged. This is defined as resistance to first- and second-line drugs[2] and was rapidly announced by the World Health Organization (WHO) as a serious emerging threat to global public health, especially in countries with a high prevalence of human immunodeficiency virus (HIV). In fact, reports have identified XDR-TB in all regions of the world and, to date, treatment outcomes have been shown to

[1] MDR-TB is defined as TB caused by *Mycobacterium tuberculosis* resistant in vitro to the effects of isoniazid and rifampicin, with or without resistance to any other drugs. Resistance is defined by specific laboratory criteria (see Chapter 6).

[2] XDR-TB is defined as TB resistant to multiple first-line drugs as well as to any one of the fluoroquinolones and to at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin).

be extremely poor (*1–4*). In one cohort from KwaZulu-Natal, South Africa, 98% of XDR-TB patients coinfected with HIV died, with a median time of death of only 16 days from the time of specimen collection.

This rapidly changing terrain requires health officials and providers to respond with novel and effective responses. These guidelines offer updated recommendations for TB control programmes and medical workers in middle- and low-income countries faced with MDR-TB and other drug-resistant forms of TB. They replace previous publications by WHO on drug-resistant TB (DR-TB) and are a direct update to the 2006 first edition of *Guidelines for the programmatic management of drug-resistant tuberculosis* (*5*). Taking account of important developments and recent evidence, the new guidelines aim to disseminate consistent, up-to-date recommendations for the diagnosis and management of MDR-TB in a variety of geographical, political, economic and social settings. The guidelines are designed to be of use to both TB control programmes and medical practitioners. The updated guidelines take into particular account a number of considerations and developments. First, access to culture and drug susceptibility testing should be available to all patients in whom DR-TB is considered likely. Secondly, there is a larger experience in treating DR-TB, and this experience can guide formal therapeutic recommendations. Thirdly, the 2006 edition insufficiently addressed DR-TB and HIV, and new knowledge can now guide revised policies. Finally, there now exist novel strategies to prevent and treat XDR-TB.

These updated guidelines expand upon the most recent general WHO guidelines for national TB control programmes (*6*), which are currently being updated to ensure full consistency with recent advances in our understanding of the programmatic management of MDR-TB.

In addition, these guidelines provide standards for registering, monitoring and reporting the treatment outcomes of patients with DR-TB. This uniform information management system will allow systematic, consistent data collection and analysis, which will play an important role in shaping future policies and recommendations.

The guidelines can be adapted to suit diverse local circumstances because they are structured around a flexible framework, combining a consistent core of principles and requirements with various alternatives that can be tailored to the specific local situation.

The guidelines also detail the recommended management protocols to enable national TB control programmes to access concessionally-priced, quality-assured second-line antituberculosis drugs through a mechanism known as the Green Light Committee (GLC), hosted by WHO.[1] The GLC was estab-

[1] For more information about the services and how to contact the Green Light Committee for technical support or apply for access to concessionally-priced, quality-assured second-line antituberculosis drugs, see the GLC web page at: http://www.who.int/tb/challenges/mdr/greenlightcommittee/en/index.html

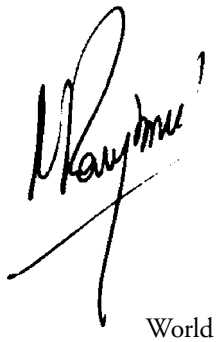
lished in June 2000 as a partnership among five categories of participants: governments of resource-limited countries; academic institutions; civil-society organizations; bilateral donors; and WHO. The GLC has successfully negotiated prices of drugs with producers; solicited creation of, and adopted sound policies for, proper management of DR-TB; established strict criteria to review proposals for DR-TB management programmes; assisted countries in developing such proposals and ensured their proper implementation; and, finally, has provided access to quality-assured second-line drugs at concessionary prices to those management programmes considered technically and scientifically sound and not at risk of producing additional drug resistance. In brief, the GLC rapidly became a model of good practice which, by providing access to previously unaffordable drugs, ensured that their use was as safe and rational as possible. Demand for technical assistance from the GLC grew rapidly and in 2002, the GLC was adopted by the newly established Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund) as its mechanism for screening proposals for DR-TB programme financing. This was a major historic milestone, and today the Global Fund is the leading financial mechanism supporting the management of MDR-TB in resource-constrained settings.

Today, a new threat – that linked to XDR-TB – now requires even more innovative thinking (*7*). In October 2006, the WHO Stop TB and HIV departments organized a meeting of the Global Task Force on XDR-TB at WHO headquarters in Geneva, Switzerland, in response to the XDR-TB emergency. During this meeting, eight recommendations were put forward to the international TB community, outlining key areas of response, beginning with strengthening of basic TB and HIV/AIDS control and proper management of MDR-TB (*8*). The eight recommendations are:

- strengthening basic activities to control TB and HIV/AIDS, as detailed in the Stop TB Strategy and the Global Plan, to avoid additional emergence of MDR-TB and XDR-TB;
- scaling-up the programmatic management of MDR-TB and XDR-TB to reach the targets set forth in the Global Plan;
- strengthening laboratory services for adequate and timely diagnosis of MDR-TB and XDR-TB;
- expanding surveillance of MDR-TB and XDR-TB to better understand the magnitude and trends of drug resistance and the links with HIV;
- fostering sound infection-control measures to avoid MDR-TB and XDR-TB transmission to protect patients, health workers, others working in congregate settings and the broader community, especially in high HIV prevalence settings;
- strengthening advocacy, communication and social mobilization for sustained political commitment and a patient-centered approach to treatment;

- pursuing resource mobilization at global, regional and country levels to ensure that necessary resources are available;
- promoting research and development into new diagnostics, drugs, vaccines, and operational research on MDR-TB management to shorten the length of treatment.

The ongoing changes in the field combined with new evidence and recommendations mandate a revision of the previous guidelines. This publication aims to underpin these recommendations with new or updated guidelines that might provide the guidance on programmatic management necessary to achieve many of the eight recommendations from the Global Task Force. We are confident that these new guidelines represent the best current knowledge regarding the management of DR-TB and MDR-TB and offer programmes and providers options for tailoring diagnosis and care to the needs evinced in different epidemiological and programmatic contexts. The recommendations, compiled by leading experts, should be followed by all national TB control programmes and their partners. With nearly half a million new cases of MDR-TB emerging every year, and an estimated global prevalence that may be as high as one million cases, the challenge is huge. At the same time, it is imperative to stress that the five elements of the DOTS strategy remain the cornerstone of TB control and the most effective tool for preventing the onset and dissemination of drug resistance. Without the essential elements of TB control fully in place, management of MDR-TB will undoubtedly fail in the long term, as one cannot control it if the tap is not turned off. These updated guidelines focus on care for DR-TB patients, in the hope that the occurrence of massive numbers of new cases can be prevented through sound TB-control practices. While further scientific advances are clearly needed in the fight against DR-TB, these guidelines outline the tools we have at our disposal to make an immediate impact on this destructive and grave epidemic.



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CHAPTER 1

Background information on DR-TB

1.1 Chapter objectives

This chapter summarizes key information on the emergence of drug-resistant TB (DR-TB), its public health impact, experience gained in the management of patients and strategies for addressing drug resistance within national TB control programmes (NTPs).

1.2 The Stop TB Strategy

The goals of the Stop TB Strategy are to reduce dramatically the burden of TB by 2015 in line with the Millennium Development Goals and the Stop TB Partnership targets and to achieve major progress in the research and development needed for TB elimination. The Stop TB Strategy continues to emphasize the basic components of the DOTS strategy (See Chapter 2 for how the basic DOTS strategy applies to DR-TB) while addressing additional constraints and challenges to TB control. The Stop TB Strategy has six principal components:

1.2.1 Pursuing high-quality DOTS expansion and enhancement

a. Political commitment with increased and sustained financing
b. Case detection through quality-assured bacteriology
c. Standardized treatment with supervision and patient support
d. Effective drug supply and management system
e. Monitoring and evaluation system and impact measurement

1.2.2 Addressing TB/HIV, MDR-TB, XDR-TB and other challenges by implementing collaborative TB/HIV activities, preventing and controlling DR-TB, including XDR-TB, and addressing prisoners, refugees and other high-risk groups and situations.

1.2.3 Contributing to health system strengthening by collaborating with other health-care programmes and general services, e.g. by mobilizing the necessary human and financial resources for implementation and impact evaluation, and by sharing and applying achievements of TB control as well as innovations from other fields.

1.2.4 Engaging all care providers, including public, nongovernmental and private providers, by scaling up public–private mix (PPM) approaches to ensure adherence to international standards of TB care, with a focus on providers for the poorest and most vulnerable groups.

1.2.5 Empowering people with TB, and communities by scaling up community TB care and creating demand through context-specific advocacy, communication and social mobilization.

1.2.6 Enabling and promoting research to improve programme performance and to develop new drugs, diagnostics and vaccines.

Emphasis on expanding laboratory capacity (sputum smear microscopy first, then culture and drug susceptibility testing (DST)) and the use of quality-assured drugs across all programmes are important aspects of this comprehensive approach to TB control.

1.3 Integration of diagnostic and treatment services to control TB

Detection and treatment of all forms of TB, including drug-resistant forms, should be integrated within NTPs. In the past, many public health authorities reasoned that scarce resources should be used for new patients with drug-susceptible TB because the cost of detecting and treating the disease was 10- to 100-fold lower than for MDR-TB. However, it has now proved feasible and cost effective to treat all forms of TB, even in middle- and low-income countries. Untreated or improperly treated patients with DR-TB are a source of

ongoing transmission of resistant strains, resulting in future added costs and mortality. The framework for the management of DR-TB presented in these guidelines can be adapted to all NTPs and integrated within the basic DOTS strategy.

1.4 Causes of DR-TB

Although its causes are microbial, clinical and programmatic, DR-TB is essentially a man-made phenomenon. From a microbiological perspective, resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. From a clinical and programmatic perspective, it is an inadequate or poorly administered treatment regimen that allows a drug-resistant strain to become the dominant strain in a patient infected with TB. Table 1.1 summarizes the common causes of inadequate treatment.

Short-course chemotherapy (SCC) for patients infected with drug-resistant strains may create even more resistance to the drugs in use. This has been termed the "amplifier effect" of SCC.

Ongoing transmission of established drug-resistant strains in a population is also a significant source of new drug-resistant cases.

TABLE 1.1 **Causes of inadequate antituberculosis treatment** (*1*)

HEALTH-CARE PROVIDERS: INADEQUATE REGIMENS	DRUGS: INADEQUATE SUPPLY OR QUALITY	PATIENTS: INADEQUATE DRUG INTAKE
Inappropriate guidelines	Poor quality	Poor adherence (or poor DOT)
Noncompliance with guidelines	Unavailability of certain drugs (stock-outs or delivery disruptions)	Lack of information
Absence of guidelines	Poor storage conditions	Lack of money (no treatment available free of charge)
Poor training	Wrong dose or combination	Lack of transportation
No monitoring of treatment		Adverse effects
Poorly organized or funded TB control programmes		Social barriers
		Malabsorption
		Substance dependency disorders

1.5 Addressing the sources of DR-TB

Any ongoing production of DR-TB should be addressed urgently before embarking on any programme designed for its control. The framework approach described in these guidelines can help to identify and curtail possible sources of DR-TB. Recent outbreaks of highly resistant TB underscore the importance of preventing the development of resistance, as mortality for patients infected with highly resistant strains is alarmingly high.

The possible contributing factors to the development of new drug-resistant cases should be reviewed (see Table 1.1 for a list of possible factors). Well-administered first-line treatment for susceptible cases is the best way to pre-

vent acquisition of resistance. Timely identification of DR-TB and adequate treatment regimens (Category IV regimens) administered early in the course of the disease are essential to stop primary transmission. Integration of DOTS with treatment of DR-TB works synergistically to eliminate all the potential sources of TB transmission.

1.6 Magnitude of the DR-TB problem

The incidence of drug resistance has increased since the first drug treatment for TB was introduced in 1943. The emergence of MDR-TB following the widespread use of rifampicin beginning in the 1970s led to the use of second-line drugs. Improper use of these drugs has fuelled the generation and subsequent transmission of highly resistant strains of TB termed extensively DR-TB, or XDR-TB. These strains are resistant to at least one of the fluoroquinolone drugs and an injectable agent in addition to isoniazid and rifampicin.

The WHO/IUATLD Global Project on Antituberculosis Drug Resistance Surveillance gathers data on drug resistance using a standard methodology in order to determine the global magnitude of resistance to four first-line antituberculosis drugs: isoniazid, rifampicin, ethambutol and streptomycin (*2*). The standard methodology includes representative sampling of patients with adequate sample sizes, standardized data collection distinguishing between new and previously treated patients and quality-assured laboratory DST supported by a network of supranational TB reference laboratories (SRLs).

Based on available information from the duration of the Global Project (*3*), the most recent data available from 116 countries and settings were weighted by the population in areas surveyed, representing 2 509 545 TB cases, with the following results: global population weighted proportion of resistance among new cases: any resistance 17.0% (95% confidence limits (CLs), 13.6–20.4), isoniazid resistance 10.3% (95% CLs, 8.4–12.1) and MDR-TB 2.9% (95% CLs, 2.2–3.6). Global population weighted proportion of resistance among previously treated cases: any resistance 35.0% (95% CLs, 24.1–45.8), isoniazid resistance 27.7% (95% CLs, 18.7–36.7), MDR-TB 15.3% (95% CLs, 9.6–21.1). Global population weighted proportion of resistance among all TB cases: any resistance 20.0% (95% CLs, 16.1–23.9), isoniazid resistance 13.3% (95% CLs, 10.9–15.8) and MDR-TB 5.3% (95% CLs, 3.9–6.6). Based on drug resistance information from these 116 countries and settings reporting to this project, as well as nine other epidemiological factors, it is estimated that 489 139 (95% CLs, 455 093–614 215) cases emerged in 2006. China and India carry approximately 50% of the global burden of MDR-TB and the Russian Federation a further 7%.

Data from the most recent collection period showed far greater proportions of resistance among new cases than found in previous reports, ranging all the way to 16% MDR-TB among new cases in Donetsk, Ukraine, 19.4% in the Republic of Moldova and 22.3% in Baku, Azerbaijan. Trends in MDR-TB

among new cases in the Baltic countries appear to have stabilized, but there were significant increases reported from the two oblasts of the Russian Federation that reported data.

Prevalent cases worldwide could be two or three times higher than the number of incident cases (*4*), as MDR-TB patients often live for several years before succumbing to the disease (*5*).

Drug resistance is strongly associated with previous treatment. In previously treated patients, the probability of any resistance was over 4-fold higher, and of MDR-TB over 10-fold higher, than for untreated patients. The overall prevalence of drug resistance was often related to the number of previously treated cases in the country. Among countries with a high burden of TB, previously treated cases ranged from 4.4% to 26.9% of all patients registered in DOTS programmes. In the two largest high-TB burden countries (China and India), re-treatment cases accounted for up to 20% of sputum smear-positive cases (*6*).

In 2006, the United States Centers for Disease Control and Prevention (CDC) and WHO conducted a drug resistance survey to determine the extent of resistance to second-line drugs. Surveying the WHO/IUATLD network of SRLs, over 17 000 isolates from 49 countries were included, all of which had been tested for resistance to at least three classes of second- line drugs. These are not population-based data, as second-line drug testing is not routinely carried out in most countries. The survey found that of the isolates tested against second-line drugs in the 49 contributing countries, 20% were MDR-TB and 2% were XDR-TB (*7*). Strains of XDR-TB have been reported in every region of the world, with as many as 19% of MDR-TB strains found to be XDR-TB, a proportion that has more than tripled in some areas since 2000 (*8*). When capacity allows, these guidelines recommend testing all MDR-TB isolates for resistance to a fluoroquinolone and the second-line injectable agents to define the proportion XDR-TB among MDR-TB (see Chapter 5 and 6).

Despite the association with previous treatment, drug-resistant strains including XDR-TB are readily transmissible and outbreaks have been reported, often in populations with high HIV prevalence. In one outbreak of XDR-TB in KwaZulu-Natal, half of the patients had never received antituberculosis treatment (*9*). The overlapping epidemics of HIV and TB are significantly worsened by XDR-TB, as outbreaks of these strains appear to cause higher and more rapid mortality in HIV-infected patients. Such strains pose a serious threat to global TB control, as detection is challenging in settings where laboratory resources and treatment options are severely limited.

1.7 Management of DR-TB, the Green Light Committee and the global response to DR-TB

The Working Group on DOTS-Plus for MDR-TB (currently the Working Group on MDR-TB) was established in 1999 to lead the global effort to

control MDR-TB. This working group, part of the Stop TB Partnership, formed the Green Light Committee (GLC) in 2000 to provide technical assistance to DOTS programmes, promote rational use of second-line drugs worldwide and improve access to concessionally-priced quality-assured second-line drugs. As DR-TB has emerged as a growing threat to DOTS programmes, new recommendations described in these updated guidelines must become a part of routine national TB control activities.

The GLC has developed a mechanism to assist countries in adapting the framework described in these guidelines to country-specific contexts. Countries that meet the framework requirements, with a strong DOTS foundation and a solid plan to manage DR-TB, can benefit from quality-assured second-line drugs at reduced prices. The GLC also offers technical assistance before implementation of programmes for control of DR-TB and monitors approved projects.[1]

A well-functioning DOTS programme is a prerequisite for GLC endorsement and for continuation of GLC support. Experience has shown that implementing a DR-TB control programme substantially strengthens overall TB control for both drug-susceptible and drug-resistant cases (*10*).

For control of DR-TB worldwide, WHO and its partners recommend integrating management of the disease into essential services for TB control and expanding treatment for DR-TB as rapidly as human, financial and technical resources will allow.

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[1] For more information about the services of the GLC and for technical support or to apply for access to concessionally-priced quality-assured second-line antituberculosis drugs, see the GLC web page at: http://www.who.int/tb/challenges/mdr/greenlightcommittee/en/index.html

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CHAPTER 2

Framework for effective control of DR-TB

2.1 Chapter objectives

This chapter describes the five essential components of the DOTS framework as they apply to the management of DR-TB. It also introduces a systematic approach for tailoring these components to the local situation, with integration into a DOTS-based NTP.

2.2 DOTS framework as applied to the management of DR-TB

The framework for DR-TB is organized around the five components of the DOTS strategy because the underlying principles are the same (*1–2*):

a. Sustained political commitment
b. A rational case-finding strategy including accurate, timely diagnosis through quality-assured culture and DST

c. Appropriate treatment strategies that use second-line drugs under proper case management conditions
d. Uninterrupted supply of quality-assured antituberculosis drugs
e. Standardized recording and reporting system

Each of these components involves more complex and costly operations than those for controlling drug-susceptible TB. However, addressing DR-TB usually strengthens the NTP.

2.2.1 Sustained political commitment

Sustained political commitment is essential to establish and maintain the other four components. It requires both long-term investment and leadership to ensure an appropriate environment for integrating the management of DR-TB into NTPs. An appropriate environment includes adequate infrastructure, development and retention of human resources, interagency cooperation, enactment of necessary legislation, TB control policies enabling rational implementation of the programme and facilitation of the procurement of quality-assured second-line drugs. In addition, the NTP must be strengthened to prevent the emergence of more MDR-TB and XDR-TB cases.

2.2.2 A rational case-finding strategy including accurate, timely diagnosis through quality-assured culture and DST

Accurate, timely diagnosis is the backbone of a sound NTP. DR-TB must be diagnosed correctly before it can be treated effectively. Case-finding strategies may vary depending on the epidemiological situation and local capacity. In some settings, all TB patients are tested with culture and DST. However, in most settings, only patients with an increased risk of DR-TB are tested (strategies on which risk groups to test are discussed in Chapter 5). In areas where XDR-TB threatens TB control, laboratories should develop the capacity for DST to second-line injectable agents and the fluoroquinolones in order to diagnose XDR-TB.

Quality-assured culture and DST are indispensable. Non-viable cultures, culture contamination and unreliable DST results have major consequences for both individual patients and the NTP as a whole. Internal quality control and external quality assurance should therefore be in place, including a link for proficiency testing with a recognized reference laboratory such as one of the WHO-recognized SRLs.

2.2.3 Appropriate treatment strategies that use second-line drugs under proper case management conditions

An appropriate treatment strategy consists of a rational method for designing the optimal treatment regimen, a patient-centered approach for delivering this regimen with direct observation, and a plan for monitoring and managing

adverse drug reactions. Designing an optimal regimen requires professional expertise to consider several factors together, including:

- representative data on drug resistance surveillance (DRS) of well-defined local groups of TB patients, distinguishing new cases and different types of re-treatment cases;
- history of drug use in the country and in the individual;
- specific array of available second-line drugs;
- availability of DST to first- and selected second-line drugs;
- reliable options for delivering directly observed therapy (DOT) for up to two years;
- addressing patients coinfected with HIV;
- proper infection control policies implemented.

A standardized regimen for certain groups of patients may be more appropriate than an individualized regimen in some countries, while in others the converse may be best.

The choice between hospitalization and ambulatory treatment depends on several factors in addition to the severity of the disease. Such factors include the availability of hospital beds with adequate infection control measures to prevent nosocomial transmission; the availability of trained personnel at hospitals and clinics to administer treatment and manage adverse drug reactions; the availability of a social support network to facilitate adherence to ambulatory treatment; and the presence of other clinical or social conditions in patients.

2.2.4 Uninterrupted supply of quality-assured antituberculosis drugs

Management of second-line drugs is complex, especially when individualized treatment regimens are used. Drugs are frequently changed as a result of adverse effects, delayed DST results and poor response to treatment. In addition, most second-line drugs have a short shelf-life, global production of quality-assured drugs is limited, and drug registration may be a lengthy and costly process that is not always attractive to drug manufacturers. Steps to ensure an uninterrupted drug supply must begin six months or more in advance of the anticipated need, and drug needs must be estimated as accurately as possible. Countries should use only drugs that have been quality-assured by a stringent drug regulatory authority recognized by WHO, a WHO prequalification programme or that meet WHO GMP standards.

2.2.5 Standardized recording and reporting system

The specific characteristics of a DR-TB control programme include a recording system with differently defined categories for patient registration, culture and DST results, and monitoring of treatment delivery and response for 24

months. Cohort analysis includes interim indicators and treatment outcomes after two or more years, as well as treatment outcomes by treatment regimen and DST results. The set of case registration groups and treatment outcome definitions for MDR-TB used in these guidelines (Chapter 4) were developed through a process that involved the Stop TB Working Group on DOTS-Plus for MDR-TB (*3*). They can be used for conducting cohort analyses in DR-TB control programmes. The redesigned recording and reporting system (see Chapter 18) is essential for evaluating programme performance and treatment effectiveness.

2.3 A plan for tailored integration of management of DR-TB into national programmes

Management of DR-TB should be fully integrated into the NTP. The challenge involved in this integration should not be underestimated. However, the complexity of the process should not deter programmes from taking the steps necessary to allow all patients with DR-TB access to life-saving treatment. If many of the patients with DR-TB are treated in the private sector, integration can be facilitated through PPM approaches. Box 2.1 depicts the three key steps of a plan for integrating the management of DR-TB into NTPs.

The most important consideration is the political will to deliver rational treatment to patients with DR-TB as part of a sound NTP. Following confirmation of political will, a needs assessment should be carried out. Box 2.2 lists the most relevant variables to consider.

The needs assessment will facilitate the design and implementation of a plan to meet the gaps identified, in terms of both infrastructure and functioning of the health-care system. Once the infrastructure is in place and the key functions such as a quality-assured TB laboratory are operating, a stepwise integration of activities to control DR-TB can proceed within the NTP. Stepwise integration means that those districts or administrative areas where the integration is more likely to succeed should be prioritized.

The design and implementation of a DR-TB control programme may vary between and within countries, depending on the local needs and resources available. Despite a wide range of acceptable strategies, essential requirements such as quality-assured laboratories for diagnosis and monitoring of treatment response, delivery of DOT and use of quality-assured second-line drugs should be met under all conditions to ensure proper case management and prevent the emergence of resistance to second-line drugs.

2.4 Summary

The DOTS framework approach to management of DR-TB, summarized in Box 2.3, includes five essential components that form the basis for every NTP that includes detection and treatment of DR-TB.

BOX 2.1

Key steps for integrating management of DR-TB into national TB control programmes

1. Assessment of political will to deliver rational treatment to patients with drug-resistant TB.
2. Needs assessment for drug-resistant TB control activities.
3. Design and implementation of a plan for management of drug-resistant TB and its stepwise integration into the national TB control programme.

BOX 2.2

List of variables to consider when assessing needs for integrating management of DR-TB into national TB control programmes

- Magnitude and distribution of DR-TB
- Magnitude of HIV
- Prevailing patterns of drug resistance
- Options for case-finding
- Existing infrastructure of the health-care system
- Available laboratory capacity
- Resources available for DOT over a prolonged period
- Infection control policy in place and adequate funding available for control measures
- Quality standards of the laboratory network
- Availability of human resources
- Training needs
- Existing legal framework for management of second-line drugs
- Needs for external technical assistance

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BOX 2.3 FIVE COMPONENTS OF DOTS AS APPLIED TO DR-TB

1. Sustained political commitment

- Addressing the factors leading to the emergence of MDR-TB
- Long-term investment of staff and resources
- Coordination of efforts between communities, local governments and international agencies
- A well-functioning DOTS programme

2. Appropriate case-finding strategy including quality-assured culture and DST

- Rational triage of patients into DST and the DR-TB control programme
- Relationship with supranational TB reference laboratory

3. Appropriate treatment strategies that use second-line drugs under proper case management conditions

- Rational treatment design (evidence-based)
- DOT
- Monitoring and management of adverse effects
- Properly trained human resources

4. Uninterrupted supply of quality-assured second-line antituberculosis drugs

5. Recording and reporting system designed for DR-TB control programmes that enables monitoring of performance and evaluation of treatment outcomes

CHAPTER 3

Political commitment and coordination

3.1 Chapter objectives

Sustained political commitment is a prerequisite for control of DR-TB. This chapter considers how political commitment can be translated into practical measures to support all aspects of the framework for control of DR-TB, and the practical implications for NTPs. The main elements are described and a checklist for programme managers is provided.

3.2 General considerations

Sustained political commitment and leadership are the foundation for any sound programme to control TB. The legal and regulatory context defines the potential as well as the structure and policies of NTPs and DR-TB control programmes. Political commitment is expressed through adequate financial support and appropriate infrastructure, including facilities and trained staff. Coordination among the different components of public and private health-care programmes and organizations is essential for successful programme implementation. Sufficient training and retention of medical and public health personnel depend on long-term government planning and support.

3.3 Political commitment

Political commitment must be expressed at all stages of the health intervention process, from planning and implementation to monitoring and evaluation.

Political support needs to be garnered from sources including government ministries and regional departments responsible for TB control, nongovernmental organizations and the private sector, the pharmaceutical industry, academic and research institutions, professional medical societies and the donor community. This commitment takes the form of financial and human resources, training, legal and regulatory documents, infrastructure and coordination of all stakeholders involved in all aspects of the framework for control of DR-TB.

3.3.1 Sufficient economic support

The NTP budget must be sufficient to develop and retain an adequate workforce with interest and expertise in DR-TB without weakening the workforce of the national programme as a whole. The financial resources needed to support the framework should be provided. There should be no financial barriers to patients' accessing appropriate care for DR-TB. Human resource needs are discussed in Chapter 16.

3.3.2 Regulatory and operational documents

Before embarking on a DR-TB control programme, national and regional authorities need to develop policies as a foundation for any subsequent legal, administrative and technical support necessary for the initiation, implementation and monitoring of the programme. Regulatory document(s) should consider how the programme will be integrated into the NTP. The following are examples of the use of regulatory and operational documents:

- Legislation can be drafted to ensure proper registration, availability, quality, safety and distribution of second-line drugs. (Often, strict control of second-line drugs is possible only after establishment of the programme to provide quality-assured drugs free of charge to patients.)
- A local steering committee or expert committee can be formed to meet periodically to consult on individual patients and to address programmatic problems.
- A memorandum of understanding delineating responsibilities and funding is often necessary if multiple organizations are involved. In settings where programmes involve different ministries or departments (including, for example, the prison system or the social security system), an interministerial or interdepartmental agreement should be signed that codifies the mechanism for coordinating services for diagnosis of TB and treatment of patients between all authorities.
- A programme manual can be the vehicle for disseminating operational and clinical protocols to ensure consistency. It should be officially endorsed by the relevant authorities. The manual describes treatment protocols, defines

responsibilities for different health-care providers and delineates the human resources that will be needed. It specifically defines how disease will be diagnosed and how patients will be registered, reported, treated and followed up, in addition to programme monitoring and evaluation. Items to be included in the programme manual are proposed in Box 3.1.

BOX 3.1 PROPOSED ELEMENTS OF THE DR-TB CONTROL PROGRAMME MANUAL

- Background information on the DOTS programme and its integration with treatment of patients with DR-TB
- Organization and management of the DR-TB control programme
- Case detection, diagnosis, classification of and reporting requirements for drug-resistant TB
- Organization of the laboratory network, including quality control procedures for laboratories providing culture and DST
- Treatment regimens for drug-resistant TB
- Management of adverse effects caused by antituberculosis drugs
- Management of drug-resistant TB in special populations and situations (including children; pregnant or lactating women; diabetes mellitus; HIV; renal or hepatic insufficiency; the elderly; alcohol and drug-dependent patients; prisoners)
- Case management system including DOT, transition to ambulatory care, patient assistance and defaulter tracing
- Standards for evaluation and monitoring of treatment and of overall project performance
- Plan for infection control in health facilities and other methods to prevent drug-resistant TB

3.4 Coordination

Coordination needs to include the contributions of all the key stakeholders, organizations and external partners, as considered below.

- **National TB control programme.** The NTP is the central coordinating body for the activities described in the strategic framework. Commitment of the necessary resources, particularly for a strong central management team, ensures that all elements are in place, from the procurement of second-line drugs to the appropriate implementation and monitoring of the DR-TB control programme. As needed, the national programme may build partnerships with all relevant health-care providers.
- **Local health system.** DR-TB control programmes should be tailored to fit the local infrastructure. The precise organizational structure of the programme may vary greatly between different settings depending on how the local health care is provided. Transfer from hospitals to outpatient settings or between DOT centres requires care, advance planning and good communication. Given the type of care required during the treatment of DR-TB patients, a team of health workers including physicians, nurses and social workers is often used.

- **Community level.** Community involvement and communication with community leaders can greatly facilitate implementation of treatment and respond to needs that cannot be met by medical services alone. Community education, involvement and organization around TB issues can foster community ownership of control programmes and reduce stigma. In some circumstances, communities have helped to address the interim needs of patients, including the provision of DOT, food and/or housing. Community health workers often play a critical role in ambulatory care of DR-TB patients.
- **Coordination with prisons** (*1*)**.** Transmission in prisons is an important source of spread of DR-TB in some countries, and infection control measures can reduce incidence substantially. In many cases, inmates are released from prison before they finish treatment. Close coordination and communication with the civilian TB control programme, advance planning, targeted social support and specific procedures for transferring care will help ensure that patients complete treatment after release from prison.
- **All health-care providers (both public and private)** (*2*)**.** In some countries, private practitioners manage most cases of DR-TB. In these settings, it is important to involve the private sector in the design and technical aspects of the programme. Many PPM programmes have demonstrated effective and mutually beneficial cooperation (*3*). In PPM systems, patients and information move in both directions. For example, private providers can be compensated fairly through negotiated systems of reimbursement, and the public health system may provide clinic- or community-based DOT as well as registering patients and their treatment outcomes. Similar PPM mixes can be established for treatment of patients with DR-TB, but they require exceptional coordination. The public health system may also get involved in training on national guidelines for DR-TB.
- **International level.** International technical support through WHO, the GLC, SRLs and other technical agencies is recommended. The NTP should set up and lead an interagency body that ensures clear division of tasks and responsibilities.

3.5 Proposed checklist

From the earliest planning phase, the full range of issues encompassed in political commitment needs to be addressed. These include adequate financial support, an enabling regulatory environment, sufficient human resources, adequate physical infrastructure and good coordination. In addition, a communication strategy should be established to ensure that information is disseminated effectively from the central level to the periphery and that reports from the peripheral level are received centrally. Box 3.2 provides a checklist for programme managers, summarizing the key aspects of a DR-TB control programme.

BOX 3.2 SUMMARY CHECKLIST FOR DR-TB CONTROL PROGRAMME MANAGERS

Prevention

- ❑ Sound implementation of DOTS programme
- ❑ Infection control measures taken where all DR-TB patients will be treated
- ❑ Contact tracing for MDR-TB cases in place

Laboratory

- ❑ Testing and maintenance of equipment
- ❑ Biosafety measures in place
- ❑ Reagents supply
- ❑ Supervision and quality assurance system (relationship with SRL established)
- ❑ System for reporting laboratory results to the treatment centre
- ❑ Laboratory for monitoring of electrolytes, creatinine, lipase, thyroid function, liver enzymes, and hematocrit in place
- ❑ Point-of-care HIV testing, with counselling and referral available
- ❑ Pregnancy testing

Patient care

- ❑ Council of experts or steering committee set up
- ❑ Adequate capacity and trained staff at the health centre for DOT and patient support
- ❑ DOT in place and plan to ensure case holding
- ❑ System to detect and treat adverse effects, including supply of appropriate medications
- ❑ Patient and family support to increase adherence to treatment, such as support group, psychological counselling, transportation subsidy, food baskets
- ❑ Patient, family and community health education, including stigma reduction

Programme strategy

- ❑ Integration with DOTS programme
- ❑ Sources of DR-TB identified and corrected
- ❑ Legislation for treatment protocols accepted
- ❑ Project manual published and disseminated
- ❑ Agreement of criteria for prioritization of patient waiting lists
- ❑ Location of care defined and functional (ambulatory vs hospitalization)
- ❑ Integration of MDR-TB services with HIV care
- ❑ Integration of all health-care providers into the DR-TB control programme

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CHAPTER 4

Definitions: case registration, bacteriology and treatment outcomes

4.1 Chapter objectives

This chapter establishes case definitions, patient registration categories, bacteriological terms, treatment outcome definitions and cohort analysis procedures for patients who meet WHO Category IV diagnostic criteria.[1] It is an extension of the basic DOTS information system (*1*, *2*).

The categories, definitions and procedures defined in this chapter will facilitate the following:

- standardized patient registration and case notification;
- assignment to appropriate treatment regimens;
- case evaluation according to disease site, bacteriology and history of treatment;
- cohort analysis of registered Category IV patients and Category IV treatment outcomes.

[1] *Treatment of tuberculosis: guidelines for national programmes* (*1*) recommends treatment regimens based on different TB diagnostic categories. The diagnostic categories are:

Category I – New smear-positive patients; new smear-negative pulmonary TB (PTB) with extensive parenchymal involvement; severe concomitant HIV disease or severe forms of extrapulmonary TB.
Category II – Previously treated sputum smear-positive PTB: relapse; treatment after interruption; failures.
Category III – New smear-negative PTB (other than in Cat I) and less severe forms of extrapulmonary TB.
Category IV – Chronic cases (still sputum-positive after supervised re-treatment) and MDR-TB.

4.2 Definitions of drug resistance and diagnostic Category IV

DR-TB is **confirmed** through laboratory tests that show that the infecting isolates of *Mycobacterium tuberculosis* grow in vitro in the presence of one or more antituberculosis drugs (see Chapter 6 for further information on laboratory requirements). Four different categories of drug resistance have been established:

- **Mono-resistance**: resistance to one antituberculosis drug.
- **Poly-resistance**: resistance to more than one antituberculosis drug, other than both isoniazid and rifampicin.
- **Multidrug-resistance**: resistance to at least isoniazid and rifampicin.
- **Extensive drug-resistance**: resistance to any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin), in addition to multidrug-resistance.

Diagnostic Category IV includes patients with:

- **Confirmed MDR-TB**.
- **Suspected MDR-TB**. This requires that the relevant health authority (such as a review panel) recommends that the patient should receive Category IV treatment. Patients may be entered in the Category IV register and started on Category IV treatment before MDR-TB is confirmed **only** if representative DST surveys or other epidemiologic data indicate a very high probability of MDR-TB (see Chapter 5).
- **Poly-resistant TB**. Some cases of poly-resistant TB will require Category IV treatments. These patients require prolonged treatment (18 months or more) with first-line drugs combined with two or more second-line drugs (see Chapter 8, Table 8.1) and should be entered into the Category IV register. (Most programmes choose to keep cases of mono- and poly-resistance that do not require second-line drugs or require only one second-line drug, in the District TB Register).

4.3 Site of drug-resistant TB disease (pulmonary and extrapulmonary)

In general, recommended treatment regimens for drug-resistant forms of TB are similar, irrespective of site. The importance of defining site is primarily for recording and reporting purposes.

- **Pulmonary TB**. Tuberculosis involving only the lung parenchyma.
- **Extrapulmonary TB**. Tuberculosis of organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormali-

ties in the lungs, therefore constitutes a case of extrapulmonary TB. The definition of an extrapulmonary case with several sites affected depends on the site representing the most severe form of disease.

Patients with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.

4.4 Bacteriology and sputum conversion

Bacteriological examinations used in patients with DR-TB include sputum smear microscopy and culture. Sputum smear microscopy and culture should be performed and results reported according to international standards (*3*). These examinations should be done at the start of treatment to confirm TB disease and to group the patients according to infectiousness, sputum smear-positive being most infectious.

At least one sputum sample for smear and culture should always be taken at the time of Category IV treatment start. In order for a patient to be considered culture- or sputum smear-positive at the start of Category IV treatment, the following criteria must be met: at least one pre-treatment culture or smear was positive; the collection date of the sample on which the culture or smear was performed was less than 30 days before, or 7 days after, initiation of Category IV treatment.

Sputum conversion is defined as two sets of consecutive negative smears and cultures, from samples collected at least 30 days apart. Both bacteriological techniques (smear and culture) should be used to monitor patients throughout therapy (see Chapter 11). The date of the first set of negative cultures and smears is used as the date of conversion (and the date to determine the length of the initial phase and treatment).

The recording and reporting system assesses the smear- and culture-status 6 months after the start of treatment as an interim outcome. Programmes often use the smear and culture conversion rate at 6 months to assess programme performance (see Chapter 18).

4.5 Category IV patient registration group based on history of previous antituberculosis treatment

Category IV patients should be assigned a registration group based on their treatment history, which is useful in assessing the risk for MDR-TB.

The registration groups describe the history of previous treatment and do not purport to explain the reason(s) for drug resistance.[1]

[1] These guidelines do not use the terms "primary" and "acquired" resistance because these types of resistance cannot be distinguished in most DR-TB control programmes. If DST is done before the start of the patient's first antituberculosis treatment, any resistance documented is primary resistance. If new resistance is found when DST is later repeated and genetic testing confirms that it is the same strain, only then can it be concluded that the strain has acquired resistance. Otherwise, it may be caused by re-infection with a new strain.

Each Category IV patient should be classified in two different ways:

I. Classification according to history of previous drug use, mainly to assign the appropriate treatment regimen.

- **New**. A patient who has received no or less than one month of antituberculosis treatment. Patients are placed in this group if they had sputum collected for DST at the start of a Category I regimen and were then switched to a Category IV regimen because MDR-TB was later confirmed. They should be considered "new" if DST was performed within one month of the start of treatment (even if they had received more than one month of Category I treatment by the time the results of DST returned and they were registered as Category IV).
- **Previously treated with first-line drugs only**. A patient who has been treated for one month or more for TB with only first-line drugs.
- **Previously treated with second-line drugs**. A patient who has been treated for one month or more for TB with one or more second-line drugs, with or without first-line drugs.

II. Classification according to the history of their previous treatment (commonly referred to as the patient's "registration group"). The registration groups are the established groups used in the DOTS recording and reporting system, with additional subgrouping of patients treated after failure. The number of groups will depend on the country policy on target groups for DST. This grouping allows analysis of the target groups for DST, epidemiological monitoring and projection of future numbers of MDR-TB cases. Again, classification is determined by treatment history at the time of collection of the sputum sample that was used to confirm MDR-TB. The groups are as follows:

- **New**. (Same definition as in classification according to previous drug use). A patient who has received no or less than one month of antituberculosis treatment.
- **Relapse**. A patient whose most recent treatment outcome was "cured" or "treatment completed", and who is subsequently diagnosed with bacteriologically positive TB by sputum smear microscopy or culture.
- **Treatment after default**. A patient who returns to treatment, bacteriologically positive by sputum smear microscopy or culture, following interruption of treatment for two or more consecutive months.
- **Treatment after failure of Category I**. A patient who has received Category I treatment for TB and in whom treatment has failed. Failure is defined as sputum smear positive at five months or later during treatment.

- **Treatment after failure of Category II**. A patient who has received Category II treatment for TB and in whom treatment has failed. Failure is defined as sputum smear positive at five months or later during treatment.
- **Transfer in**. A patient who has transferred in from another register for treatment of DR-TB to continue Category IV treatment.
- **Other**. There are several types of patients who may not fit into any of the above categories. Programmes are encouraged to classify these patients into groups that are meaningful according to the local epidemiology of disease. Examples include the following: sputum smear positive patients with unknown previous treatment outcome; sputum smear positive patients who received treatment other than Category I or II (possibly in the private sector); previously treated patients with extrapulmonary TB; patients who have received several unsuccessful treatments, were considered incurable by health staff and who have lived with active TB disease with no or inadequate treatment for a period of time (duration depends on country situation) until Category IV treatment became available (so-called "back-log" patients; see also Chapter 18.5).

While persistently positive smears at month five constitute the definition of failure, many programmes may want to perform culture and DST earlier based on the overall clinical picture. Patients found to have MDR-TB will need to be switched to Category IV regimens before they meet the traditional diagnosis of failure. When possible, these patients should be classified separately. This will allow assessment of the value of these end-points to predict MDR-TB, and thereby the utility of routine DST in these groups. Otherwise, they should be classified together with the failures of the regimens they received.

HIV status is also recorded at the start of treatment and, if unknown, point-of-care testing is encouraged (see Chapter 18).

4.6 Definitions for diagnostic Category IV treatment outcomes

The following are mutually exclusive Category IV outcome definitions (*4*) that rely on the use of laboratory smear and culture as a monitoring tool and will be reported in Forms 01, 02 and 07 (see Chapter 18). They have been constructed to parallel the six DOTS outcomes for drug-susceptible TB (*1*, *4*). All patients should be assigned the first outcome they experience for the treatment being evaluated for recording and reporting purposes.

- **Cured**. A Category IV patient who has completed treatment according to programme protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.

- **Treatment completed**. A Category IV patient who has completed treatment according to programme protocol but does not meet the definition for cure because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final 12 months of treatment).
- **Died**. A Category IV patient who dies for any reason during the course of MDR-TB treatment.
- **Failed**. Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive. (Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early because of poor clinical or radiological response or adverse events. These latter failures can be indicated separately in order to do subanalysis).
- **Defaulted**. A Category IV patient whose treatment was interrupted for two or more consecutive months for any reason without medical approval.
- **Transferred out**. A Category IV patient who has been transferred to another reporting and recording unit and for whom the treatment outcome is unknown.

Patients who have transferred in should have their outcome reported back to the treatment centre from which they originally were registered. The responsibility of reporting their final outcomes belongs to the original treatment centre.

4.7 Cohort analysis

All patients should be analysed in two different cohorts (groups of patients) depending on the purpose:

- **The treatment cohort** includes only patients who start Category IV treatment. It is defined by the date of start of Category IV treatment. The purpose is mainly to assess result of treatment and trends over time.
- **The diagnostic cohort** includes patients diagnosed with MDR-TB (identified in the DST register by date of DST result) during a specific period of time. The purpose is mainly to assess the number of patients with DR-TB, in subgroups and over time. This allows the programme to evaluate delay in treatment start and proportion of patents who started treatment.

The recommended timeframe for Category IV treatment cohort analysis reflects the long duration of Category IV regimens. Cohort analyses should be carried out at 24 months and, if needed, repeated at 36 months after the last patient starts treatment (see Chapter 18 and Form 07). For each treatment cohort, an interim status should be assessed at 6 months after the start of treatment to monitor programme progress (see Chapter 18 and Form 06).

BOX 4.1 HELPFUL HINTS ON REGISTRATIONS AND DEFINITIONS

Assigning the first outcome. All patients should be assigned the first outcome they experience for recording and reporting purposes. For example, a patient defaults on a Category IV regimen and returns 14 months later to be re-registered and is cured with a second Category IV treatment. This patient should receive a final outcome of "defaulted" in the cohort in which he or she was first registered and "cured" in the second cohort.

Transfer out. A patient who is "transferred out" must be transferred out to another DR-TB treatment centre. For example, a patient in a district with a good DR-TB programme has completed 8 months of a Category IV regimen and is doing well and has converted his sputum in month two. He informs the DR-TB control programme that he is returning to his home district (500 km away) and that the district does not have a DR-TB control programme. His uncle is going to purchase the medicines, which he will swallow under the supervison of a local physician. There are no culture facilities in his home district. This patient should be counted as a default, because he is leaving a DR-TB control programme that will not be able to track him. A patient must go to another DR-TB control programme that can report back the final result to be considered as transferred-out.

Transferred in. A patient who "transfers in" does not get counted in the cohort of the centre in which he completes his treatment. The receiving centre must report back the final outcome of the patient to the original treatment centre. The original centre should confirm with the receiving centre that the patient transferred in and the final treatment outcome.

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3. *Laboratory services in tuberculosis control [Parts I, II and III]*. Geneva, World Health Organization, 1998 (WHO/TB/98.258).
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CHAPTER 5

Case-finding strategies

5.1 Chapter objectives

This chapter describes strategies for case-finding and diagnosis of patients with either suspected or confirmed DR-TB. Several approaches to case-finding and enrolment into DR-TB control programmes are discussed, taking into consideration that such programmes may have limited technical and financial capacity. The strategies range from testing all patients with TB to testing only a selected group of patients.

The chapter reviews case-finding of patients with DR-TB with respect to:

- risk factors for drug resistance;
- strategies for case-finding in programmes with minimal access to DST and limited resources;
- information on DST collection;
- the use of rapid DST methods[1] to identify drug resistance;

[1] Rapid DST methods in these guidelines refer to molecular techniques that detect the genetic determinants of resistance. However, liquid, agar and other validated DST media that determine the presence of resistance within 2–3 weeks can often be substituted as rapid DST method when molecular methods are not available.

- the use of DST of second-line drugs and case detection of XDR-TB;
- important issues in case-finding of drug resistance in the HIV-infected patient.

Key recommendations (* indicates updated recommendation)

- Patients at risk of DR-TB should be screened for drug resistance;
- In people living with HIV, when possible, DST should be performed at the start of anti-TB therapy to avoid mortality due to unrecognized DR-TB;*
- For the initial screening of DR-TB, rapid DST methods should be used whenever possible;
- Patients at increased risk of XDR-TB should be screened for resistance with DST of isoniazid, rifampicin, the second-line injectable agents and a fluoroquinolone.*

5.2 Background information and general considerations

Programme strategies strive to identify patients and initiate adequate treatment for drug-resistant cases in a timely manner. Timely identification and prompt initiation of treatment prevent the patient from spreading the disease to others, acquiring further resistance and progressing to a state of permanent lung damage.

It is strongly recommended that programmes have representative DRS data for new patients and for the different categories of re-treatment patients (failure of Category I, failure of re-treatment, default and relapse) as well as other high-risk groups. Without this information, or when it is only partially available, designing an effective case-finding strategy is difficult and may be impossible. DRS data also enable a programme to estimate the number of patients who should enrol, which in turn greatly facilitates strategy planning and drug procurement.

5.3 Targeting risk groups for DST

These guidelines assume a general understanding of case-finding and diagnosis of active TB. This information can be reviewed in reference books on TB, including WHO publications (*1*, *2*).

Routine DST at the start of treatment may be indicated for all TB patients or only in specific groups of patients at increased risk for drug resistance. Specific elements of the history that suggest an increased risk for drug resistance are listed in Table 5.1. Stronger risk factors are placed higher in the table. Risk factors for XDR-TB are discussed in section 5.10.

The prevalence of resistance in specific risk groups can vary greatly across different settings. The routine use of DST and Category IV treatment for patients with any risk factor listed in Table 5.1 is therefore not recommended. Programmes should instead examine DRS data from risk groups, together

TABLE 5.1 **Target groups for DST**

RISK FACTORS FOR DRUG-RESISTANT TB	COMMENTS
Failure of re-treatment regimens and chronic TB cases	Chronic TB cases are defined as patients who are still sputum smear-positive at the end of a re-treatment regimen. These patients have perhaps the highest MDR-TB rates of any group, often exceeding 80% (*1*, *2*).
Exposure to a known DR-TB case	Most studies have shown close contacts of MDR-TB patients to have very high rates of MDR-TB. Management of DR-TB contacts is described in Chapter 14.
Failure of Category I	Failures of Category I are patients who while on treatment are sputum smear-positive at month 5 or later during the course of treatment. Not all patients in whom a regimen fails have DR-TB, and the percentage may depend on a number of factors, including whether rifampicin was used in the continuation phase and whether DOT was used throughout treatment. More information on regimen implications for Category I failures is given below in this chapter and in Chapter 7.
Failure of antituberculosis treatment in the private sector	Antituberculosis 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 antituberculosis drugs may have been used, and this is important information for designing the re-treatment regimen.
Patients who remain sputum smear-positive at month 2 or 3 of SCC	Many programmes may choose to do culture and DST on patients who remain sputum smear-positive at months 2 and 3. This group of patients is at risk for DR-TB, but rates can vary considerably.
Relapse and return after default without recent treatment failure	Evidence suggests that most relapse and return after default cases do not have DR-TB. However, certain histories may point more strongly to possible DR-TB; for example, erratic drug use or early relapses.
Exposure in institutions that have DR-TB outbreaks or a high DR-TB prevalence	Patients who frequently stay in homeless shelters, prisoners in many countries and health-care workers in clinics, laboratories and hospitals can have high rates of DR-TB.
Residence in areas with high DR-TB prevalence	DR-TB rates in many areas of the world can be high enough to justify routine DST testing in all new cases.
History of using antituberculosis drugs of poor or unknown quality	The percentage of DR-TB caused by use of poor-quality drugs is unknown but considered significant. It is known that poor-quality drugs are prevalent in all countries. All drugs should comply with quality-assured WHO standards.

TABLE 5.1 (*continued*)

RISK FACTORS FOR DRUG-RESISTANT TB	COMMENTS
Treatment in programmes that operate poorly (especially recent and/or frequent drug stock-outs)	These are usually non-DOTS or DOTS programmes with poor drug management and 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-noninfected or -infected patients.
HIV in some settings	Data from the 2002–2006 Global Surveillance project (*9*) suggest an association between HIV and MDR-TB in some parts of the world, and numerous DR-TB outbreaks have been documented in HIV patients (see Chapter 10). The data are still limited and specific factors involved in this association have not been determined.

with their technical capacity and resources, to determine which groups of patients should get routine DST and/or inclusion into Category IV regimens.

5.4 Strategies for programmes with minimal access to DST and limited resources

Access to DST is required in all programmes. Under exceptional circumstances, and while building the laboratory capacity to perform DST, programmes may use strategies to enrol patients with a very high risk of DR-TB in Category IV regimens without individual DST. For example, the results of representative DRS may identify a group or groups of patients with a very high percentage of DR-TB, which can justify the use of Category IV regimens in all patients in the group.

The three groups that are most likely to be considered for direct enrolment in Category IV regimens are discussed below.

- **Category II failures (chronic TB cases)** (*3*, *4*)**.** Patients in whom Category II treatment has failed in sound NTPs often have DR-TB (*1*, *2*). If the quality of DOT is poor or unknown (i.e. if regular ingestion of the medicines during Category II treatment is uncertain), patients may fail Category II treatment for reasons other than DR-TB.
- **Close contacts of DR-TB cases who develop active TB disease**. Close contacts of DR-TB patients who develop active TB disease can be enrolled for treatment with Category IV regimens. (See Chapter 14 for more detail on the management of contacts of DR-TB patients.)
- **Category I failures**. Since the prevalence of DR-TB in this group of patients may vary greatly (*4*–*8*), the rate in this group must be document-

ed before deciding whether enrolment in DR-TB control programmes can take place without DST. Programmes should conduct DRS surveys is this group to determine whether the routine use of Category II regimens provides an adequate re-treatment regimen for patients in whom Category I treatment failed (also see Chapter 7, Table 7.2).

The rate of DR-TB in these three groups can vary. These guidelines strongly recommend confirming treatment failure by culture and testing for DR-TB through the use of DST to at least isoniazid and rifampicin for all patients who start a Category IV regimen following this strategy. All programmes should therefore have capacity for DST of at least isoniazid and rifampicin.

5.5 DST specimen collection

If DST is chosen as part of the case-finding strategy, it is recommended that two sputum specimens be obtained for culture and that DST be performed with the specimen that produces the best culture. DST does not routinely need to be carried out in duplicate. Procedures for collecting and managing specimens for culture and DST are described in Chapter 6, which also addresses different techniques, limitations, quality assurance requirements and other issues of culture and DST.

Previously treated patients may have had DST in the past but it may no longer reflect the resistance pattern of the strain they had at the time of enrolment in the DR-TB control programme. Programmes that base treatment on DST (see Chapter 7) should repeat DST in all patients who have received treatment since the collection of their previous DST specimen.

5.6 Case-finding in paediatric patients

Paediatric cases require adjustments in diagnostic criteria and indications for treatment. Younger children in particular may not be able to produce sputum specimens on demand. Programmes should not exclude children from treatment solely because sputum specimens are not available; smear- and culture-negative children with active TB who are close contacts of patients with DR-TB can be started on Category IV regimens (see Chapter 9, section 9.5 and Chapter 14, section 14.4).

5.7 Case-finding in HIV-infected patients

Cases of HIV infection also require adjustment in diagnostic criteria and indications for treatment. The diagnosis of TB in HIV-infected people is more difficult and may be confused with other pulmonary or systemic infections. People living with HIV are more likely to have smear-negative TB or extrapulmonary TB. These and other WHO guidelines (*10*) recommend the use of clinical algorithms that include the use of chest X-ray and culture to improve the ability to diagnose TB in smear-negative patients living with HIV. Because unrecognized MDR- and XDR-TB are associated with such high mortality

in these patients, many programmes perform culture and DST testing for all patients living with HIV and with active TB. Programmes without facilities or resources to screen all patients living with HIV for DR-TB should put significant efforts into obtaining them, especially if DR-TB rates are moderate or high. Some programmes may adopt a strategy of targeted DST for patients with increased risk of DR-TB or low CD4 count (See Chapter 10, Section 10.4). Rapid diagnostic techniques for people living with HIV with active TB can be very useful to promptly identify those with DR-TB (see section 5.9). If XDR-TB is prevalent, people living with HIV who have MDR-TB should be screened for XDR-TB with the use of liquid media or another validated rapid technique for DST of second-line injectable agents and a fluoroquinolone (see Section 5.9). In some cases (as described in Chapters 7 and 10), smear-negative patients may need to be enrolled empirically into Category IV regimens.

5.8 Case-finding of patients with mono- and poly-drug resistance

Mono- and poly-drug resistant strains are strains that are resistant to antituberculosis drugs but not to both isoniazid and rifampicin. Most diagnostic strategies used by DR-TB control programmes will also identify cases of mono- and poly-drug resistance, in addition to MDR-TB cases. Patients with mono- or poly-drug resistance may require modifications to their SCC regimens or to be moved to Category IV regimens (see Chapter 8).

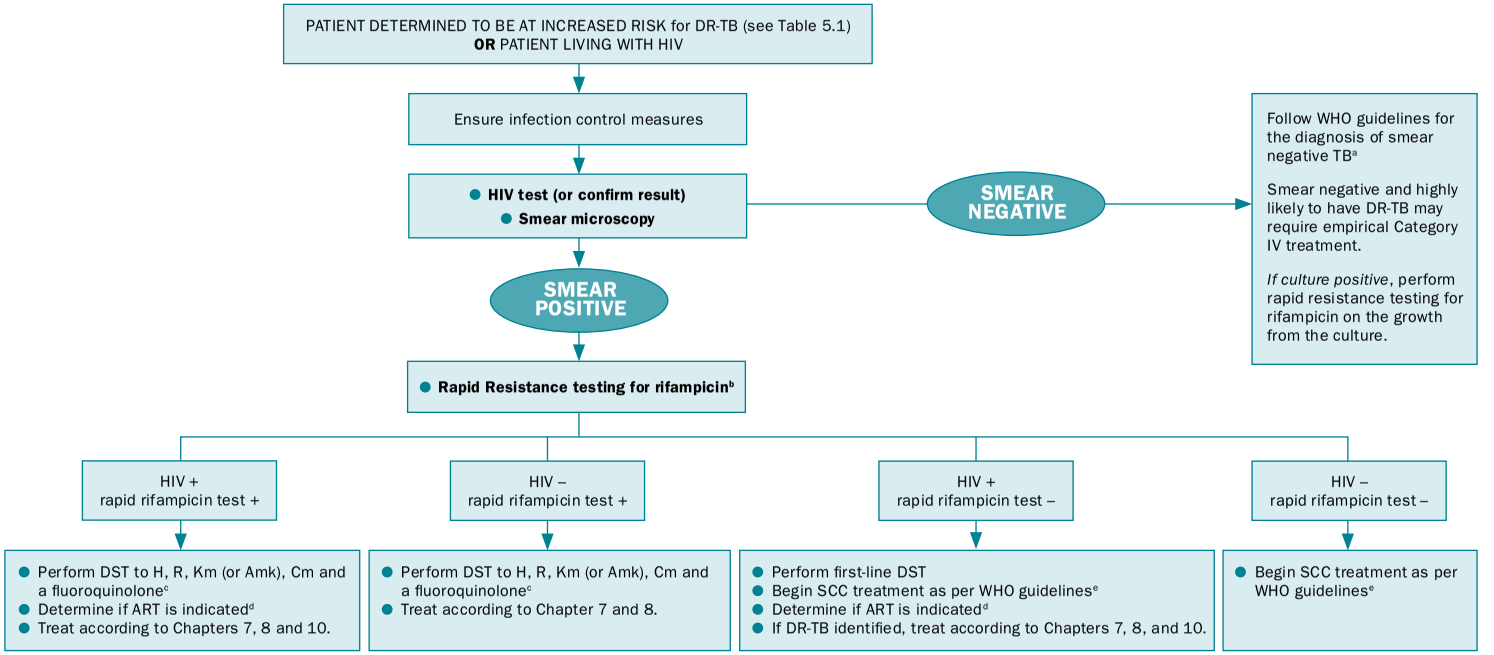
5.9 Use of rapid drug-resistance testing

Case-finding strategies can be greatly enhanced with rapid drug-resistance testing, which significantly improves the ability to identify earlier cases of DR-TB that can be isolated and started on treatment.

Rifampicin is the most potent antituberculosis drug of the first-line regimen, and rifampicin resistance most commonly occurs with concomitant isoniazid resistance. A positive rapid test for rifampicin resitance is a strong indicator that a patient may have MDR-TB (*11*, *12*), while a negative test makes a final diagnosis of MDR-TB highly unlikely.

Figure 5.1 is a suggested algorithm on the use of rapid drug-sensitivity testing for identification and initial management of patients suspected of TB who are at increased risk of DR-TB. It is based upon the important considerations outlined in this chapter regarding risk factors and case-finding strategies and is applicable to situations of both high and low HIV prevalence. The algorithm relies on determining the risk of drug resistance and involves HIV testing of all TB suspects, sputum smear microscopy and results from rapid sensitivity testing for at least rifampicin. It also includes the indications for the use of empirical treatment regimens for DR-TB while awaiting more complete DST results.

Figure 5.1 Algorithm for the use of rapid drug-resistance testing



[a] *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/2007.01).
[b] Where rapid rifampicin testing is not available, the algorithm can be followed using liquid methods.
[c] Because of the high and quick possibility of death with XDR-TB in HIV-infected individuals, liquid media and other validated rapid techniques for DST of first- and second-line drugs (H, R, Km (or Amk), Cm and a fluoroquinolone) are recommended for HIV-infected individuals with risk factors for XDR-TB.
[d] *Antiretroviral Therapy for HIV Infection in Adults and Adolescents*. 2006 revision WHO, Geneva, 2004
[e] *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003.313).

BOX 5.1 COUNTRY EXAMPLES OF CASE-FINDING STRATEGIES

Example 1. Country A has an MDR-TB prevalence of 8% in new TB cases (patients who have received no or less than one month of antituberculosis therapy). The country has quality-assured DST laboratories for the first-line antituberculosis drugs. The national TB control programme has decided their programme has the capacity and resources to do DST in all new patients. Patients identified with resistance will enter Category IV (options on how to design Category IV regimens and whether to do further DST testing are discussed in Chapters 7 and 8).

Example 2. Country B has an MDR-TB incidence of 3% in new cases, and there has been minimal use of second-line drugs for the treatment of TB. The country has a very high incidence of TB, exceeding 350 new cases per 100 000 people per year. It has access to quality-assured DST laboratories for first-line drugs but not the capacity or resources to conduct DST for every TB case. The national TB control programme has decided to test all failures, relapses and returns after default for resistance to HRES. In addition it will apply a rapid rifampicin test to all patients living with HIV and follow the algorithm in Figure 5.1. A standardized Category IV regimen is designed for all patients with DR-TB (options on how to design Category IV regimens and whether to do further DST testing are discussed in Chapters 7 and 8).

Example 3. Country C has fairly good access to DST and resources to do testing. Rates of MDR-TB in new cases without history of previous antituberculosis treatment are low at 1.2%. Country C chooses to do DST to H,R, E, S, Km, Cm, and Ofx for any patient who remains sputum smear-positive after month 2 of SCC and for all HIV-infected patients at the start of SCC. When DST results return, regimens are adjusted if resistance is found.

Example 4. Country D has high rates of HIV, TB, MDR-TB and XDR-TB. The country decides to quickly develop rapid molecular testing for rifampicin resistance and rapid liquid testing for H, R, Km, Cm and FQ. All patients with a positive smear get a rapid rifampicin test and all smear-negative TB suspects with HIV are worked-up with chest x-rays and culture. If culture is positive a rapid rifampicin test is performed. All positive rifampicin tests get DST to H, R, Km, Cm and FQ. Treatment is according to Chapters 7, 8 and 10.

Administrative infection control measures including isolation should start as soon as a patient is identified as a TB suspect. Rapid testing can identify DR-TB quickly and allows patients to be taken off general TB wards where they may infect others with resistant strains. (See Chapter 15 for more information about infection control and HIV.)

5.10 Use of second-line DST in case-finding and diagnosing XDR-TB

Not all DR-TB control programmes have the capacity to perform DST of second-line drugs. These guidelines recommend that all programmes develop the ability to do DST to isoniazid and rifampicin and, when proficient at those, to develop the ability to test the second-line injectable agents (kan-

amycin, amikacin and capreomycin) and a fluoroquinolone. This will enable programmes to perform case-finding for XDR-TB and to assure proper treatment.

The two strongest risk factors for XDR-TB are:

(i) Failure of an anti-TB regimen that contains second-line drugs including an injectable agent and a fluoroquinolone.

(ii) 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 suspects of XDR-TB should have DST of isoniazid and rifampicin, the second-line injectable agents and a fluoroquinolone. For people living with HIV who are at risk of XDR-TB, given the high and rapid risk of death with coinfection, liquid or other validated rapid techniques for DST of first- and second-line drugs is recommended.

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CHAPTER 6

Laboratory aspects

6.1 Background

A definitive diagnosis of DR-TB requires that *M. tuberculosis* be isolated on culture, identified and DST completed. Major challenges remain around the capacity of laboratories to meet the demand for scaling-up DR-TB treatment programmes within the context of routine TB control. Laboratory constraints relate to infrastructure, equipment, quality assurance and biosafety. Compounded by an urgent need for reliable and reproducible methodologies – especially for second-line DST – rational use of culture and DST in treatment programmes is therefore imperative.

6.2 Chapter objectives

This chapter describes standards for laboratory services needed to diagnose and treat DR-TB in the context of existing laboratory capacity and technological constraints.

Key recommendations (* indicates updated recommendation)

- All patients suspected of DR-TB need access to laboratory services for adequate and timely diagnosis of DR-TB;
- Laboratories should develop proficiency to isoniazid and rifampicin as a minimum and then consider DST of other drugs (Figure 6.1);*
- Laboratories should develop DST of the fluoroquinolones and second-line injectable agents where adequate capacity and expertise exist;*
- DR-TB strains can be transported safely across international borders if international procedures and guidelines are followed (section 6.6);*
- Laboratories should follow all standardized protocols for infection control and biosafety;
- Quality control and quality assurance should be in place for microscopy, culture and DST. Links with supranational TB reference laboratories are strongly encouraged.

6.3 General definitions for the laboratory and DST

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

- **Critical drug concentration.** The lowest concentration of drug that will inhibit 95% (90% for pyrazinamide) of wild strains of *M. tuberculosis* that have never been exposed to drugs, while at the same time not inhibiting clinical strains of *M. tuberculosis* that are considered to be resistant (e.g. from patients who are not responding to therapy).
- **Minimum inhibitory drug concentration.** The lowest concentration of drug that will inhibit growth of the *M. tuberculosis* isolate in vitro.
- **Reproducibility.** The ability of a test or experiment to be accurately reproduced, or replicated, under independent conditions. Reproducibility relates to the agreement of test results across different laboratories and laboratory technicians or technologists.
- **Reliability.** The extent to which a test result remains consistent when repeated under identical conditions. Reliability does not imply validity. A reliable test generates a consistent result that may not necessarily be accurate, e.g. clinical efficacy may not be accurately predicted, even if a test is highly reliable.
- **Cross-resistance.** Resistance mutations to one antituberculosis drug may confer resistance to some or all of the members of the drug family and, less commonly, to members of different drug families.

6.4 General considerations

Procedures for microscopy, culture and DST of first-line antituberculosis drugs have been standardized internationally and are well described in the literature, with consensus on methodologies, critical drug concentrations, and reliability and reproducibility of testing.

On the other hand, surveys on practices for second-line DST in specialized laboratories and a few multi-centre laboratory studies have revealed important methodological differences. No studies have systematically evaluated all available DST methods for all available second-line drugs, established critical concentrations for all available second-line drugs, or evaluated a large number of clinical isolates for microbiological and clinical end-points. Most importantly, the correlation of in vitro DST results with clinical outcome has not been established, and the prognostic value of in vitro resistance to second-line antituberculosis drugs is therefore not known.

Given the urgent need for expansion of laboratory services in support of DR-TB control programmes, WHO recently issued new policies on the expanded use of liquid culture and interim policy guidance on second-line DST, outlining the current evidence for reliability and reproducibility of DST methods, consensus agreement on critical drug concentrations to define resistance and providing recommendations for rational use of DST under programmatic conditions (*1*).

This chapter builds on existing laboratory standards outlined in guidelines published by WHO (*2*, *3*) and the IUATLD (*4*) on laboratory services for TB control, incorporating key points from new WHO policies on the use of liquid culture (*5*) and second-line DST (*1*). The latter constitutes current international consensus and has gone through extensive external review by laboratory experts, members of the GLC, members of the SRL network, members of the WHO Stop TB Partnership Working Group on MDR-TB, and members of the WHO Stop TB Partnership Global Laboratory Initiative.

6.5 Essential laboratory services and infrastructure

Optimal management of DR-TB requires both mycobacterial and clinical laboratory services. At a minimum, the mycobacteriology laboratory service should provide culture, confirmation of *M. tuberculosis* and DST of isoniazid and rifampicin. Clinical laboratory services should provide basic haematology, biochemistry, serology and urine analysis, required for the adequate evaluation and monitoring of patients (see Chapter 11).

In addition to diagnostic services, laboratories supporting DR-TB control programmes have a critical role in surveillance of prevailing drug resistance patterns and trends. Surveillance of antituberculosis drug resistance is essential for providing information on the magnitude of and trends in drug resistance, for developing appropriate treatment modalities and for evaluating the impact of control programme interventions.

Adequate allocation of resources (human and financial) to laboratory services is essential to ensure availability of sufficient, adequately qualified and trained laboratory staff and a safe and functioning laboratory infrastructure with appropriate and well-maintained equipment and sufficient laboratory consumables.

DR-TB control programmes should have a rapid, reliable and safe means of collecting and transferring specimens, cultures and information from the patient and physician to appropriate levels of the laboratory service, and for returning the results. Specimens from patients suspected of having DR-TB as well as cultures of *M. tuberculosis* pose a significant public health risk if not properly transported. Cultures in particular constitute enriched infectious material containing large numbers of viable organisms, and the risk is compounded when cultures of resistant strains are transported. Details on transport of infectious substances are given in section 6.6.

Transmission of TB – including MDR-TB and XDR-TB – is a well-recognized risk for laboratory workers (*6*, *7*). *M. tuberculosis* is classified as a Risk Group 3 laboratory pathogen by WHO, requiring specific laboratory containment measures (see section 6.10) (*7*). Adequately equipped laboratory services to ensure safe handling of drug-resistant strains, especially during aerosol-producing procedures such as mycobacterial culture and DST, are therefore paramount. Appropriate engineering controls, maintenance of essential laboratory safety equipment, and laboratory staff training are equally important.

Comprehensive systems for managing the quality of laboratory services are mandatory, including internal quality control and external quality assurance.

6.6 Organization of the laboratory network

Conventional TB laboratory networks have a pyramidal structure based on an appropriately large number of peripheral (Level I) laboratories accessible to all TB suspects and patients, a moderate number of intermediate (Level II) laboratories located in mid-sized population centres and health facilities, and a single (or more than one in large countries) central (Level III) laboratories at the provincial, state or national levels. This chapter concentrates on the activities of Level III laboratories as outlined in Table 6.1; the organization and operation of Level I and II laboratories are well described in other publications (*3*, *4*).

Since 1994, the network of SRLs has been instrumental in supporting drug resistance surveys in all regions of the world, providing quality assurance through proficiency testing and validation of DST data. The SRL network is being expanded to meet the challenges of scaling up the response to DR-TB. Central reference laboratories supporting DR-TB control programmes should establish formal links with one of the SRLs to ensure adequate expert input on infrastructure development, budgeting and training. A sustained link with an

TABLE 6.1 **Functions and responsibilities of the different levels of laboratory services**

LEVEL I

The peripheral (often district) laboratory

- Receipt of specimens
- Preparation and staining of smears
- Ziehl-Neelsen microscopy and recording of results
- Dispatch of results
- Maintenance of laboratory register
- Cleaning and maintenance of equipment
- Management of reagents and laboratory supplies
- Internal quality control

LEVEL II

The intermediate (often regional) laboratory

- All the functions of a Level I laboratory
- Fluorescence microscopy (optional)
- Digestion and decontamination of specimens
- Culture and identification of *M. tuberculosis*
- Training of microscopists
- Support to and supervision of peripheral-level staff with respect to microscopy
- Preparation and distribution of reagents for microscopy in peripheral laboratories
- Quality improvement and proficiency testing of microscopy at peripheral laboratories

LEVEL III

The central (often national) laboratory

- All the functions of Level I and II laboratories
- DST of *M. tuberculosis* isolates
- Identification of mycobacteria other than *M. tuberculosis*
- 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 and on quality assurance
- Close collaboration with the central level of the national TB control programme
- Supervision of intermediate laboratories regarding bacteriological methods and their support (particularly training and supervision) to the peripheral laboratories
- Quality assurance of microscopy and culture performed at intermediate laboratories
- Training of intermediate-level laboratory staff
- Organization of antituberculosis drug resistance surveillance
- Operational and applied research relating to the laboratory network, coordinated with the requirements and needs of national TB control programmes

SRL is also strongly recommended for DR-TB control programmes in order to maintain external quality assurance and validation of DST results, as outlined below. Documented first-line DST proficiency of central laboratories, preferably by one of the SRLs, is a prerequisite for applications by DR-TB control programme to the GLC.

Implementation of laboratory services for culture and DST requires a reasonable balance between cost and turnaround time. Such services are most likely to be economically affordable and provide optimal results if based on direct delivery of specimens to a central mycobacteriology laboratory that has large enough operational volume to ensure technical proficiency, has well-trained personnel and is properly equipped.

DST of isoniazid and rifampicin is needed as a minimum in any DR-TB control programme; DST of other first-line antituberculosis drugs is also desirable, although less essential. In the initial phase of treatment for DR-TB, DST of second-line drugs is best left to supranational or other TB reference laboratories with documented capacity, expertise and proficiency. Once DST of first-line drugs operates at a consistently high level of proficiency, laboratories serving populations and patients with significant previous exposure to second-line drugs may consider extending their services to DST of second-line drugs (see section 6.7).

Routine DST of second-line drugs is not recommended unless the required laboratory infrastructure and capacity have been established, rigorous quality assurance is in place and sustainable proficiency has been demonstrated to isoniazid and rifampicin.

6.7 Transport of infectious substances

Given the risks associated with transport of specimens and/or cultures from patients suspected of having DR-TB, programmes should ensure appropriate systems for safe packaging and transportation of infectious materials.

International organizations such as the Universal Postal Union, the International Civil Aviation Organization and the International Air Transport Association have developed strict guidelines and procedures to facilitate the safe and expeditious shipment of infectious substances (*8*, *9*).

Exchange of *M. tuberculosis* cultures between countries (e.g. for diagnostic DST, retesting or proficiency testing) is always subject to international regulations, including national import and export regulations specific to individual countries.

6.8 Microscopy, culture and identification of *M. tuberculosis* in DR-TB control programmes

Detailed information on sputum smear examination and culture can be found in the WHO manuals *Laboratory Services in Tuberculosis Control, Parts I, II and III* (*2*).

6.8.1 Microscopy

Microscopy for acid-fast bacilli (AFB) cannot distinguish viable from non-viable organisms, nor differentiate between drug-susceptible and drug-resistant *M. tuberculosis* or between different species of mycobacteria. The main uses of microscopy for DR-TB are therefore limited to assessing the initial infectiousness of patients, triaging specimens to different algorithms for culture and DST, and confirming that organisms growing on (or in) culture media are mycobacteria rather than contaminants.

As AFB sputum smear microscopy is unable to distinguish between viable and non-viable bacilli, its utility for monitoring patient infectiousness and

response to treatment is also limited. For example, even with adequate treatment, specimens from DR-TB patients may remain sputum smear-positive after they become culture-negative, suggesting that the bacilli are non-viable. (Caution is nonetheless recommended for patients who are sputum smear-positive and culture-negative; they should be considered as possibly infectious and evaluated for progression of active disease.)

6.8.2 Culture

Quality of laboratory processing is of crucial importance. Delays in specimen transport, excessively harsh or insufficient decontamination, poor-quality culture media or incorrect incubation temperature can adversely affect the culture yield. Laboratory errors, such as mislabelling or cross-contamination between specimens during aerosol-producing procedures, may lead to false-negative or false-positive results. In this context, laboratory findings should always be correlated with the patient's clinical condition and any diagnostic test should be repeated if necessary. Low positive culture results on solid medium (<10 colonies) are not well correlated with clinical prognosis and should be interpreted with caution, especially if a single culture with low colony counts is reported. However, persistent positive cultures or any positive culture in the setting of clinical deterioration should be regarded as significant.

The pros and cons of different culture media and techniques are discussed in other published references (*3*, *4*).

6.8.3 Identification of *M. tuberculosis*

In countries with a high burden of TB, the vast majority of mycobacterial isolates will be *M. tuberculosis*. The prevalence of non-tuberculous mycobacteria (NTM) varies from country to country and can be more common in patients living with HIV. Unless the species is confirmed as *M. tuberculosis*, mycobacterial isolates appearing phenotypically resistant to first-line drugs may represent infection with NTM and not DR-TB. Treatment of NTM is entirely different from treatment of DR-TB. As a minimum, laboratories supporting DR-TB control programmes should be able to identify *M. tuberculosis* by conventional biochemical identification tests or at least two other methods that follow international guidelines.

6.8.4 Drug susceptibility testing

Identification and treatment of patients with, or at high risk of, DR-TB can be based on a range of strategies (see Chapter 5 and 7). In vitro DST plays a key role in all of these strategies, under a rational and systematic approach to implementation of the required laboratory infrastructure (see section 6.8). These guidelines strongly recommend that NTPs develop the capacity to provide access to DST for any patient in whom resistance is considered likely. This recommendation is consistent with international standards for TB care

endorsed by WHO and other partners (*10*) and resolutions on TB endorsed by the World Health Assembly in 2007 calling for universal access to DST by 2015 (*11*).

A number of different techniques are available for DST. Classic phenotypic methods involve culturing of *M. tuberculosis* in the presence of antituberculosis drugs to detect inhibition of growth. Phenotypic methods allow the detection of drug resistance regardless of mechanism or molecular basis. Phenotypic DST methods can be performed as direct or indirect tests on solid media. In the direct test, a set of drug-containing and drug-free media is inoculated directly with a concentrated specimen. An indirect test involves inoculation with a pure culture grown from the specimen. Indirect phenotypic tests have been extensively validated and are currently regarded as the gold standard. Three methods are commonly used: proportion, absolute concentration, and resistance ratio. Several rounds of proficiency testing in the SRL network have shown that DST results do not differ between the three methods for first-line antituberculosis drugs. For second-line DST, broth or liquid methods and the proportion method on solid medium have been studied; methods for the absolute concentration or resistance ratio on solid medium have not been validated. The current status of DST methodology, consensus on reliability and reproducibility, and critical concentrations for different methodologies can be found in a WHO policy guidance document on rational use of second-line DST (*1*).

Genotypic approaches detect the genetic determinants of resistance rather than the resistance phenotype. Most genotypic methods involve two steps: first, a molecular nucleic amplification method such as polymerase chain reaction is used to amplify sections of the *M. tuberculosis* genome known to be altered in resistant strains. In the second step, amplification products (amplicons) are assessed for specific mutations correlated with resistance.

Novel technologies for rapid detection of drug resistance are under development. Most are in early development phase, undergoing laboratory validation or in early stages of large-scale field studies to assess their feasibility, cost effectiveness and cost benefit. Technologies focused on rapid rifampicin resistance testing as a proxy for MDR-TB testing are most advanced. In the majority of settings, particularly where fixed-dose combination (FDC) first-line antituberculosis drugs are used, resistance to rifampicin is almost invariably associated with resistance to isoniazid. Detection of rifampicin resistance therefore serves as a reliable (although not complete) proxy for MDR-TB. The advantages of rapid rifampicin testing include earlier identification of patients on inappropriate first-line regimens, prompt screening of patients at risk of MDR-TB and early interruption of MDR-TB transmission.

Several tests for rapid detection of rifampicin resistance have been validated in laboratory-based studies. The use of rapid rifampicin resistance testing is recommended in high-risk MDR-TB settings (including high-burden

HIV settings); however, confirmation of MDR-TB by conventional DST is still regarded as the gold standard, and adequate laboratory capacity to ensure a quality-assured diagnosis of MDR-TB therefore remains a fundamental requirement. Chapter 5 provided an algorithmic approach to using rapid rifampicin tests in the setting of high HIV prevalence.

No rapid molecular tests for detection of XDR-TB are currently available; as a result, conventional and the newer liquid DST techniques are considered the most reliable methods for determining XDR-TB. Some of the newer liquid and agar techniques can determine the presence of XDR-TB within 14 days.

6.8.5 Limitations of DST

The accuracy of DST (performed under optimal circumstances) varies with the drug tested: for the first-line antituberculosis drugs, DST is most accurate for rifampicin and isoniazid; it is less reliable and reproducible for streptomycin, ethambutol and pyrazinamide (*1*).

Testing of in vitro susceptibility of second-line antituberculosis drugs is much more problematic, as outlined in WHO policy guidance on second-line DST (*1*): aminoglycosides, polypeptides and fluoroquinolones have been tested in different laboratory environments and shown to have relatively good reliability and reproducibility. Data on the reproducibility and reliability of DST for the other second-line drugs are much more limited, have not been established or the methodology for testing does not exist (*1*).

Susceptibility testing of second-line drugs is hampered by technical difficulties due to in vitro drug instability, drug loss due to protein binding, heat inactivation, incomplete dissolution, filter sterilization and/or varying drug potency. Moreover, the critical concentration defining resistance is often very close to the minimal inhibitory concentration (MIC) required to achieve antimycobacterial activity, increasing the probability for misclassification of susceptibility or resistance and leading to poor reproducibility of DST results. In addition, laboratory technique, medium pH, incubation temperature and incubation time may also affect DST results.

Cross-resistance and a lack of understanding of the molecular mechanisms underlying TB drug resistance further compound the problem. Emerging evidence shows a clear association between phenotypic drug resistance and specific molecular mutations; however, not all mutations conferring resistance to second-line drugs have been described, nor have the underlying molecular mechanisms for the detected mutations been elucidated.

Cross-resistance between the later- generation fluoroquinolones (ciprofloxacin and ofloxacin) is almost complete. Limited evidence suggests that the third-generation fluoroquinolones (notably moxifloxacin) do not have complete cross-resistance with the older generations (*12–15*) and may have enhanced clinical benefit due to their low MICs, enhanced antimycobacterial activity, and improved biochemical structure providing metabolic stabil-

ity and long half-life, theoretically reducing the selection of resistant mutants (*16*). While the clinical benefit of newer-generation fluoroquinolones has been validated in one small retrospective study (*17*), more clinical and laboratory research is needed to understand the extent of fluoroquinolone cross-resistance and its clinical relevance.

Cross-resistance between the aminoglycosides and/or the polypeptides is complex and data are very limited. The aminoglycosides kanamycin and amikacin have very high cross-resistance. Cross-resistance between other aminoglycoside and polypeptides appears relatively low, but more studies are needed (*1*).

6.9 Rational use of DST in DR-TB control programmes

Complex, incomplete and even contradictory information on cross-resistance, limited knowledge of the genotypes conferring resistance in second-line drugs and the technical limitations of second-line DST have important implications for laboratory infrastructure and design of treatment modalities in DR-TB control programmes. Proficiency in DST is a combination of laboratory technique and workload, requiring adequate numbers of specimens to be tested. In most settings, this implies centralization of laboratory services for DST and – particularly for DR-TB programmes with small numbers of patients – consideration towards outsourcing such DST services, for example, to one of the laboratories in the SRL network.

Current WHO policy guidance on DST is as follows (*1*):

- Laboratory capacity to reliably detect MDR-TB through quality-assured DST of isoniazid and rifampicin resistance is a minimum prerequisite for DR-TB control programmes.
- Formal links with one of the laboratories in the SRL network are preferable to ensure adequate expert input on laboratory design, specimen and process flow, biosafety, maintenance of equipment and external quality assurance of DST result.
- Strategies for laboratory services in support of DR-TB control programmes should follow a systematic approach and take into account the constraints of DST outlined above. DST should be focused on those drugs for which a reliable and reproducible methodology is available.
- Routine DST of second-line drugs is not recommended unless the required laboratory infrastructure and capacity have been established, rigorous quality assurance is in place and sustainable proficiency has been demonstrated for isoniazid and rifampicin. In order to retain proficiency and expertise, it is recommended that second-line DST only be performed if at least 200 specimens from high-risk patients are expected per year.

- At this time, routine DST of drugs in groups 4 (ethionamide, protionamide, cycloserine, terizidone, *p*-aminosalicylic acid) and 5 drugs (clofazimine, linezolid, amoxicillin–clavulanate, thioacetazone, clarithromycin, imipenem) is not recommended as reliability and reproducibility of laboratory testing cannot be guaranteed.

Figure 6.1 provides an outline for systematic DST of first- and second-line antituberculosis drugs under routine programmatic conditions.

6.10 Time for testing and reporting: turnaround time

Growth detection and identification of *M. tuberculosis* may take 3–8 weeks on solid media and 1–2 weeks in broth media. DST of an *M. tuberculosis* isolate takes an additional 2–4 weeks in solid media and 1 week in broth media. To ensure rapid diagnosis of *M. tuberculosis* and DR-TB, laboratories should define standard turnaround times, which should be strictly followed.

6.11 Infection control and biosafety in the laboratory

The relative hazards of infective microorganisms handled in the laboratory are 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 (*7*). Related biosafety levels for laboratories have been defined, taking into account the pathogenic agent, the facilities available, and the equipment, practices and procedures required to ensure a safe laboratory working environment (*7*).

M. tuberculosis is classified by WHO as a Risk Group 3 laboratory pathogen (*7*). Mycobacteriological culture and DST generate high-concentration aerosols requiring biosafety level 3 containment precautions.

Laboratory standards require the following essential measures to be in place and enforced:

- appropriate and specific administrative controls (including good laboratory practice, standard operating procedures and accident management plans);
- appropriate engineering controls functioning adequately as designed;
- personal protective equipment appropriate for the tasks being performed;
- proper waste management procedures;
- proper procedures for general laboratory safety (including physical, electrical and chemical safety).

Biosafety level 3 containment requires 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. Published guidelines on biosafety level 3 precautions should be rigorously followed and expert engineering consultation sought when establishing laboratory infrastructure for DST (*1*, *7*).

Figure 6.1 Systematic approach to implementation of DST under routine programmatic conditions (*1*)

Step 1: isoniazid rifampicin	High proficiency in DST of isoniazid and rifampicin should first be established as DST of these drugs is the most reliable and reproducible. As a minimum performance indicator, proficiency testing should correctly identify resistance to isoniazid and rifampicin in more than 90% in two out of three recent rounds of proficiency testing.
Step 2: ethambutol streptomycin pyrazinamide	Steps 1 and 2 may be merged if indicated by epidemiological considerations and/or treatment modalities (e.g. standardized or individualized MDR-TB regimens still involving fist-line drugs) and if resources allow extended DST capacity.
Step 3: amikacin, kanamycin, capreomycin ofloxacin[a] (or fluoroquinolone of choice in treatment strategy)	Steps 1 and 3 may be merged in settings where XDR is a concern in order 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 all aminoglycosides (including streptomycin) as well as capreomycin be tested for resistance where possible. Selection of the most appropriate fluoroquinolone for use is based on treatment strategy.[a]

[a] Strains should be tested for resistance to the fluoroquinolone(s) used in a programme's treatment strategy. Because cross-resistance is not complete between older-generation and newer-generation fluoroquinolones. it cannot be assumed that resistance to one confers resistance to all fluoroquinolones.

Health and medical surveillance of laboratory personnel involved in mycobacteriological culture and DST are strongly recommended. Surveillance should include a detailed medical history, targeted baseline health assessment, monitoring of respiratory signs and symptoms, and a proactive plan for appropriate medical investigations when indicated.

Laboratory workers who choose to disclose that they are living with HIV, should be offered safer work responsibilities and should be discouraged from working with DR-TB specimens. Pregnant women should be reassigned until after childbirth and lactation.

Routine BCG vaccination is not recommended as a means of preventing DR-TB in laboratory workers. The use of infection control measures is discussed in more detail in Chapter 15.

6.12 Quality control and quality assurance

A diagnosis of DR-TB has profound implications for the individual patient; therefore, accuracy of the laboratory diagnosis is crucial, and a comprehensive laboratory quality assurance programme must be in place to ensure the accuracy, reliability and reproducibility of DST results. Quality control or quality assurance procedures should be performed regularly as an integral part of laboratory operations.

Procedures for quality assurance of microscopy, culture and DST are described in detail in laboratory manuals and technical documents.

Central reference laboratories involved in DR-TB control programmes should establish formal links with one of the laboratories in the SRL network to help ensure the quality of laboratory services and the validation of DST results. The SRL network consists – at the time of press – of 26 laboratories, including a global coordinating centre in Belgium.

The SRL network ensures DST standards by a system of external quality assurance that should preferably be established before the implementation of DR-TB control programmes. As a minimum, external quality assurance with an SRL should comprise:

- an initial assessment visit;
- proficiency testing with an adequate number of coded isolates;
- periodic rechecking of isolates obtained within the DR-TB control programme.

Proficiency testing by the SRL involves regular distribution to national TB reference laboratories of panels of coded *M. tuberculosis* strains with predefined drug resistance profiles. The test results by the reference laboratory are compared with the coded SRL results in blinded fashion and specific performance indicators (sensitivity, specificity, reproducibility) calculated for each drug and for the reference laboratory as a whole.

As a minimum performance indicator, proficiency testing should correctly identify resistance to isoniazid and rifampicin in more than 90% in two out of three recent rounds of panels.

The SRL network is in agreement that panels for second-line proficiency testing should not include XDR strains of *M. tuberculosis*; rather, panels with different permutations of mono-resistance to second-line drugs are currently being developed, which will be compiled to allow reliable assessment of the overall capability of national reference laboratories to identify XDR-TB. Panels including isolates with second-line drug resistance will be made available through the SRL network in 2008.

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CHAPTER 7

Treatment strategies for MDR-TB and XDR-TB

7.1 Chapter objectives

Any patient with chronic or DR-TB requiring treatment with second-line drugs falls under WHO diagnostic category IV and will require specialized regimens (termed "Category IV regimens" in these guidelines). This chapter provides guidance on the strategy options, including standardized, empirical and individualized approaches, to treat MDR-TB as well as the more highly resistant strains such as XDR-TB. In the absence of large-scale randomized clinical trials, these recommendations are largely based on expert opinion and results of cohort and case series analyses. For a complete description and weight-based dosing of drugs used in these guidelines, see Annexes 1 and 2.

Key recommendations (* indicates updated recommendation)

- Design treatment regimens with a consistent approach based on the hierarchy of the five groups of antituberculosis drugs;
- Promptly diagnose DR-TB and initiate appropriate therapy;
- Use at least four drugs with either certain, or almost certain, effectiveness;
- DST should generally be used to guide therapy; however do not depend on DST in individual regimen design for ethambutol, pyrazinamide, and Group 4 and 5 drugs;
- Do not use ciprofloxacin as an antituberculosis agent;*
- Design a programme strategy that takes into consideration access to high-quality DST, rates of DR-TB, HIV prevalence, technical capacity and financial resources (Table 7.2);
- Treat for 18 months past culture conversion;
- Use adjunctive measures appropriately, including surgery and nutritional and social support;
- Aggressively treat XDR-TB whenever possible;
- Treat adverse effects immediately and adequately.

7.2 Essential assessments before designing a treatment strategy

Programmes should design a treatment strategy when both the DRS data and the frequency of use of antituberculosis drugs in the country have been assessed. Programmes that plan to introduce a treatment strategy for DR-TB should be familiar with the prevalence of drug resistance in new patients as well as in different groups of re-treatment cases (failures, relapse, return after default, and chronic cases). It is essential to determine which, and with

what frequency, second-line antituberculosis drugs have been used in the area served by the DR-TB control programme. Some second-line antituberculosis drugs may have been used only rarely and will likely be effective in DR-TB regimens, while others may have been used extensively and therefore have a high probability of ineffectiveness in patients with resistant strains.

It is recognized that some programmes may have to design strategies based on limited data, as treatment for many patients cannot wait until the full assessment information has been obtained. 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 described in this section.

7.3 Definitions of terms used to describe treatment strategies

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

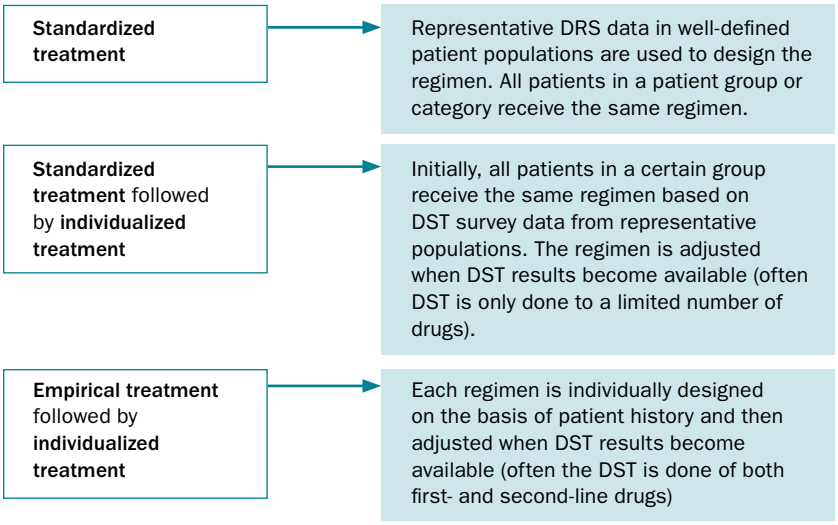
- **Standardized treatment.** DRS data from representative patient populations are used to base regimen design in the absence of individual DST. All patients in a defined group or category receive the same regimen. Suspected MDR-TB should be confirmed by DST whenever possible.
- **Empirical treatment.** Each regimen is individually designed based on the patient's previous history of antituberculosis treatment and with consideration of DRS data from the representative patient population. Commonly, an empirical regimen is adjusted when DST results on the individual patient become available.
- **Individualized treatment.** Each regimen is designed based on the patient's previous history of antituberculosis treatment and individual DST results.

Combinations of these treatment strategies are often used as illustrated in Figure 7.1. These strategies are discussed in more detail in section 7.8, which addresses using these strategies under programmatic conditions.

7.4 Classes of antituberculosis drugs

The classes of antituberculosis drugs have traditionally been divided into first- and second-line drugs, with isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin being the primary first-line drugs. These guidelines often refer to this classification but also use a group system based on efficacy, experience of use and drug class. These groups are referred to in the following sections and are very useful for the design of treatment regimens. The different groups are shown in Table 7.1. Not all drugs in the same group have the same efficacy or safety. For more information, see the individual descriptions of each group in this section and the drug information sheets provided for each individual drug in Annex 1.

Figure 7.1 Common treatment strategies for DR-TB



Group 1. Group 1 drugs, the most potent and best tolerated, should be used if there is good laboratory evidence and clinical history to suggest that a drug from this group is effective. If a Group 1 drug was used in a previous regimen that failed, its efficacy should be questioned even if the DST result suggests susceptibility. 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-generation rifamycins, such as rifabutin, have very high cross-resistance to rifampicin.

Group 2. All patients should receive a Group 2 injectable agent if susceptibility is documented or suspected. These guidelines suggest the use of kanamycin or amikacin as the first choice of an injectable agent, given the high rates of streptomycin resistance in DR-TB patients. In addition, both these agents are low cost, have less otoxicity than streptomycin and have been used extensively for the treatment of DR-TB throughout the world. Amikacin and kanamycin are considered to be very similar and have a high frequency of cross-resistance. 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 should be used.

Group 3. All patients should receive a Group 3 medication if the strain is susceptible or if the agent is thought to have efficacy. Ciprofloxacin is no longer recommended to treat drug-susceptible or drug-resistant TB (*1*). Currently, the most potent available fluoroquinolones in descending order based

TABLE 7.1 **Alternative method of grouping antituberculosis agents**

GROUPING	DRUGS
Group 1 – First-line oral agents	isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z); rifabutin (Rfb)[a]
Group 2 – Injectable agents	kanamycin (Km); amikacin (Am); capreomycin (Cm); streptomycin (S)
Group 3 Fluoroquinolones	moxifloxacin (Mfx); levofloxacin (Lfx); ofloxacin (Ofx)
Group 4 – Oral bacteriostatic second-line agents	ethionamide (Eto); protionamide (Pto); cycloserine (Cs); terizidone (Trd); *p*-aminosalicylic acid (PAS)
Group 5 – Agents with unclear efficacy (not recom mended by WHO for routine use in MDR-TB patients)	clofazimine (Cfz); linezolid (Lzd); amoxicillin/clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high-dose isoniazid (high-dose H);[b] clarithromycin (Clr)

[a] Rifabutin is not on the WHO List of Essential Medicines. It has been added here as it is used routinely in patients on protease inhibitors in many settings.
[b] High-dose H is defined as 16–20 mg/kg/day.

on in vitro activity and animal studies are: moxifloxacin = gatifloxacin > levofloxacin > ofloxacin (*2*, *3*). While ofloxacin is commonly used because of relatively lower cost, the later-generation fluoroquinolones, moxifloxacin and levofloxacin, are more effective and have similar adverse effect profiles (*1*, *4*). Furthermore, the later-generation fluoroquinolones may have some efficacy against ofloxacin-resistant strains (*5*). Although similar to moxifloxacin in its efficacy against TB, gatifloxacin is associated with serious cases of hypoglycaemia, hyperglycaemia and new-onset diabetes. If gatifloxacin is used, it should undergo close monitoring and follow-up; gatifloxacin has been removed from the markets of many countries. For this reason, it has not been placed in the tables throughout this guideline. While levofloxacin or moxifloxacin are considered to be more effective against *M. tuberculosis* than ofloxacin, based on animal and EBA data, levofloxacin is, for the time being, the fluoroquinolone of choice until more data confirm the long-term safety of moxifloxacin. In resource-constrained areas, ofloxacin is an acceptable choice for ofloxacin-susceptible DR-TB. Gatifloxacin should only be used when there is no other option of a later-generation fluoroquinolone and where close follow up can be assured. A later-generation fluoroquinolone is recommended for treatment of XDR-TB (see section 7.14), although there is inadequate evidence on whether this is an effective strategy. Because the data on long-term use of fluoroquinolones are limited, vigilance in monitoring is recommended for all fluoroquinolones (see Chapter 11).

Group 4. Group 4 medications are added based on estimated susceptibility, drug history, efficacy, side-effect profile and cost. Ethionamide or protiomamide is often added because of low cost; however, these drugs do have some

cross-resistance with isoniazid. If cost is not a constraint, PAS may be added first, given that the enteric-coated formulas are relatively well tolerated and it shares no cross-resistance to other agents. When two agents are needed, cycloserine is used often in conjunction with ethionamide or protionamide or PAS. Since the combination of ethionamide or protionamide and PAS often causes a high incidence of gastrointestinal adverse effects and hypothyroidism, these agents are usually used together only when three Group 4 agents are needed: ethionamide or protionamide, cycloserine and PAS. Terizidone contains two molecules of cycloserine. Terizidone is being used in some countries instead of cycloserine and is assumed tto be as efficacious; however, there are no direct studies comparing the two drugs, and terizidone is therefore not yet recommended by WHO. The approach of slowly escalating drug dosage is referred to as "drug ramping". The drugs in Group 4 may be started at a low dose and escalated over two weeks (for more on drug ramping, see section 7.7.3).

Group 5. Group 5 drugs are not recommended by WHO for routine use in DR-TB treatment because their contribution to the efficacy of multidrug regimens is unclear. Although they have demonstrated some activity in vitro or in animal models, there is little or no evidence of their efficacy in humans for the treatment of DR-TB. Most of these drugs are expensive, and in some cases require intravenous administration. However, they can be used in cases where adequate regimens are impossible to design with the medicines from Groups 1–4. They should be used in consultation with an expert in the treatment of DR-TB. If a situation requires the use of Group 5 drugs, these guidelines recommend using at least two drugs from the group, given the limited knowledge of efficacy. While thioacetazone is a drug with known efficacy against TB, it is placed in Group 5 because its role in DR-TB treatment is not well established. Thioacetazone has cross-resistance with some of the other antituberculosis agents (see Table 7.3) and overall is a weak bacteriostatic drug. Thioacetazone is not recommended in HIV-positive individuals (*6*) given the serious risk of adverse reaction that can result in Stevens-Johnson syndrome and death. People of Asian descent also have a higher incidence of Stevens-Johnson syndrome. Many experts feel that high-dose isoniazid can still be used in the presence of resistance to low concentrations of isoniazid (>1% of bacilli resistant to 0.2 µg/ml but susceptible to 1 µg/ml of isoniazid), whereas isoniazid is not recommended for high-dose resistance (>1% of bacilli resistant to 1 µg/ml of isoniazid) (7). One study from a low-resource setting where a standardized regimen is used (and DST of isoniazid at different concentrations is not available) suggests that routine inclusion of high-dose isoniazid (16–20 mg/kg/day) could improve outcomes (*8*).

There is well-known cross-resistance between some of the antibiotics used in treating TB. Cross-resistance between specific antituberculosis agents is summarized in Box 7.1.

7.5 Standard code for antituberculosis treatment regimens

There is a standard code for writing out antituberculosis regimens. Each drug has an abbreviation (shown in Table 7.1 and in the list of abbreviations at the front of these guidelines). A DR-TB regimen consists of two phases: the first phase is the period in which the injectable agent is used and the second phase is after it has been stopped. The number shown before each phase stands for phase duration in months and is the minimum amount of time that 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. An alternative drug(s) appears as a letter(s) in parentheses. The drugs in the higher groups are written first followed by the others in descending order of potency. Examples are given in Box 7.2.

BOX 7.1 KNOWN CROSS-RESISTANCE BETWEEN ANTITUBERCULOSIS AGENTS

- All rifamycins have high levels of cross-resistance (*9–12*). Fluoroquinolones are believed to have variable cross-resistance between each other, with in vitro data showing that some later-generation fluoroquinolones remain susceptible when earlier-generation fluoroquinolones are resistant (*13–15*). In these cases, it is unknown if thelater-generation fluoroquinolones remain effective clinically.
- Amikacin and kanamycin have very high cross-resistance (*16*, *17*). Capreomycin and viomycin have high cross-resistance (*18*). Other aminoglycosides and polypeptides have low cross-resistance (*19–24*). Protionamide and ethionamide have 100% cross-resistance. Ethionamide can have cross-resistance to isoniazid if the inhA mutation is present (*25–29*). Thioacetazone cross-resistance to isoniazid, ethionamide and PAS has been reported but is generally considered to be low (*30–34*).

7.6 Role of drug susceptibility testing

Countries vary greatly in their access to reliable mycobacterial laboratories, and many do not have regular access to DST. The inability to do routine DST in all patients should not be a barrier for patients that need Category IV treatment. Fully standardized regimens using second-line antituberculosis drugs have been shown to be feasible and cost-effective in DR-TB treatment (*35*).

In countries where reliable DST is not available, every effort should be made to improve laboratory capacity, for the following reasons:

- DST surveys are needed to identify groups of patients that are at high risk for DR-TB. General nationwide surveys may not reflect DST patterns of specific groups of patients. For example, the DST patterns of all previously treated patients may be very different from those that failed SCC.
- Even in the setting of a strong DOTS programme, some patients in high-risk groups (e.g. Category II failures) will not have DR-TB. These

BOX 7.2 EXAMPLES OF STANDARD DRUG CODE USED TO DESCRIBE DRUG REGIMENS

Example 7.1

6Z-Km(Cm)-Ofx-Eto-Cs/12Z-Ofx-Eto-Cs

The initial phase consists of five drugs and lasts for at least six months or six months past conversion, depending on country protocol. 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 18 months. The injectable is kanamycin, but there is an option for capreomycin. Sometimes only the initial treatment is written and the assumption is that either the regimen will be adjusted with DST or the injectable will be stopped according to the programme protocol. This type of notation is used without a coefficient, i.e. **Z-KM-Ofx-Eto-Cs**

guidelines strongly recommend confirming treatment failure by culture and testing for DR-TB through the use of DST of at least isoniazid and rifampicin.

- In the era of HIV and rapid spread of highly resistant (e.g. XDR) strains, a detailed history of previous tuberculosis treatment may not adequately predict the resistance pattern of the infecting strain, as many patients with DR-TB may have been infected originally with a resistant strain (*36*).

Even in countries where reliable DST is available, standardized regimens may be chosen as a strategy over individualized regimens for the following reasons:

- Interpretation of DST to some of the first- and second-line drugs is difficult and could mislead regimen design. Standardized regimens can give guidance to clinicians and prevent basing decisions on DST that is not reliable. These guidelines do not recommend using DST of ethambutol, pyrazinamide and the drugs in Groups 4 and 5 to base individual regimen design.
- Turnaround time for many culture-based DST methods is long. In general, patients at increased risk for DR-TB should be placed on an empirical Category IV regimen until DST results are available.
- The laboratory may not perform DST of certain drugs, or may perform them at different times. Results from rapid methods (molecular) may be available within days, but only for certain first-line drugs such as isoniazid and rifampicin. Many laboratories perform second-line DST only after resistance to first-line drugs is confirmed.

In summary, regular access to quality-assured DST is recommended for all programmes, even those using a standardized regimen. Delays in treatment while awaiting DST can result in increased morbidity and mortality, as well as

longer periods of infectiousness. DST to many of the second-line drugs should not be relied upon for individual regimen design (also see Chapter 6 for more discussion on DST).

7.7 Designing a treatment regimen

This section describes the methods for designing a treatment regimen. It applies to standardized, empirical and individualized regimens.

7.7.1 General principles

The following are the basic principles involved in any regimen design:

- Regimens should be based on the history of drugs taken by the patient.
- Drugs commonly used in the country and prevalence of resistance to first-line and second-line drugs should be taken into consideration when designing a regimen.
- Regimens should consist of at least four drugs with either certain, or almost certain, effectiveness. If the evidence about the effectiveness of a certain drug is unclear, the drug can be part of the regimen but it should not be depended upon for success. Often, more than four drugs may be started if the susceptibility pattern is unknown, effectiveness is questionable for an agent(s) or if extensive, bilateral pulmonary disease is present.
- When possible, pyrazinamide, ethambutol and fluoroquinolones should be given once per day as the high peaks attained in once-a-day dosing may be more efficacious. Once-a-day dosing is permitted for other second-line drugs depending on patient tolerance, however ethionamide/protionamide, cycloserine and PAS have traditionally been given in split doses during the day to reduce adverse effects.
- The drug dosage should be determined by body weight. A suggested weight-based dosing scheme is shown in Annex 2.
- Treatment of adverse drug effects should be immediate and adequate in order to minimize the risk of treatment interruptions and prevent increased morbidity and mortality due to serious adverse effects (see Chapter 11).
- An injectable agent (an aminoglycoside or capreomycin) is used for a minimum of six months and at least four months past culture conversion (see Section 7.9 on duration of injectable use).
- The minimum length of treatment is 18 months after culture conversion (see Section 7.10 on duration of treatment).
- Each dose is given as directly observed therapy (DOT) throughout the treatment. A treatment card is marked for each observed dose.

- DST of drugs with high reproducibility and reliability (and from a dependable laboratory) should be used to guide therapy. It should be noted that the reliability and clinical value of DST of some first-line and most of the second-line antituberculosis drugs have not been determined (see Section 7.6 and Chapter 6). DST does not predict with 100% certainty the effectiveness or ineffectiveness of a drug (*37*). DST of drugs such as ethambutol, streptomycin and Group 4 and 5 drugs does not have high reproducibility and reliability; these guidelines strongly caution against basing individual regimens on DST of these drugs.
- Pyrazinamide can be used for the entire treatment if it is judged to be effective. Many DR-TB patients have chronically inflamed lungs, which theoretically produce the acidic environment in which pyrazinamide is active. Alternatively, in patients doing well, pyrazinamide can be stopped with the injectable phase if the patient can continue with at least three certain, or almost certain, effective drugs.
- Early DR-TB detection and prompt initiation of treatment are important factors in determining successful outcomes.

Figure 7.2 describes the steps for building a regimen for DR-TB treatment.

7.7.2 Dosing of drugs

Dosing of anti-tuberculosis drugs is based on the weight of the patient. Dosing is described in Annexes 1 and 2. Dosing for pediatric patients is described in Chapter 9.

7.7.3 Dose escalation (drug ramping)

Most drugs should be started at full dose, except cycloserine, ethionamide and PAS, in which case the dose of the drug can be increased over a two-week period (*38*).

7.8 Designing a programme treatment strategy

Treatment strategies for programmes may vary depending on access to DST, rates of DR-TB, HIV prevalence (see Chapter 10), technical capacity and financial resources. Despite the variability, there are uniform recommendations for programme treatment strategies that the GLC has developed. Table 7.2 is a treatment strategy guide for programmes. It is based on different situations in resource-constrained areas with limited access to DST and what strategy the GLC has generally recommended in that situation. The table attempts to cover most situations; however, the NTP may need to adjust the strategy to meet special circumstances. It assumes that DST of isoniazid, rifampicin, the fluoroquinolones and the injectable agents is fairly reliable. It also assumes DST of other agents is less reliable and that basing individualized treatments on DST of these agents should be avoided.

Figure 7.2 How to build a treatment regimen for MDR-TB[a]

STEP 1	Use any available **Group 1: First-line oral agents** pyrazinamide ethambutol	Begin with any first-line agents that have certain, or almost certain, efficacy. If a first-line agent has a high likelihood of resistance, do not use it. (For example, most Category IV regimens used in treatment failures of Category II do not include ethambutol because it is likely to be resistant based on treatment history.)
STEP 2	Plus one of these **Group 2: Injectable agents** kanamycin (or amikacin) capreomycin streptomycin	Add an injectable agent based on DST and treatment history. Avoid streptomycin, even if DST suggests susceptibility, because of high rates of resistance with DR-TB strains and higher incidence of ototoxicity.
STEP 3	Plus one of these **Group 3: Fluoroquinolones** levofloxacin moxifloxacin ofloxacin	Add a fluoroquinolone based on DST and treatment history. In cases where resistance to ofloxacin or XDR-TB is suspected, use a higher-generation fluoroquinolone, but do not rely upon it as one of the four core drugs.
STEP 4	Pick one or more of **Group 4: Second-line oral bacteriostatic agents** *p*-aminosalicylic acid cycloserine (or terizadone) ethionamide (or protionamide)	Add Group 4 drugs until you have at least four drugs likely to be effective. Base choice on treatment history, adverse effect profile and cost. DST is not standardized for the drugs in this group.
STEP 5	Consider use of these **Group 5: Drugs of unclear role in DR-TB treatment** clofazimine linezolid amoxacillin/clavulanate thioacetazone[b] imipenem/cilastatin high-dose isoniazid clarithromycin	Consider adding Group 5 drugs in consultation with an MDR-TB expert if there are not four drugs that are likely to be effective from Groups 1–4. If drugs are needed from this group, it is recommended to add at least two. DST is not standardized for the drugs in this group.

[a] Adapted from *Drug-resistant tuberculosis: a survival guide for clinicians*. San Francisco, Francis J. Curry National Tuberculosis Center and California Department of Health Services, 2004.

[b] Thioacetazone is contraindicated in HIV-infected individuals given the serious risk of life-threatening adverse reaction.

TABLE 7.2 **Recommended strategies for different programmatic situations**

PATIENT GROUP	BACKGROUND SUSCEPTIBILITY DATA[a]	RECOMMENDED STRATEGY[b]
New patient with active TB	Resistance *uncommon* to *moderately common* (i.e. a country where a low to moderate rate of new cases have MDR-TB)	● Start **Category I treatment** ● Perform DST of at least H and R in patients not responsive to Category I[c] ● Rapid DST techniques are preferable
	Resistance *common* (i.e. a country where a high rate of new cases have MDR-TB)	● Perform DST of H and R in all patients before treatment starts ● Rapid DST techniques are preferable ● Start **Category I** treatment while awaiting DST ● Adjust regimen to a Category IV regimen if DST reveals DR-TB
Patient in whom Category I failed	*Low* percentage of failures of Category I have MDR-TB Second-line drug resistance is *rare*	● Perform DST of H and R at a minimum in all patients before treatment starts ● Rapid DST is preferable ● Start **Category II** treatment while awaiting DST ● Adjust regimen to a Category IV regimen if DST reveals DR-TB
	High percentage of failures of Category I have MDR-TB Second-line drug resistance is *rare*	● Perform DST of isoniazid and rifampicin at a minimum in all patients before treatment starts ● Start Category IV treatment: **IA-FQ- two Group 4 agents- +/– Z**
	High percentage of failures of Category I have MDR-TB Second-line drug resistance is *common*	● Perform DST of H, R, IA, FQ before treatment starts ● Start **Category IV treatment: IA-FQ- three Group 4 agents- +/– Z** while awaiting DST ● Adjust regimen according to DST results if using an individualized approach
Patient in whom Category II failed	*High* percentage of failures of Category II have MDR-TB Second-line drug resistance is *rare*	● Perform DST of H and R at a minimum in all patients before treatment starts ● Start **Category IV treatment: IA-FQ- two Group 4 agents- +/– Z** while awaiting DST ● Adjust regimen according to DST results if using an individualized approach
	High percentage of failures of Category II have MDR-TB Second-line drug resistance is *common*	● Perform DST of H, R, IA, FQ before treatment starts ● Start **Category IV treatment: IA-FQ- three Group 4 agents- +/– Z** while awaiting DST ● Adjust regimen according to DST results if using an individualized approach

TABLE 7.2 (*continued*)

PATIENT GROUP	BACKGROUND SUSCEPTIBILITY DATA[a]	RECOMMENDED STRATEGY[b]
Patient with history of relapse or patient returning after default	*Low to moderate* rate of MDR-TB in this group of patients is common	• Perform DST of H and R at a minimum in all patients before treatment starts • Start **Category II treatment** while awaiting DST • Adjust regimen to a Category IV regimen if DST returns DR-TB
Contact of MDR-TB patient now with active TB Contact resistance pattern known	*Close* contact with *high* risk of having the same strain	• Perform rapid diagnosis and DST of H and R at a minimum in all patients before treatment starts • Start **Category IV treatment** based on the DST pattern and treatment history of the contact (see Chapter 14) while awaiting DST • Adjust regimen according to DST results
	Casual contact with *low* risk of having the same strain	• Perform rapid diagnosis and DST of H and R at a minimum in all patients before treatment starts • Start **Category I treatment** while awaiting DST • Adjust regimen according to DST results
Patient with documented MDR-TB	Documented, or almost certain, susceptibility to a FQ and IA	• Start **Category IV treatment: IA-FQ-two Group 4 agents- +/– Z**
	Documented, or almost certain, susceptibility to FQ Documented, or almost certain, resistance to an IA	• **Start Category IV treatment: IA-FQ-three Group 4 agents- +/– Z** • Use an IA with documented susceptibility • If the strain is resistant to all IAs, use one for which resistance is relatively rare
	Documented, or almost certain, resistance to a FQ Documented, or almost certain, susceptibility to IA	• Start **Category IV treatment: IA-FQ-three Group 4 agents- +/– Z** • Use a later-generation FQ
	Documented, or almost certain, resistance to a FQ and IA	• Start **Category IV treatment** for XDR-TB (see section 7.14)

TABLE 7.2 (*continued*)

PATIENT GROUP	BACKGROUND SUSCEPTIBILITY DATA[a]	RECOMMENDED STRATEGY[b]
Patient in whom Category IV failed or **Patient with documented MDR-TB and history of extensive second-line drug use**	*Moderate* to *high* rate of XDR-TB in this group of patients	● Perform DST of IA and FQ (and H and R if not already done) before treatment starts ● Start **Category IV treatment** for XDR-TB (see section 7.14) while awaiting DST ● Adjust regimen according to DST results
Patient with documented XDR-TB	Documented resistance to H, R, IA, and FQ	● Start Category IV treatment for XDR-TB (see section 7.14)

[a] All strategies in Table 7.2 assume they will be implemented in resource-constrained areas with limited access to DST. There are no absolute thresholds for low, moderate or high resistance. Programmes are encouraged to consult an expert on which recommended strategies in Table 7.2 are best indicated based on resistance levels and available resources.

[b] Whenever possible, perform DST of injectable agents (IA, aminoglycosides or capreomycin) and a fluoroquinolone (FQ) if MDR-TB is documented.

[c] Persistently positive smears at 5 months constitute the definition of Category I failure; however some may wish to consider DST earlier based on overall clinical picture, for example if patient is HIV-positive.

A number of principles in Table 7.2 require explanation. First, DST surveillance data for different groups of patients (new, failures of Category I, failures of Category II, relapse and default, and failures of Category IV) will help greatly in determining rates of MDR-TB and of resistance to other antituberculosis drugs. This is essential for developing appropriate treatment strategies and for evaluating the impact of control programme interventions.

Screening all MDR-TB strains for second-line drug resistance is recommended when capacity and resources are available. Because of the relatively good reliability and reproducibility of DST of aminoglycosides, polypeptides and fluoroquinolones, and since resistance to these drugs defines XDR-TB, DST of these second-line drugs constitutes a priority for surveillance and treatment (see Chapter 6 for a recommended hierarchy of DST).

For a standardized empirical regimen that will treat the vast majority of patients with four effective drugs, it is often necessary to use five or six drugs to cover all possible resistance patterns. As Table 7.2 illustrates, for most cases, an injectable agent and a fluoroquinolone make the core of the regimen.

If using a standardized regimen, DR-TB control programmes are strongly encouraged to order other drugs that are not included in the standard regimen. For example, a programme that uses a 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 DR-TB who cannot take all the drugs in the standard regimen; (iii) as part of a "salvage

regimen" for those who fail the standardized regimen. In fact, all programmes are encouraged to have a "salvage regimen" for when the standardized regimen fails. See Box 7.3 for an example of how to design a standardized regimen.

These guidelines caution against using DST of ethambutol, pyrazinamide and the drugs in Groups 4 and 5 to base the design of individual regimens. The reliability and reproducibility of these drugs are questionable. Individually designed regimens are based on history of previous drug use and DST of isoniazid, rifampicin, the second-line injectable agents and a fluoroquinolone.

If DST results are not readily available, an empirical regimen based on the patient's treatment history and contact history is strongly recommended since most DST methods have a turnaround time of several months. Placing a patient on an empirical regimen while DST results are pending is done to avoid

BOX 7.3 EXAMPLES OF HOW TO DESIGN STANDARDIZED REGIMENS

Example 1. Survey data from 93 consecutively enrolled relapse patients from a resource-constrained area show that 11% have MDR-TB. Of these MDR-TB cases, 45% are resistant to E and 29% are resistant to S. Resistance to other drugs is unknown; however, there is virtually no 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 relatively low rate of MDR-TB in this group, the following strategy is planned. All relapse patients will be started on the WHO Category II regimen (HRZES). DST of H and R will be done at the start of treatment to identify the 11% of MDR-TB patients who will not do well on Category II regimen. Those identified with MDR-TB will be switched to the standardized regimen 8Z-Km-Ofx-Pto-Cs/12Ofx-Pto-Cs. The regimen contains four new drugs rarely used in the area, and is also relatively inexpensive. A small DST survey is planned to document the prevalence of resistance to the regimen's five drugs in 30 relapse patients found to have MDR-TB. If this survey shows high resistance to any of the proposed drugs, redesign of the regimen will be considered. (Note: the regimen proposed in this answer is only one example of an adequate regimen; many others based on the principles in this chapter would be just as adequate.)

Example 2. A programme uses a standardized Category IV regimen of Z-KM-Ofx-Cs-Eto in patients in whom Category II regimen failed. For such patients, it is determined that 40% have XDR-TB. The programme has limited access to DST of fluoroquinolones and injectable agents and wishes to design a standard "salvage" regimen for patients in whom the standardized Category IV regimen has failed. What regimen is recommended?

Answer: Given the high rate of XDR-TB it is best to use a regimen designed to cure XDR-TB. An example of such a regimen is given below:

CM-Mfx-PAS-2 or 3 Group 5 agents +/– Cs

Some experts would include Cs in the regimen because the rate of development of resistance appears to be low. However, evidence about the true rate of development of resistance in patients who are not cured with a Cs-containing regimen is very limited.

clinical deterioration and prevent transmission to contacts. There are a few exceptions. It may be convenient to wait for DST results if the laboratory uses a rapid method with a turnaround time of 1–2 weeks. In addition, in chronic cases who have been treated multiple times with second-line antituberculosis drugs, waiting for DST results may be prudent even if the turnaround time is several months, as long as the patient is clinically stable and appropriate infection control measures are in place.

Every effort should be made to supplement the patient's memory with objective records from previous health-care providers. A detailed clinical history can help suggest which drugs are likely to be ineffective. Although resistance can develop in some cases in less than one month (*39*), as a general rule if a patient has used a drug for over a month with persistently positive smears or cultures, the strain should be considered as "probably resistant" to that drug, even if by DST it is reported as susceptible.

The results of DST should complement rather than invalidate other sources of data about the likely effectiveness of a specific drug. For example, if a history of previous antituberculosis drug use suggests that a drug is likely to be ineffective, this drug should not be relied on as one of the four core drugs in the regimen even if the strain is susceptible by DST. Alternatively, if the strain is resistant to a drug by DST, but the patient has never taken the drug and resistance to it is extremely uncommon in the community, this may be a case of a laboratory error or a result of the limited specificity of DST for some second-line drugs.

Another important constraint is that because of the turnaround time necessary for DST, the patient may have already received months of a standardized or empirical treatment regimen by the time DST results become available from the laboratory. The possibility of further acquired resistance during this time must be considered. If there is a high probability of acquired resistance to a drug after the specimen for DST was collected, this drug should not be counted as one of the four drugs in the core regimen but can be included as an adjunctive agent.

Some laboratories may report that a strain has a low or intermediate level of resistance to a certain drug. There is very little clinical evidence to support this type of designation, particularly if the patient received the drug previously. Box 7.4 gives examples of how to design individualized regimens.

7.9 Completion of the injectable agent (intensive phase)

The recommended duration of administration of the injectable agent, or the intensive phase, is guided by culture conversion. The injectable agent should be continued for at least six months and at least four months after the patient first becomes and remains smear- or culture-negative.

The use of an individualized approach that reviews the cultures, smears,

BOX 7.4 EXAMPLES OF HOW TO DESIGN AN INDIVIDUALIZED REGIMEN

Example 1. A patient in whom Category I and II treatments failed. 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 3 months since the date of the DST. What individualized regimen is recommended?

Answer: Since the patient received two courses containing E and Z, and was on functional monotherapy with E for at least 3 months, the utility of these drugs must be questioned despite the DST results. The same drugs can be included in the regimen but they should not be relied on as one of the four core drugs. The injectable choice may depend on the prevalence of resistance in the community, but since this patient never received Km, Km is low in cost and the DST is reported to be susceptible, it may be the first choice in this case:

- Km(Cm)-Ofx-Eto(Pto)-Cs
  (Many clinicians will add Z to this regimen; others may use PAS instead of Eto or Pto.)

Example 2. A patient in whom Category I and II treatments failed. A review of DST results reveals that the infecting strain is resistant to H-R-Z-E-S-Km and susceptible to the medications Cm-Ofx. The patient has not received any antituberculosis drugs since the date of the DST. What individualized regimen is recommended?

Answer: Below are two possible options in this case:

1. Cm-Ofx-Pto(Eto)-Cs
   Regimen 1 may have the advantage of increased compliance since it requires the minimum number of drugs and avoids the adverse effects of the combination of PAS and Pto(Eto). However, if one or more of the DST results is wrong (and the reliability of DST of second-line drugs even to Cm and Ofx are only moderately reliable), the patient may be effectively on a regimen of only two or three drugs. Prevalence of resistance to second-line drugs and their availability in the country can help in the decision.
2. Cm-Ofx-Pto-Cs-PAS
   Regimen 2 takes into consideration the uncertainty of DST of second-line drugs. It places the patient on an additional drug as a precaution in case one of the DST results does not reflect the efficacy of any of the drugs tested. Pto and PAS, while difficult to take together, are frequently tolerated by many patients, especially with good patient support. A regimen with these five drugs is also preferred if there is extensive damage to the lungs or if susceptibility to any of these drugs is uncertain, given a patient's history.

X-rays and the patient's clinical status may also help in deciding whether to continue an injectable agent longer than the above recommendation, particularly in the case of patients for whom the susceptibility pattern is unknown, effectiveness is questionable for an agent(s), or extensive or bilateral pulmonary disease is present.

Intermittent therapy with the injectable agent (three times a week) can also be considered in patients in whom the injectable has been used for a prolonged

period of time and when toxicity becomes a greater risk. If the patient was on an empirical regimen of five or six drugs, drugs other than the injectable can be considered for suspension once the DST results are available and the patient continues with at least three of the most potent agents.

7.10 Duration of treatment

The recommended duration of treatment is guided by culture conversion. Despite emerging evidence that shorter regimens may be efficacious, these guidelines recommend continuing therapy for a minimum of 18 months after culture conversion until there is conclusive evidence to support a shorter duration of treatment. Extension of therapy to 24 months may be indicated in chronic cases with extensive pulmonary damage.

7.11 Extrapulmonary DR-TB

Extrapulmonary DR-TB is treated with the same strategy and duration as pulmonary DR-TB. If the patient has symptoms suggestive of central nervous system involvement and is infected with DR-TB, the regimen should use drugs that have adequate penetration into the central nervous system (*40*, *41*). Rifampicin, isoniazid, pyrazinamide, protionamide/ethionamide and cycloserine have good penetration into the cerebrospinal fluid (CSF); kanamycin, amikacin and capreomycin do so only in the presence of meningeal inflammation; PAS and ethambutol have poor or no penetration. The fluoroquinolones have variable CSF penetration, with better penetration seen in the later generations.

7.12 Surgery in Category IV treatment

The most common operative procedure in patients with pulmonary DR-TB is resection surgery (taking out part or all of a lung). Large case-series analysis has shown resection surgery to be effective and safe under appropriate surgical conditions (*42*). It is considered an adjunct to chemotherapy and appears to be beneficial for patients when skilled thoracic surgeons and excellent postoperative care are available (*43*). It is not indicated in patients with extensive bilateral disease.

Resection surgery should be timed to offer the patient the best possible chances 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 is lower, for example, when the disease is still localized to one lung or one lung lobe. In other words, surgery should not be considered as a last resort. Generally, at least two months of therapy should be given before resection surgery in order to decrease the bacterial infection in the surrounding lung tissue. Even with successful resection, an additional 12–24 months of chemotherapy should be given.

Specialized surgical facilities should include stringent infection control measures, since infectious substances and aerosols are generated in large quantities during surgery and during mechanical ventilation and postoperative 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 who 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 are recommended as part of the preoperative work-up. Programmes with suboptimal surgical facilities and no trained thoracic surgeons should refrain from resection surgery, as the result may be an increase in morbidity or mortality.

7.13 Adjuvant therapies in DR-TB treatment

A number of other modalities are used to lessen adverse effects and morbidity as well as improve DR-TB treatment outcomes.

7.13.1 Nutritional support

In addition to causing malnutrition, DR-TB can be exacerbated by poor nutritional status. Without nutritional support, patients, especially those already suffering from baseline hunger, can become enmeshed in a vicious cycle of malnutrition and disease. The second-line antituberculosis medications can also further decrease appetite, making adequate nutrition a greater challenge.

Vitamin B6 (pyridoxine) should also be given to all patients receiving cycloserine or terizidone to prevent neurological adverse 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 patients have these deficiencies. If minerals are given (zinc, iron, calcium, etc.) they should be dosed apart from the fluoroquinolones, as they can interfere with the absorption of these drugs.

7.13.2 Corticosteroids

The adjuvant use of corticosteroids in DR-TB patients has been shown not to increase mortality and can be beneficial in conditions such as severe respiratory insufficiency, and central nervous system or pericardial involvement. Prednisone is commonly used, starting at approximately 1 mg/kg and gradually decreasing the dose to 10 mg per week when a long course is indicated. Corticosteroids may also alleviate symptoms in patients with an exacerbation of obstructive pulmonary disease. In these cases, prednisone may be given in a short taper over 1–2 weeks, starting at approximately 1 mg/kg and decreasing the dose by 5–10 mg per day. Injectable corticosteroids are often used initially when a more immediate response is needed.

7.14 Treatment of XDR-TB

Since it was first described, XDR-TB has been reported on 6 continents in at least 37 countries, constituting up to 10% of all MDR-TB strains (*44*, *45*). It has proven much more difficult to treat than MDR-TB and is extremely difficult to treat in HIV-positive patients (*36*, *45–47*). While reports of HIV-positive patients being promptly diagnosed with XDR-TB and placed on an adequate regimen are non-existent to date, reports of cohorts of HIV-negative patients have been shown to have cure rates that exceed 50% (*45*, *46*). Figure 7.3 summarizes the latest expert consensus on how to manage XDR-TB. There are very limited data on different clinical approaches to XDR-TB.

Figure 7.3 Management guidelines for patients with documented, or almost certain, XDR-TB

1. Use any Group 1 agents that may be effective;
2. 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, it is recommended to use one the patient has never used before;[a]
3. Use a later-generation fluoroquinolone such as moxifloxacin;
4. Use all Group 4 agents that have not been used extensively in a previous regimen or any that are likely to be effective;
5. Use two or more agents from Group 5;
6. Consider high-dose isoniazid treatment if low-level resistance is documented;
7. Consider adjuvant surgery if there is localized disease;
8. Ensure strong infection control measures;
9. Treat HIV (as per Chapter 10);
10. Provide comprehensive monitoring (see Chapter 11) and full adherence support (see Chapter 12).

[a] This recommendation is made because, while the reproducibility and reliability of DST to injectables are good, there are little data on clinical efficacy of the test. 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.

7.15 Conclusion

Programmatic management of DR-TB is a complex health intervention, and no one strategy will fit all situations. Programme managers need to consider the epidemiological, financial and operational factors when deciding which strategy to use. Table 7.3 summarizes the principles of designing regimens.

BOX 7.5 EXAMPLE OF XDR-TB TREATMENT

Example 1. A patient in whom a standardized regimen of Z-Km-Ofx-Eto failed remains sputum smear-positive after 8 months of treatment. The DST done from a specimen taken 4 months ago reveals resistance to HRZE-Km-Cm and susceptibility to Ofx.

What treatment regimen is recommended?

Answer: This patient may now be resistant to Ofx. Eto and Ofx cannot be relied upon in a new regimen, limiting treatment options. A later-generation fluoroquinolone may have some effect. The recommended regimen is:

- Cm-Mfx-Cs-PAS plus two Group 5 drugs (Cfz and Amx/Clv are perhaps the two most common Group 5 drugs used in this circumstance).

Table 7.3 Summary of the general principles for designing treatment regimens

BASIC SUMMARY PRINCIPLES	COMMENTS
1. Use at least 4 drugs certain to be effective If at least 4 drugs are not certain to be effective, use 5–7 drugs depending on the specific drugs and level of uncertainty.	Effectiveness is supported by a number of factors (the more present, the more likely the drug will be effective in the patient): ● DST results show susceptibility (for drugs in which there is good laboratory reliability). ● No previous history of treatment failure with the drug. ● No known close contacts with resistance to the drug. ● DRS documents resistance is rare in similar patients. ● The drug is not commonly used in the area.
2. Do not use drugs for which there is the possibility of cross-resistance	● Many antituberculosis agents exhibit cross-resistance both within and across drug classes. Knowledge of these relationships is essential in designing regimens for DR-TB (see Box 7.1).
3. Eliminate drugs that are not safe in the patient	● Known severe allergy or unmanageable intolerance. ● High risk of severe adverse effects such as renal failure, deafness, hepatitis, depression and/or psychosis. ● Quality of the drug is unknown.
4. Include drugs from Groups 1–5 in a hierarchal order based on potency	● Use any of the first-line oral agents (Group 1) that are likely to be effective (see the first section in this table as to what predicts effectiveness). ● Use an effective aminoglycoside or polypeptide by injection (Group 2). ● Use a fluoroquinolone (Group 3). ● Use the remaining Group 4 drugs to complete a regimen of at least 4 effective drugs. ● For regimens with fewer than 4 effective drugs, consider adding Group 5 drugs. The total number of drugs will depend on the degree of uncertainty, and regimens often contain 5–7 drugs.

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CHAPTER 8

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

8.1 Chapter objectives

This chapter describes the recommended treatment strategies for patients with DR-TB other than MDR-TB. These include patients with mono-resistant TB and patients with poly-resistant TB other than MDR-TB. Mono-resistance refers to resistance to a single first-line drug, and poly-resistance refers to resistance to two or more first-line drugs but not to both isoniazid and rifampicin.

8.2 General considerations

Cases with mono- or poly-resistance will be identified during the course of case-finding for MDR-TB. Treatment of patients infected with mono- or poly-resistant strains using standardized SCC has been associated with increased risk of treatment failure and further acquired resistance, including the development of MDR-TB (*1–2*). While the likelihood of poor outcomes is relatively low with many types of mono- and poly-resistance (i.e. the majority of patients with mono- or poly-resistant strains will be cured with SCC), programmes can use different regimens based on DST patterns as described below.

8.3 Consequences for reporting

Patients whose regimens require minor adjustments should be recorded in the traditional District Tuberculosis Register. These regimens are considered "modifications" of Category I or Category II treatment. They are not classified as Category IV treatments, which are regimens designed to treat MDR-TB. The adjustment should be noted in the comments section of the Register and the adjusted treatment continued for the indicated length of time.

8.4 Treatment of patients with mono- and poly-resistant strains

Definitive randomized or controlled studies have not been performed to determine the best treatment for various patterns of drug resistance, except for streptomycin resistance. The recommendations in these guidelines are based on evidence from the pre-rifampicin era, observational studies, general principles of microbiology and therapeutics in TB, extrapolations from established evidence and expert opinion. When a decision has been made to modify standardized SCC, the most effective regimen should be chosen from the start to maximize the likelihood of cure; effective drugs should not be withheld for later use.

Table 8.1 gives suggested regimens for different DST patterns. When using this table, it is essential to consider whether resistance has been acquired to any of the drugs that will be used in the recommended regimen.

- **Development of further resistance.** Further resistance should be suspected if the patient was on the functional equivalent of only one drug for a significant period of time (usually considered as one month or more, but even periods of less than one month on inadequate therapy can lead to resistance). Sometimes resistance develops if the patient was on the functional equivalent of two drugs, depending on the drugs concerned. For example, pyrazinamide is not considered a good companion drug to prevent resistance. If a patient was receiving functionally only rifampicin and pyrazinamide in the initial phase (because of resistance to isoniazid and ethambutol), resistance to rifampicin may develop. Thus, it is crucial to consider which functional drugs the patient received between the time of DST specimen collection and the time of the new regimen design (i.e. consider whether resistance has developed to any of the functional drugs).

- **DST results.** The DST result that prompts a change in treatment may not accurately reflect the bacterial population at the time it is reported since it reflects the bacterial population at the time the sputum was collected. The regimens in Table 8.1 are based on the assumption that the pattern of drug resistance has not changed during this interval. Table 8.1 should therefore **not** be used if further resistance to any of the agents in the suggested regimen is suspected. It is also important to note that a high level of confidence in the laboratory is needed for effective use of Table 8.1. As mentioned in Chapters 6 and 7, DST of ethambutol and pyrazinamide is not highly reproducible.

Table 8.1 assumes that pyrazinamide susceptibility is being tested, which is not the case for many countries. If DST of pyrazinamide is not being carried out, pyrazinamide cannot be depended upon as being an effective drug in the regimen. In such situations, regimens from Table 8.1 that assume the

TABLE 8.1 **Suggested regimens for mono- and poly-drug resistance[a] (when further acquired resistance is not a factor and laboratory results are highly reliable)**

PATTERN OF DRUG RESISTANCE	SUGGESTED REGIMEN	MINIMUM DURATION OF OF TREATMENT (MONTHS)	COMMENTS
H (± S)	R, Z and E	6–9	A fluoroquinolone may strengthen the regimen for patients with extensive disease.
H and Z	R, E and fluoro-quinolones	9–12	A longer duration of treatment should be used for patients with extensive disease.
H and E	R, Z and fluoro-quinolones	9–12	A longer duration of treatment should be used for patients with extensive disease.
R	H, E, fluoroquinolones, plus at least 2 months of Z	12–18	An injectable agent may strengthen the regimen for patients with extensive disease.
R and E (± S)	H, Z, fluoroquinolones, plus an injectable agent for at least the first 2–3 months	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.
R and Z (± S)	H, E, fluoroquinolones, plus an injectable agent for at least the first 2–3 months	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.
H, E, Z (± S)	R, fluoroquinolones, plus an oral second-line agent, plus an injectable agent for the first 2–3 months	18	A longer course (6 months) of the injectable agent may strengthen the regimen for patients with extensive disease.

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

[a] Adapted from *Drug-resistant tuberculosis: a survival guide for clinicians* (*3*)

TB strain to be resistant should be used. Some clinicians would add pyrazinamide to those regimens because a significant percentage of patients could benefit from the drug; however, it would not be counted upon as a core drug in the regimen.

The design of regimens for mono- and poly-resistant cases of TB requires experience; it is recommended for programmes with good infrastructure that are capable of treating MDR-TB. Individually designed treatments for mono- and poly-resistance are often determined by a review panel that meets

periodically. The panel reviews the treatment history, DST patterns and the possibility of strains of *M. tuberculosis* having acquired new resistance, and then determines the regimen.

Box 8.1 provides an example to illustrate the risk of additional acquired resistance while awaiting DST results.

BOX 8.1

Example of regimen design for mono- and poly-resistant strains

This example is from a setting where representative DRS data indicate that 85% of failures of Category I have MDR-TB. A patient who has received a Category I regimen of HRZE has a culture sent for DST at month 3 of treatment because of a positive smear. The initial phase is continued for an additional month, at which time the smear is negative, and the patient is placed on the continuation phase of treatment with HR. The DST returns in month 4 of treatment with resistance to HE and susceptibility to S. DST is not known for Z. The patient is sputum smear-positive at month 4. What regimen should be used?

Answer: The patient has been on at least one month of functional monotherapy with R, and, if resistant to Z, he or she may have been on monotherapy with R for four months. In this case, **do not use Table 8.1** to design the regimen; instead, assume the patient may have now developed resistance to R, and design a Category IV regimen based on the principles for MDR-TB regimen design described in Chapter 7.

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CHAPTER 9

Treatment of DR-TB in special conditions and situations

9.1 Chapter objectives

This chapter outlines the management of DR-TB in the following special conditions and situations:

- pregnancy,
- breastfeeding,
- contraception,
- children,
- diabetes mellitus,
- renal insufficiency,
- liver disorders,
- seizure disorders,
- psychiatric disorders,
- substance dependence.

HIV infection is addressed separately in Chapter 10.

9.2 Pregnancy

All female patients of childbearing age should be tested for pregnancy upon initial evaluation. Pregnancy is not a contraindication for treatment of active DR-TB, which poses great risks to the lives of both mother and fetus (*1*, *2*). However, birth control is strongly recommended for all non-pregnant women receiving therapy for DR-TB because of the potential consequences for both mother and fetus resulting from frequent and severe adverse drug reactions.

Pregnant patients should be carefully evaluated, taking into consideration gestational age and severity of the DR-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 guidelines.

- **Start treatment of drug resistance in second trimester or sooner if condition of patient is severe.** Since the majority of teratogenic effects occur in the first trimester, therapy may be delayed until the second trimester. The decision to postpone the start of treatment should be agreed by both patient and doctor after analysis of the risks and benefits. It is based primarily on the clinical judgment resulting from the analysis of life-threatening signs/symptoms and severity/aggressiveness of the disease (usually reflected in extent of weight loss and lung affection during the previous weeks). When therapy is started, three or four oral drugs with demonstrated efficacy against the infecting strain should be used and then reinforced with an injectable agent and possibly other drugs immediately postpartum (*3*).
- **Avoid injectable agents.** For the most part, aminoglycosides should not be used in the regimens of pregnant patients and can be particularly toxic to the developing fetal ear. Capreomycin may also carry a risk of ototoxicity but is the injectable drug of choice if an injectable agent cannot be avoided.
- **Avoid ethionamide.** Ethionamide can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies. If possible, ethionamide should be avoided in pregnant patients.

9.3 Breastfeeding

A woman who is breastfeeding and has active DR-TB should receive a full course of antituberculosis treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to her baby.

In lactating mothers on treatment, most antituberculosis 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 DR-TB treatment have not been established.

Therefore, when resources and training are available, it is recommended to provide infant formula options as an alternative to breastfeeding. When infant formula is provided, fuel for boiling water and the necessary apparatus (stove, heating pans and bottles) must also be provided, as well as training on how to prepare and use the infant formula. All this should be free of charge to poor patients, and DR-TB control programmes should therefore budget in advance for the estimated number of patients who might need this support.

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. In some settings, the mother may be offered the option of using a surgical mask or an N-95 respirator (see Chapter 15) until she becomes sputum smear-negative.

9.4 Contraception

There is no contraindication to the use of oral contraceptives with the 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 antituberculosis treatment. 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 can be tolerated.

For patients with mono- and poly-resistant TB that is 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, use of an oral contraceptive pill containing a higher dose of estrogen (50 µg); or use of another form of contraception.

9.5 Children

Children with DR-TB generally have primary resistance transmitted from an index case with DR-TB. Evaluation of children who are contacts of DR-TB patients is discussed in Chapter 14. When DST is available, it should be used to guide therapy, although children with paucibacillary TB are often culture-negative. Nevertheless, every effort should be made to confirm DR-TB bacteriologically by the use of DST and to avoid exposing children unnecessarily to toxic drugs.

The treatment of culture-negative children with clinical evidence of active TB disease and contact with a documented case of DR-TB should be guided

by the results of DST and the history of the contact's exposure to antituberculosis drugs (also see Chapter 14) (*4*).

There is only limited reported experience with the use of second-line drugs for extended periods in children. The risks and benefits of each drug should be carefully considered in designing a regimen. Frank discussion with family members is critical, especially at the outset of therapy. DR-TB is life-threatening, and no antituberculosis drugs are absolutely contraindicated in children. Children who have received treatment for DR-TB have generally tolerated the second-line drugs well (*4*, *5*).

Although fluoroquinolones have been shown to retard cartilage development in beagle puppies (*6*), experience with the use of fluoroquinolones has not demonstrated similar effects in humans (*7*, *8*). It is considered that the benefit of fluoroquinolones in treating DR-TB in children outweighs any risk. Additionally, ethionamide, PAS and cycloserine have been used effectively in children and are well tolerated.

In general, antituberculosis drugs should be dosed according to body weight (see Table 9.1). Monthly monitoring of body weight is therefore especially important in paediatric cases, with adjustment of doses as children gain weight (*9*).

All drugs, including the 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 DR-TB, as it is more difficult to monitor for optic neuritis in children.

In children who are not culture-positive initially, treatment failure is difficult to assess. Persistent abnormalities on chest radiograph do not necessarily signify a lack of improvement. In children, weight loss or, more commonly, failure to gain weight adequately, 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.

TABLE 9.1 **Paediatric dosing of second-line antituberculosis drugs (*4, 10*)**

DRUG	DAILY DOSE (MG/KG)	FREQUENCY	MAXIMUM DAILY DOSE
streptomycin	20–40	Once daily	1 g
kanamycin	15–30	Once daily	1 g
amikacin	15–22.5	Once daily	1 g
capreomycin	15–30	Once daily	1 g
ofloxacin	15–20	Twice daily	800 mg
levofloxacin	7.5–10	Once daily	750 mg
moxifloxacin	7.5–10	Once daily	400 mg
ethionamide	15–20	Twice daily	1 g
protionamide	15–20	Twice daily	1 g
cycloserine	10–20	Once or twice daily	1 g
p-aminosalicylic acid	150	Twice or thrice daily	12 g

Anecdotal evidence suggests that adolescents are at high risk for poor treatment outcomes. Early diagnosis, strong social support, individual and family counselling and a close relationship with the medical provider may help to improve outcomes in this group.

9.6 Diabetes mellitus

Diabetic patients with MDR-TB are at risk for poor outcomes. In addition, the presence of diabetes mellitus may potentiate the adverse effects of antituberculosis drugs, especially renal dysfunction and peripheral neuropathy. Diabetes must be managed closely throughout the treatment of DR-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 DR-TB but may require the patient to increase the dosage. Use of ethionamide or protionamide may make it more difficult to control insulin levels. Creatinine and potassium levels should be monitored more frequently, often weekly for the first month and then at least monthly thereafter.

9.7 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 9.2.

9.8 Liver disorders

The first-line drugs isoniazid, rifampicin and pyrazinamide are all 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, protionamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with the fluoroquinolones.

Patients with a history of liver disease can receive the usual DR-TB chemotherapy 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 antituberculosis 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

BOX 9.1 EXAMPLE OF REGIMEN DESIGN FOR PAEDIATRIC CASES

A mother who has been on treatment for MDR-TB for 9 months has been smear- and culture-negative for 6 months. She brings her child to the health centre for evaluation. The child is 14 months old and weighs 6.9 kg. She had BCG at birth and now presents with 4 months of failure to thrive, poor appetite and intermittent low grade fever for 3 months. Tuberculin (PPD) skin testing is 16 mm, and chest radiography reveals hilar adenopathy but no infiltrates. There are no other known TB contacts. TB was first diagnosed in the mother shortly after giving birth to the child; she is a patient who had both Category I and II treatment failure. Her resistance pattern from the start of treatment for DR-TB is:

Resistance to H,R,Z,E,S

Susceptible to Amk-Cm-Ofx

DST of PAS, Eto and Cs were not done because the laboratory cannot guarantee reproducibility of these agents.

What advice and regimen do you prescribe for the child?

Answer: It should be well explained to the mother that the child very likely has TB, most probably MDR-TB. If available, DST should be attempted (see Chapter 14). While waiting for the DST results, or if the diagnostic procedure is not available, the child should be started on an empirical regimen based on the DST pattern of the mother. The following regimen is indicated:

injectable agent-fluoroquinolone-Eto(Pto)-Cs

or

injectable agent-fluoroquinolone-PAS-Cs

The injectable agent can be any drug except S, in this case Km, Cm or Amk.

To illustrate dose calculation, the example for the regimen of Km-Ofx-Pto-Cs is given below. Both the low and high doses for the child's weight are calculated; a convenient dosing is then chosen between the two numbers (if necessary a pharmacist can mix the exact dose so that any milligram amount can be selected, and dosing is not limited to 1/4 or 1/2 tablets):

Kanamycin: (15 mg x 6.9 kg = 103 and 30 mg x 6.9 kg = 207). Select a dose between the two numbers, e.g. **200 mg per day, single dose**.

Ofloxacin: (15 mg x 6.9 kg = 103 and 20 mg x 6.9 kg = 138). A convenient dosing is 100 mg/day; this is the full daily dose. Table 9.1 indicates that the daily dose is given in divided doses, so the patient would receive **50 mg (1/4 tablet) in the morning and 50 mg (1/4 tablet) in the evening**.

Protionamide: (15 mg x 6.9 kg = 103 and 20 mg x 6.9 kg = 138). A convenient dosing is 125 mg/day; this is the full daily dose. Table 9.1 indicates that the daily dose is given in divided doses, so the patient would receive **62.5 mg (1/4 tablet) in the morning and 62.5 mg (1/4 tablet) in the evening**.

Cycloserine: (15 mg x 6.9 kg = 103 and 20 mg x 6.9 kg = 138). A convenient dosing is 125 mg/day. This is the full daily dose. Table 9.1 indicates that the daily dose is given in divided doses, so the patient would receive **62.5 mg (1/4 capsule) in the morning and 62.5 mg (1/4 capsule) in the evening**.

AS THE CHILD GAINS WEIGHT, THE DOSES WILL HAVE TO BE ADJUSTED (CHECK WEIGHT EVERY MONTH)

TABLE 9.2 **Adjustment of antituberculosis medication in renal insufficiency[a,b]**

DRUG	CHANGE IN FREQUENCY?	RECOMMENDED DOSE[b] AND FREQUENCY FOR PATIENTS WITH CREATININE CLEARANCE <30 ml/min OR FOR PATIENTS RECEIVING HAEMODIALYSIS
isoniazid	No change	300 mg once daily, or 900 mg three times per week
rifampicin	No change	600 mg once daily, or 600 mg three times per week
pyrazinamide	Yes	25–35 mg/kg per dose three times per week (not daily)
ethambutol	Yes	15–25 mg/kg per dose three times per week (not daily)
ofloxacin	Yes	600–800 mg per dose three times per week (not daily)
levofloxacin	Yes	750–1000 mg per dose three times per week (not daily)
moxifloxacin	No change	400 mg once daily
cycloserine	Yes	250 mg once daily, or 500 mg/dose three times per week[d]
terizidone	–	Recommendations not available
protionamide	No change	250–500 mg per dose daily
ethionamide	No change	250–500 mg per dose daily
p-aminosalicylic acid[e]	No change	4 g/dose, twice daily
streptomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)[f]
capreomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)[f]
kanamycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)[f]
amikacin	Yes	12–15 mg/kg per dose two or three times per week (not daily)[e]

[a] Adapted from *Treatment of tuberculosis* (*11*).

[b] For Group 5 drugs see manufacturers' recommendations on adjustment in renal insufficiency.

[c] To take advantage of the concentration-dependent bactericidal effect of many antituberculosis drugs, standard doses are given unless there is intolerance.

[d] 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).

[e] 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.

[f] Caution should be used with the injectable agents in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity.

is unrelated to TB or antituberculosis treatment. In this case, clinical judgement is necessary. In some cases, it is possible to defer antituberculosis treatment until the acute hepatitis has been resolved. In other cases when it is necessary to treat DR-TB during acute hepatitis, the combination of four non-hepatotoxic drugs is the safest option.

9.9 Seizure disorders

Some patients requiring treatment for DR-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 anti-seizure medication. If the seizures are not under control, initiation or adjustment of anti-seizure medication will be needed before the start of DR-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 anti-seizure 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 made together with the patient.

In mono- and poly-resistant cases, the use of isoniazid and rifampicin may interfere with many of the anti-seizure medications. Drug interactions should be checked before their use (see Annex 1 for drug interactions).

Seizures that present for the first time during antituberculosis therapy are likely to be the result of an adverse effect of one of the antituberculosis drugs. More information on the specific strategies and protocols to address adverse effects is provided in Chapter 11.

9.10 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 DR-TB. The initial evaluation documents any existing psychiatric condition and establishes 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 MDR-TB, often connected with the chronicity and socioeconomic stress factors related to the disease.

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 MDR-TB patients and may be helpful for patients with or without

psychiatric conditions. (Adequate measures to prevent infection risk should be in place for the group therapy.)

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 DR-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's being a danger to him or herself or others. Additional information on psychiatric adverse effects is provided in Chapter 11, Table 11.3.

9.11 Substance dependence

Patients with substance dependence disorders should be offered treatment for their addiction. Complete abstinence from alcohol or other substances should be strongly encouraged, although active consumption is not a contraindication for antituberculosis treatment. If the treatment is repeatedly interrupted because of the patient's dependence, therapy should be suspended until successful treatment or measures to ensure adherence have been established. Good DOT 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. However, if cycloserine is considered important to the regimen, it should be used and the patient closely observed for adverse effects, which are then adequately treated.

9.12 HIV-infected patients

Given the important interaction between HIV infection and drug-susceptible and DR-TB, a full chapter (Chapter 10) is devoted to this subject.

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CHAPTER 10

DR-TB and HIV

10.1 Chapter objectives

This chapter aims to illustrate where the management of DR-TB differs in the presence of known or suspected HIV infection and to provide guidance on recent developments in the approach to TB/HIV.[1] The chapter outlines:

[1] TB/HIV is the term used in the context of the overlapping of the two epidemics of TB and HIV/AIDS, and is often used to describe joint TB and HIV/AIDS activities. Patients with HIV-associated TB should be referred to as such.

- recommended collaborative TB/HIV activities that may be used alongside specific activities to mitigate the problem of DR-TB in HIV-infected persons;
- diagnostic and clinical guidelines for management of DR-TB in HIV-infected patients;
- potential drug interactions, toxicities and monitoring requirements in the concomitant treatment of DR-TB and HIV;
- infection control implications in the context of HIV and TB.

Key recommendations (* indicates updated recommendation)

- Perform provider-initiated HIV testing and counselling in all TB suspects.*
- Use standard algorithms to diagnose pulmonary and extrapulmonary TB.
- Use mycobacterial cultures and, where available, newer more rapid methods of diagnosis.
- Perform DST at the start of antituberculosis therapy to avoid mortality due to unrecognized DR-TB in HIV-infected individuals.*
- Determine the extent (or prevalence) of antituberculosis drug resistance in patients with HIV.
- Introduce antiretroviral therapy promptly in DR-TB/HIV patients.
- Consider empirical therapy with second-line antituberculosis drugs.*
- Provide co-trimoxazole preventive therapy as part of a comprehensive package of HIV care to patients with active TB and HIV.*
- Arrange treatment follow-up by a specialized team.
- Implement additional nutritional and socioeconomic support.
- Ensure effective infection control.
- Involve key stakeholders in DR-TB/HIV control activities.
- Monitor for overlying toxicity with ART and DR-TB therapy.

10.2 General considerations

HIV coinfection is a significant challenge for the prevention, diagnosis and treatment of DR-TB, especially in the case of MDR-TB and XDR-TB. Reports have shown high mortality rates among HIV-infected patients with DR-TB (*1*, *2*), and alarming mortality rates in patients coinfected with XDR-TB and HIV (*3*). Early diagnosis of DR-TB and HIV, prompt treatment with adequate regimens, sound patient support and strong infection control measures are all essential components in the management of DR-TB in HIV-infected people.

Recent global drug resistance surveillance suggests an association between HIV and MDR-TB in some parts of the world, although specific factors involved in this association have not been determined HIV is a powerful risk factor for all forms of TB, and DR-TB outbreaks, including XDR-TB outbreaks in HIV-infected patients, appear to be common (*3*–*7*). DR-TB is often associated with higher mortality rates in the HIV-infected compared with the

non-infected; however, the use of ART in addition to treatment of DR-TB has been reported to improve outcomes of DR-TB in the HIV-infected (*8*, *9*).

10.3 Recommended collaborative TB/HIV activities

WHO recommends that certain collaborative activities are carried out to decrease the joint burden of TB and HIV (see Table 10.1) (*10–12*).

These activities are the backbone of the WHO TB/HIV collaborative strategy that, along with the implementation of effective DOTS programmes, will strengthen and increase the success of DR-TB/HIV control and treatment activities.

These guidelines recommend whenever possible the highest standard of care. The activities described below are based on the TB/HIV activities listed in Table 10.1 and are adapted to be specifically applicable to DR-TB.

- **Perform provider-initiated HIV testing and counselling in all TB suspects.** Given the high levels of HIV and TB coinfection in many settings, provider-initiated HIV counselling and testing is recommended for all TB suspects (*13*, *14*). Provider-initiated testing can be done at the same time the sputum is sent for smear microscopy (or culture). This is more efficient and more likely to be successful than referring patients elsewhere for HIV testing and counseling (*15*). Provider-initiated counselling and testing can serve as a gateway to lifesaving prevention, care and treatment interventions.
- **Use standard algorithms to diagnose pulmonary and extrapulmonary TB.** New recommendations for improving the diagnosis and treatment of

TABLE 10.1 **WHO-recommended collaborative TB/HIV activities**[a]

A. ESTABLISH THE MECHANISMS FOR COLLABORATION
A.1 Set up a coordinating body for TB/HIV activities effective at all levels
A.2 Conduct surveillance of HIV prevalence among TB patients
A.3 Carry out joint TB/HIV planning
A.4 Conduct monitoring and evaluation
B. DECREASE THE BURDEN OF TB IN PEOPLE LIVING WITH HIV/AIDS
B.1 Establish intensified TB case-finding and contact tracing
B.2 Introduce isoniazid preventive therapy
B.3 Ensure TB infection control in health-care and congregate settings
C. DECREASE THE BURDEN OF HIV IN TB PATIENTS
C.1 Provide HIV testing and counselling
C.2 Introduce HIV prevention methods
C.3 Introduce co-trimoxazole preventive therapy
C.4 Ensure HIV/AIDS care and support
C.5 Introduce antiretroviral therapy

[a] A detailed description of each of the activities listed in Table 10.1 can be found in the WHO document *Interim policy on collaborative TB/HIV activities* (*10*).

smear-negative pulmonary and extrapulmonary TB have been put forth by WHO (*16*). Also see section 10.4 below.

- **Use mycobacterial cultures and, where available, newer more rapid methods of diagnosis.** Mycobacterial cultures of sputum or other fluids and tissues are recommended to help in the diagnosis of sputum smear-negative and extrapulmonary TB (*16*). The heavy reliance on smear microscopy has significant limitations and is insufficient to reliably diagnose a significant proportion of HIV-coinfected patients, especially as the degree of immunosuppression advances (*17*). Rapid methods such as liquid culture or molecular techniques should be considered (*18*). See Chapter 6 for more information on culture methods.
- **Perform DST at the start of antituberculosis therapy.** Unrecognized DR-TB carries a high risk of mortality in patients with HIV (*19*). Prompt initiation of appropriate antituberculosis treatment (and subsequent initiation of ART) can reduce mortality among HIV-infected patients infected with DR-TB (*29*, *21*). Because unrecognized MDR-TB and XDR-TB are associated with such high mortality in HIV-infected patients, many international protocols dictate the performance of DST and/or rapid drug-resistance testing for all HIV-infected patients with established active TB. (See Chapter 5 and section 10.4 below for more discussion on rapid tests and diagnosing DR-TB in HIV patients.) While performing DST for all TB/HIV coinfected patients is the standard of care for many areas, these guidelines recognize that this may be difficult or impossible in many resource-limited settings. Alternative strategies are provided in section 10.4 for programmes with resource constraints. However, universal access to DST is the long-term goal for all settings.
- **Determine the extent (or prevalence) of TB drug resistance in patients with HIV.** Programmes should determine the extent of the overlap of the DR-TB and HIV epidemics. This can be done in two ways: (i) data from population-based TB DRS can be linked with HIV testing of those TB patients included (*22*); and/or (ii) when implementing HIV surveillance among TB patients (or provider-initiated testing and counselling for all TB patients), DST can be included in all, or an unbiased sub-set of, HIV-infected patients. The latter technique is more complex if rates of DR-TB in HIV-infected and negative patients are to be compared, as a control group of HIV-negative TB infected patients would also need to be established.
- **Introduce ART promptly in DR-TB/HIV patients.** These guidelines recommend the prompt initiation of ART in HIV-infected patients with DR-TB according to WHO guidelines (*23*) (see section 10.5 and Table 10.2 on when to initiate HIV treatment in DR-TB). Where indicated, pro-

tocols to manage immune reconstitution inflammatory syndrome (IRIS) should be followed (see section 10.5.6 for more information on IRIS).

- **Consider empirical therapy with second-line antituberculosis drugs.** Patients with a very high risk of DR-TB can be empirically started on Category IV regimens. This strategy can be applied to all patients regardless of HIV status but is especially important in those with HIV. (Note: empirical use of Category IV is reserved for patients who have an extremely high rate of MDR-TB, such as failures of Category II or very close contacts of DR-TB. See Chapter 5 for more information on the use of empirical Category IV).
- **Provide CPT for patients with active TB and HIV.** CPT should be provided to all patients with HIV according to WHO recommendations (*24*). This therapy is not known to interact significantly with any of the second-line antituberculosis agents. There are overlapping toxicities between ART, antituberculosis therapy and CPT, and vigilance in terms of monitoring adverse effects is required (see Table 10.3 below and Chapter 11).
- **Arrange treatment follow-up by a specialized team.** The team of care providers should be familiar with the treatment of both DR-TB and HIV, with close monitoring of potential additive adverse effects and nutritional status as well as periodic assessments of therapeutic response for both infections.
- **Implement additional nutritional and socioeconomic support.** Patients with DR-TB and HIV may suffer from severe wasting, diarrhoeal diseases, and malabsorption syndromes. Coinfected patients often come from socially marginalized groups or from families with low economic resources. Additionally, DR-TB therapy with second-line antituberculosis medications may result in adverse effects that affect treatment adherence and require more frequent visits to health facilities. Wherever possible, patients with DR-TB/HIV and limited means should be offered socioeconomic and nutritional support (*25*) (also see Chapter 12 for more information on treatment support).
- **Ensure effective infection control.** Infection control procedures can reduce the risk of *M. tuberculosis* transmission in HIV/AIDS care facilities. Infection control issues concerning DR-TB, including issues regarding HIV, are discussed in Chapter 15 and in other documents published by WHO (*26*).
- **Involve key stakeholders in DR-TB/HIV activities.** The local/national TB/HIV coordinating bodies, community groups and key stakeholders should be involved in the planning and monitoring of DR-TB/HIV activities and programmes.

10.4 Clinical features and diagnosis of DR-TB in HIV-infected patients

The diagnosis of TB (including MDR-TB and XDR-TB) in HIV-infected people 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 (*27*). This can result in misdiagnosis or delays in diagnosis, and in turn, higher morbidity and mortality. Algorithms have recently been published by the WHO with the aim of improving the diagnosis of smear-negative pulmonary and extrapulmonary TB (*16*). The new algorithms emphasize the use of clinical criteria first and, if needed, the use of additional laboratory data (culture) and radiography to diagnose TB. Clinical criteria have been shown to have an 89–96% positive predictive value of smear-negative and extrapulmonary TB when compared with culture (*28*). For patients with advanced HIV disease, 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 HIV patients with TB are screened for drug- resistance with DST. Rapid drug-resistance testing is the DST technique of choice 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 DR-TB.

Programmes without facilities or resources to screen all HIV-infected patients for DR-TB should put significant efforts into obtaining them, especially if DR-TB rates are moderate or high. Some programmes may adopt a strategy of targeted DST for patients with increased risk of DR-TB (such as those in whom treatment has failed or who are contacts of DR-TB cases (see Chapter 5)). Programmes may also choose to use targeted DST for those with lower CD4 counts (e.g. less than 200 cells/mm^3) since these patents are at a very high risk of death due to unrecognized DR-TB.

10.5 Concomitant treatment of DR-TB and HIV

The treatment of DR-TB in patients with HIV is very similar to that in patients without HIV and is described in Chapter 7, with the following exceptions:

- ART plays a crucial role, as mortality in MDR-TB/HIV patients without the use of ART is extremely high (91–100% as reported in one analysis of MDR-TB outbreaks in 9 different institutions) (*7*).
- Adverse effects are more common in patients with HIV. The multiple medicines involved in DR-TB with recognized high toxicity risks, often combined with ART, results in a high incidence of adverse effects. Some toxicities are common to both antituberculosis treatment and ART, which may result in added rates of adverse events.

- Monitoring needs to be more intense for both response to therapy and adverse effects.
- The use of thioacetazone is not recommended for patients with HIV (*29*) or for routine use in populations with high rates of HIV.
- IRIS may complicate therapy.

10.5.1 Initiating ART treatment in patients with DR-TB

The use of ART in HIV-infected patients with TB improves survival for both drug-resistant and susceptible disease (*9*, *16*, *30*). As stated above, cohorts of patients treated for DR-TB without the benefit of ART have experienced mortality rates often exceeding 90% (*3*, *7*). However, the likelihood of adverse effects could compromise the treatment of either HIV or DR-TB if both treatments are started simultaneously. On the other hand, undue delay in the start of ART could result in significant risk of HIV-related death among patients with advanced disease (*31*). The optimal timing for the introduction of ART in patients receiving TB treatment is unknown. Table 10.2, based on WHO guidelines for the treatment of HIV infection in adults and adolescents (*23*), provides recommendations for initiating ART in relationship to starting therapy for DR-TB.

TABLE 10.2 **Timing of ART in the ART-naive patient starting antituberculosis therapy for DR-TB**

CD4 CELL COUNT	ART RECOMMENDATIONS	TIMING OF ART IN RELATION TO START OF DR-TB TREATMENT
CD4 <200 cells/mm^3	Recommend ART	At two weeks or as soon as DR-TB treatment is tolerated
CD4 between 200 and 350 cells/mm^3	Recommend ART	After eight weeks[a]
CD4 >350 cells/mm^3	Defer ART[b]	Re-evaluate patient monthly for consideration of ART start. CD4 testing is recommended every three months during DR-TB treatment.
Not available	Recommend ART[c]	Between two and eight weeks

[a] Clinical evaluation may prompt earlier initiation of ART.
[b] ART should be started if other non-TB stage 3 or 4 events are present.
[c] This recognizes that some patients may be prematurely placed on life-long ART.

10.5.2 DR-TB in patients already receiving ART

There are two issues to consider in patients who are diagnosed with DR-TB while on ART. The first is whether modification of ART is needed due to drug–drug interactions or to decrease the potential of overlapping toxicities. These concerns are discussed below.

The second issue is whether the presentation of active DR-TB in a patient on ART constitutes ART failure. The principles of determining failure in such cases are described in other WHO documents (*23*). If ART failure has been diagnosed, it is not recommended to begin a new second-line ART regimen at the same time as initiation of a DR-TB regimen. Instead, continue the present ART regimen and switch to the second-line ART regimen 2–8 weeks after the start of DR-TB treatment.

10.5.3 Important drug–drug interactions in the treatment of HIV and DR-TB

Currently, little is known about drug–drug interactions between second-line antituberculosis agents and antiretroviral therapy. There are several known interactions between drugs used to treat HIV and TB, which are summarized below.

- **Rifamycin derivatives.** While rifamycin derivatives are not routinely used in DR-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 PI-based regimens) is available elsewhere (*23*, *32*).
- **Quinolones and didanosine.** Buffered didanosine contains an aluminium/magnesium-based antacid and, if given jointly with fluoroquinolones, may result in decreased fluoroquinolone absorption (*33*); 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 (EC) formulation of didanosine can be used concomitantly without this precaution.
- **Ethionamide/protionamide.** Based on limited existing information of the metabolisim of the thiamides (ethionamide and protionamide), this drug class may have interactions with antiretroviral drugs. Ethionamide/protionamide is thought to be metabolized by the CYP450 system, although it is not know which of the CYP enzymes are responsible. Whether doses of ethionamide/protionamide and/or certain antiretroviral drugs should be modified during the concomitant treatment of DR-TB and HIV is completely unknown (*34*).
- **Clarithromycin.** Clarithromycin is a substrate and inhibitor of CYP3A and has multiple drug interactions with protease inhibitors and NNRTIs. If possible, the use of clarithromycin should be avoided in patients coinfected with DR-TB and HIV because of both its weak efficacy against DR-TB and multiple drug interactions.

10.5.4 Potential drug toxicity in the treatment of HIV and DR-TB

There is limited evidence on the frequency and severity of toxicities and adverse events from ART and second-line antituberculosis therapy. 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 reactions increases with the degree of immunosuppression (*27*, *35*, *36*, *37*). Identifying the source of adverse effects in patients receiving concomitant therapy for DR-TB and HIV is difficult. Many of the medications used to treat DR-TB and HIV have overlapping, or in some cases additive, toxicities. Often, it may not be possible to link adverse effects to a single drug, as the risk of resistance for ART therapy precludes the typical medical challenge of stopping all medications and starting them one by one (*38*).

Adverse effects that are common to both antiretroviral and antituberculosis drugs are listed in Table 10.3. It should be noted that relatively very little is known about the rates of adverse effects in the concomitant treatment of DR-TB and HIV. Table 10.3 is meant to alert the clinician to potentially overlapping and additive toxicities, and as of the writing of these guidelines is based on preliminary, non-published data and expert opinion.

When possible, avoid the use of agents with shared adverse 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, these guidelines recommend increased monitoring of adverse effects rather than disallowing a certain combination. See Chapter 11 and section 10.5.5 for monitoring adverse effects in HIV-infected patients.

10.5.5 Monitoring of DR-TB and HIV therapy in coinfected patients

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

The complexity of antiretroviral regimens and second-line antituberculosis treatment, each with its own toxicity profiles and some of which may be potentiated by concomitant therapy, demands rigorous clinical monitoring (*39*). Chapter 11, Table 11.1 describes the monitoring requirements while on DR-TB therapy and indicates where any extra monitoring is required for patients coinfected with HIV and/or on ART.

If the patient shows signs of antituberculosis treatment failure, the same evaluation described in Chapter 13 is warranted. In addition, the ART regi-

TABLE 10.3 **Potential overlying and additive toxicities of ART and antituberculosis therapy**

Drugs that are more strongly associated with adverse effects appear in bold.

TOXICITY	ANTIRETROVIRAL AGENT	ANTITUBERCULOSIS AGENT	COMMENTS
Peripheral neuropathy	**D4T**, **ddI**, **ddC**	**Lzd**, **Cs**, **H**, Amino glycosides, Eto/Pto, E	Avoid use of D4T, ddI and ddC in combination with Cs or Lzd because of theoretically increased peripheral neuropathy. If these agents must be used and peripheral neuropathy develops, replace the ARV agent with a less neurotoxic agent and treat according to Chapter 11.
Central nervous system (CNS) toxicity	**EFV**	**Cs**, H, Eto/Pto, Fluoroquinolones	Efavirenz has a high rate of CNS adverse effects (confusion, impaired concentration, depersonalization, abnormal dreams, insomnia and dizziness) in the first 2–3 weeks, which typically resolve on their own. If these effects do not resolve on their own, consider substitution of the agent. At present, there are limited data on the use of EFV with Cs; concurrent use is accepted practice with frequent monitoring for CNS toxicity. Frank psychosis is rare with EFV alone.
Depression	**EFV**	**Cs**, Fluoroquinolones, H, Eto/Pto	Severe depression can be seen in 2.4% of patients receiving EFV.[a] Consider substituting for EFV if severe depression develops. The severe socioeconomic circumstances of many patients with chronic disease can also contribute to depression.
Headache	**AZT**, **EFV**	**Cs**	Rule out more serious causes of headache such as bacterial meningitis, cryptococcal meningitis, CNS toxoplasmosis, etc. Use of analgesics (ibuprofen, paracetamol) and good hydration may help. Headache secondary to AZT, EFV and Cs is usually self-limited.
Nausea and vomiting	**RTV**, **D4T**, NVP, and most others	**Eto/Pto, PAS, H, E, Z** and others	Nausea and vomiting are common adverse effects and can be managed with modalities described in Chapter 11. Persistent vomiting and abdominal pain may be a result of developing lactic acidosis and/or hepatitis secondary to medications.

[a] (Bristol-Myers Squibb, letter to providers, March 2005).

Abdominal pain	**All ART treatment has been associated with abdominal pain**	**Cfz**, **Eto/Pto**, **PAS**	Abdominal pain is a common adverse effect and often benign; however, abdominal pain may be an early symptom of severe adverse effects such as pancreatitis, hepatitis or lactic acidosis.
Pancreatitis	**D4T**, **ddI**, **ddC**	**Lzd**	Avoid use of these agents together. If an agent causes pancreatitis suspend it permanently and do not use any of the pancreatitis producing anti-HIV medications (D4T, ddI, or ddC) in the future. Also consider gallstones or alcohol as a potential cause of pancreatitis.
Diarrhea	**All protease inhibitors, ddI (buffered formula)**	**Eto/Pto**, **PAS**, Fluoroquinolones	Diarrhoea is a common adverse effect. Also consider opportunistic infections as a cause of diarrhoea, or clostridium difficile (a cause of pseudomembranous colitis).
Hepatotoxicity	**NVP, EFV, all protease inhibitors** (RTV > other protease inhibitors), **all NRTIs**	**H**, **R**, **E**, **Z**, PAS, Eto/Pto, Fluoroquinolones	Follow hepatotoxicity treatment recommendations in Chapter 11. Also consider TMP/SMX as a cause of hepatotoxicity if the patient is receiving this medication. Also rule out viral etiologies as cause of hepatitis (Hepatitis A, B, C, and CMV).
Skin rash	**ABC**, **NVP**, **EFV**, **D4T** and others	**H**, **R**, **Z**, **PAS**, Fluoroquinolones, and others	Do not re-challenge with ABC (can result in life-threatening anaphylaxis). Do not re-challenge with an agent that caused Stevens-Johnson syndrome. Also consider TMP/SMX as a cause of skin rash if the patient is receiving this medication. Thioacetazone is contraindicated in HIV because of life-threatening rash.
Lactic acidosis	**D4T**, **ddI**, **AZT**, **3TC**	**Lzd**	If an agent causes lactic acidosis, replace it with an agent less likely to cause lactic acidosis.

TABLE 10.3 *(continued)*

Drugs that are more strongly associated with adverse effects appear in bold.

TOXICITY	ANTIRETROVIRAL AGENT	ANTITUBERCULOSIS AGENT	COMMENTS
Renal toxicity	TDF (rare)	**Aminoglycosides**, **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. There are no data on the concurrent use of TDF with aminoglycosides or Cm. Use TDF with caution in patients receiving aminoglycosides or Cm. 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 every 1 to 3 weeks is recommended (see Chapter 11). Many ARV and antituberculosis medications need to be dose adjusted for renal insufficiency.
Nephrolithiasis	**IDV**	None	No overlapping toxicities regarding nephrolithiasis have been documented between ART and antituberculosis medications. Adequate hydration prevents nephrolithiasis in patients taking IDV. If nephrolithiasis develops while on IDV, substitute with another protease inhibitor if possible.
Electrolyte disturbances	TDF (rare)	**Cm**, **Aminoglycosides**	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 (see Chapter 11). Replace AZT if bone marrow suppression develops. Consider suspension of Lzd. Also consider TMP/SMX as a cause if the patient is receiving this medication. Consider adding folinic acid supplements, especially if receiving TMP/SMX.
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.

Hyperlipidemia	**Protease inhibitors**, **EFV**	None	No overlapping toxicities regarding hyperlipidemia have been documented between ART and antituberculosis medications. Follow WHO ART guidelines for management of hyperlipidemia (*23*).
Lipodystrophy	**NRTIs** (especially D4T and ddI	None	No overlapping toxicities regarding lipodystrophy have been documented between ART and antituberculosis medications. Follow WHO ART guidelines for management of lipdystrophy (*23*).
Dysglycemia (disturbed blood sugar regulation)	**Protease inhibitors**	**Gfx**, Eto/Pto	Protease inhibitors tend to cause insulin resistance and hyperglycaemia. Eto/Pto tend to make insulin control in diabetics more difficult, and can result in hypoglycaemia and poor glucose regulation. Gatifloxacin is no longer recommended by the GLC for use in treatment of TB because of this side-effect.
Hypothyroidism	D4T	**Eto/Pto**, **PAS**	There is potential for overlying toxicity, but evidence is mixed. Several studies show subclinical hypothyroidism associated with HAART, particularly stavudine. PAS and Eto/Pto, especially in combination, can commonly cause hypothyroidism.

men should be evaluated for possible treatment failure, as described in other WHO guidelines (*23*).

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 DR-TB may require special socioeconomic, nutritional and psychosocial support in order to successfully complete treatment.

10.5.6 Immune reconstitution inflammatory syndrome

IRIS has emerged as an important complication of ART. It 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 (*40*, *41*)); 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 a previously subclinical and unrecognized opportunistic infection (*23*, *42*). 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) (*16*, *42*).

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 (*23*). IRIS can also be confused with TB treatment failure, and coinfected 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 non-steroidal anti-inflammatory drugs in mild disease and corticosteroids in moderate-severe disease. Most patients can be treated without interruption of ART.

10.6 XDR-TB and HIV

XDR-TB has been described in a number of countries, including settings with a high prevalence of HIV. An algorithm to help diagnose XDR-TB in HIV-infected individuals is provided in Chapter 5. Treatment strategies for XDR-TB are outlined in Chapter 7.

10.7 Implications of HIV for MDR-TB infection control

Delay in recognition of DR-TB, prolonged periods of infectiousness, crowded wards, and mixing TB and HIV patients all contribute to nosocomial transmission. These practices have contributed to DR-TB outbreaks that affect both HIV-infected and non-infected patients.

Implementation of adequate infection control precautions at health facili-

ties significantly reduces nosocomial transmission (*43*). Some community-based treatment programmes have used home-based measures such as separate living quarters, personal respiratory protection for visitors and adequate ventilation (*44*). Infection control measures for DR-TB, including in the setting of high HIV prevalence, are described in Chapter 15.

10.8 Coordination of HIV and TB care: involvement of the TB/HIV board

The national TB and HIV/AIDS control programmes need a joint strategic plan to collaborate successfully and systematically on carrying out the recommended joint activities. Given the high prevalence of TB among patients with HIV infection, a joint plan should be made to diagnose TB in such patients, to determine the drug susceptibility of the strain, and to provide adequate and appropriate treatment. Alternatively, components can be introduced in their respective programmes to ensure adequate diagnosis, care, treatment and referral of patients infected with both HIV and DR-TB. Coordinated training activities should focus on developing a group of providers in a specialized multidisciplinary team with adequate expertise in both areas. The roles and responsibilities of each programme at the national and district levels must be clearly defined, as well as the roles of individual team members. Communities and patients should be involved in programme design from an early stage.

10.9 Summary

DR-TB in HIV-infected patients is highly lethal and a growing problem in many parts of the world. As programmes embark on DR-TB and HIV control strategies, the activities described in section 10.3 should be strengthened, and, where absent, implemented. Improved case detection, timely and appropriate therapy, close clinical monitoring, management of adverse effects and infection control measures are the essential components of a successful programme. TB and HIV programmes realizing the control strategies put forth in this chapter will have the best chance to stem the epidemic of HIV-associated DR-TB.

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CHAPTER 11

Initial evaluation, monitoring of treatment and management of adverse effects

11.1 Chapter objectives

This chapter provides information on the identification and management of adverse effects caused by second-line antituberculosis drugs. It addresses the following:

- monitoring requirements for the treatment of DR-TB;
- monitoring actions for early detection of adverse effects;
- adverse effects associated with different second-line drugs;
- strategies for the treatment of adverse effects;
- adverse effects in HIV-coinfected patients.

11.2 Pretreatment screening and evaluation

The required initial pretreatment clinical investigation includes a thorough medical history and physical examination. The recommended initial laboratory evaluations are shown in Table 11.1. The initial evaluation serves to establish a baseline and may identify patients who are at increased risk for adverse effects or poor outcomes. 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 (diabetes mellitus,

Key recommendations (* indicates updated recommendation)

- Implement standard monitoring for all patients DR-TB treatment as per Table 11.1.
- Monitor both smear and culture monthly to evaluate treatment response.*
- Increase monitoring for HIV coinfected patients and for those on ART.*
- Health-care workers in DR-TB control programmes should be familiar with the management of common adverse effects of MDR-TB therapy.
- Ancillary drugs for the management of adverse effects should be available to the patient.

renal insufficiency, acute or chronic liver disease, thyroid disease, mental illness, drug or alcohol dependence, HIV infection, pregnancy, lactation and others). The management of DR-TB when these conditions exist is described in Chapter 9. Methods of avoiding pregnancy during treatment for women of childbearing age should be discussed.

11.3 Monitoring progress of treatment

Patients should be monitored closely for signs of treatment failure. Clinically, the most important way to monitor response to treatment is through regular history-taking and physical examination. The classic symptoms of TB – cough, sputum production, fever and weight loss – generally improve within the first few months of treatment and should be monitored frequently by health-care providers. The recurrence of TB symptoms after sputum conversion, for example, may be the first sign of treatment failure. For children, height and weight should be measured regularly to ensure that they are growing normally. A normal growth rate should resume after a few months of successful treatment.

Objective laboratory evidence of improvement often lags behind clinical improvement. The chest radiograph may be unchanged or show only slight improvement, especially in re-treatment patients with chronic pulmonary lesions. Chest radiographs should be taken at least every six months, when a surgical intervention is being considered, or whenever the patient's clinical situation has worsened. The most important objective evidence of improvement is conversion of the sputum smear and culture to negative. While sputum smear is still useful clinically because of its much shorter turnaround time, sputum culture is much more sensitive and is necessary to monitor the progress of treatment. Sputum examinations are also dependent on the quality of the sputum produced, so care should be taken to obtain adequate specimens.

Persistently positive sputums and cultures for AFB should be assessed for NTM, as overgrowth with NTM in lung damage secondary to TB is not uncommon. In such cases, although DR-TB may be adequately treated, treatment may need to be directed towards the NTM as well.

Sputum conversion is slower in DR-TB than in drug-susceptible TB. Paucibacillary culture results should not be automatically regarded as negative when treating DR-TB. Acquired drug resistance and treatment failure often begin with the growth of one or two colonies on a sputum culture. 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. The factors associated with this reconversion and its implications are under study.

Sputum smears and cultures should be monitored closely throughout treatment. These guidelines recommend that the tests be performed monthly before smear and culture conversion, with conversion defined as two consecutive negative smears and cultures taken 30 days apart. After conversion, the minimum period recommended for bacteriological monitoring is monthly for smears and quarterly for cultures (Table 11.1). Programmes with adequate culture capacity may choose to do cultures more frequently, every 1–2 months, after conversion.

Specimens for monitoring do not need to be examined in duplicate, but doing so can increase the sensitivity of the monitoring.

For patients who remain smear- and culture-positive during treatment or who are suspects for treatment failure, DST can be repeated. It is usually not necessary to repeat DST within less than three months of completion of treatment.

11.4 Monitoring for adverse effects during treatment

Close monitoring of patients is necessary to ensure that the adverse effects of second-line drugs are recognized quickly by health-care personnel. The ability to monitor patients for adverse effects daily is one of the major advantages of DOT over self-administration of DR-TB treatment.

The majority of adverse effects are easy to recognize. Commonly, patients will volunteer that they are experiencing adverse effects. However, it is important to have a systematic method of patient interviewing 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. DOT workers should be trained to screen patients regularly for symptoms of common adverse effects: rashes, gastrointestinal symptoms (nausea, vomiting, diarrhoea), psychiatric symptoms (psychosis, depression, anxiety, suicidal ideation), jaundice, ototoxicity, peripheral neuropathy and symptoms of electrolyte wasting (muscle cramping, palpitations). DOT workers should also be trained in simple adverse effect management and when to refer patients to a nurse or physician.

Laboratory screening is invaluable for detecting certain adverse effects that are more occult (not obviously noted by taking the history of the patient or by physical examination). The recommendations in Table 11.1 are an estimate of the minimal frequency of essential laboratory screening based on the

experience of several DOTS-Plus projects (*1*). More frequent screening may be advisable, particularly for high-risk patients. Table 11.1 includes monitoring recommendations for HIV-infected patients.

Nephrotoxicity is a known complication of the injectable drugs, both of the aminoglycosides and of capreomycin. This adverse effect is occult in onset and can be fatal. The optimal timing for checking serum creatinine is unknown, but most current treatment programmes for DR-TB check serum creatinine at least monthly. In addition, patients with a history of renal disease (including co-morbidities 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 may help to further stratify the risk of nephrotoxicity in these patients (see Chapter 9, section 9.7).

Electrolyte wasting is a known complication of the antituberculosis 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 high-risk patients, and in all those taking capreomycin (*2*).

Hypothyroidism is a late effect provoked by PAS and ethionamide. It is suspected by clinical assessment and confirmed by testing the serum level of thyroid stimulating hormone (TSH). The use of these agents together can produce hypothyroidism in up to 10% of patients (*3*). Since the symptoms can be subtle, it is recommended that patients are screened for hypothyroidism with a serum TSH at 6–9 months, and then tested again every 6 months or sooner if symptoms arise. The dosing of thyroid replacement therapy should be guided using serum levels of TSH. Goitres can develop due to the toxic effects of PAS, ethionamide or protionamide. In areas where iodine-deficiency goitres are endemic, treatment with iodine is indicated, in addition to assessment and treatment for hypothyroidism.

11.5 Management of adverse effects

Second-line drugs have many more adverse effects than the first-line antituberculosis drugs. Management of adverse effects is possible even in resource-poor settings (*3*). Proper management of adverse effects begins with patient education. Before starting treatment, the patient should be instructed in detail about the potential adverse effects that could be produced by the prescribed drug regimen, and if and when to notify a health-care provider.

Table 11.2 reports the number and percentage of patients who had a particular adverse event, observed in the first five GLC-approved projects. The percentage of events may vary depending on the regimens used (for example, among patients using both ethionamide and PAS, a high proportion may develop a rate of hypothyroidism above 3.5%). Nonetheless, Table 11.2 provides

TABLE 11.1 **Monitoring during treatment of DR-TB**

MONITORING EVALUATION	RECOMMENDED FREQUENCY
Evaluation by clinician	At baseline, and at least monthly until conversion, then every 2–3 months
Screening by DOT worker	At every DOT encounter
Sputum smears and cultures	Monitor smears and cultures monthly throughout treatment. (Note: programmes with limited resources may choose to do smears monthly but cultures only every other month)
Weight	At baseline and then monthly
Drug susceptibility	At baseline in programmes doing individualized treatment testing (DST) or in programmes doing standardized treatments that need to confirm MDR-TB. For patients who remain culture-positive, it is not necessary to repeat DST within less than 3 months of treatment
Chest radiograph	At baseline, and then every 6 months
Serum creatinine	At baseline, then monthly if possible while receiving an injectable drug. Every 1–3 weeks in HIV-infected patients, diabetics and other high-risk patients
Serum potassium	Monthly while receiving an injectable agent. Every 1–3 weeks in HIV-infected patients, diabetics and other high-risk patients
Thyroid stimulating hormone (TSH)	Every 6 months if receiving ethionamide/protionamide hormone and/or PAS; and monitor monthly for signs/symptoms of hypothyroidism. TSH is sufficient for screening for hypothyroidism; it is not necessary to measure hormone thyroid levels
Liver serum enzymes	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, do monthly monitoring
HIV screening	At baseline, and repeat if clinically indicated
Pregnancy tests	At baseline for women of childbearing age, and repeat if indicated
Haemoglobin and white blood count	If on linezolid, monitor weekly at first, then monthly or as needed based on symptoms; there is little clinical experience with prolonged use For HIV-positive patients on an ART regimen that includes AZT, 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, D4T, ddI, ddc.
Lactic acidosis	Indicated for work up of lactic acidosis in patients on linezolid or ART
Serum glucose	If receiving gatifloxacin, monitor glucose frequently (weekly) and educate patient on signs and symptoms of hypoglycaemia and hyperglcycaemia

DR-TB control programmes with an indication of the expected prevalence of adverse effects. Complete discontinuation of therapy because of adverse effects is rare and applied to only 2% of the patients in this report. The data presented in Table 11.2 are for patients not infected with HIV. It is likely that the incidents of adverse effects are much higher in the HIV-infected; however, data at this time are very limited.

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.

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 patients with highly resistant TB, a satisfactory replacement drug may not be available, so that 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.

The adverse effects of a number of second-line drugs are highly dose-dependent.

TABLE 11.2 **Frequency of common adverse effects among 818 patients in five DR-TB control programme sites (*1*)**

ADVERSE EVENT	NO. OF PATIENTS 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)

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 for weight classes and dosing).

Pyridoxine (vitamin B_6) 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 of the management of adverse effects. This is one of the most important roles played by DOT workers, who educate patients about their 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 antituberculosis agents and the suggested management strategies. Overlapping toxicities for HIV-infected patients on ART and DR-TB treatment are addressed in Chapter 10.

Management often requires the use of ancillary medications to eliminate or lessen the adverse effects. DR-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 lists the 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 the respective drug management and budgeting. However, programmes may choose to have available alternative medications in the same class as those in the list, or other medications not listed here, depending on the treatment methods in a particular country.

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

11.6 Summary

The timely and intensive monitoring for, and management of, adverse effects caused by second-line drugs are essential components of DR-TB control programmes. Poor management of adverse effects increases the risk of default or irregular adherence to treatment, and may result in death or permanent morbidity. The health-care worker of the control programme should be familiar with the common adverse effects of MDR-TB therapy. Patients experiencing adverse effects should be referred to health-care workers who have experience

TABLE 11.3 **Common adverse effects, suspected agent(s) and management strategies**

ADVERSE EFFECT	SUSPECTED AGENT(S)[a]	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Seizures	**Cs**, H, fluoroquinolones	1. Suspend suspected agent pending resolution of seizures. 2. Initiate anticonvulsant therapy (e.g. phenytoin, valproic acid). 3. Increase pyridoxine to maximum daily dose (200 mg per day). 4. Restart suspected agent or reinitiate suspected agent at lower dose, if essential to the regimen. 5. Discontinue suspected agent if this can be done without compromising regimen.	1. Anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agent 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. 3. Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy.
Peripheral neuropathy	**Cs**, **Lzd**, **H**, S, Km, Am, Cm, Vi, Eto/Pto, fluoroquinolones	1. Increase pyridoxine to maximum daily dose (200 mg per day). 2. Change injectable to capreomycin if patient has documented susceptibility to capreomycin. 3. Initiate therapy with tricyclic antidepressants such as amitriptyline. Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms. 4. Lower dose of suspected agent if this can be done without compromising regimen. 5. Discontinue suspected agent if this can be done without compromising regimen.	1. Patients with co-morbid 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; however, some patients may experience improvement when offending agents are suspended.
Hearing loss and vestibular disturbances	**S**, **Km**, **Am**, **Cm**, Clr	1. Document hearing loss and compare with baseline audiometry if available. 2. Change parenteral treatment to capreomycin if patient has documented susceptibility to capreomycin. 3. Decrease frequency and/or lower dose of suspected agent if this can be done without compromising the regimen (consider administration three times per week). 4. Discontinue suspected agent if this can be done without compromising the regimen.	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 generally not reversible. 3. The risk of further hearing loss must be weighed against the risks of stopping the injectable in the treatment regimen. 4. 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.

Psychotic symptoms	**Cs**, **H**, fluoroquinolones, Eto/Pto	1. Stop suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control. 2. Initiate antipsychotic therapy. 3. Lower dose of suspected agent if this can be done without compromising regimen. 4. Discontinue suspected agent if this can be done without compromising regimen.	1. Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy. 2. Previous history of psychiatric disease is not a contraindication to the use of agents listed here but may increase the likelihood of psychotic symptoms developing during treatment. 3. Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent.
Depression	**Socio-economic circumstances**, **chronic disease**, **Cs**, fluoroquinolones H, Eto/Pto	1. Improve socioeconomic conditions. 2. Offer group or individual counselling. 3. Initiate antidepressant therapy. 4. Lower dose of suspected agent if this can be done without compromising the regimen. 5. Discontinue suspected agent if this can be done without compromising 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 the agents listed but may increase the likelihood of depression developing during treatment.
Hypothyroidism	**PAS**, **Eto/Pto**	1. Initiate thyroxine therapy.	1. Completely reversible upon discontinuation of PAS or ethionamide/protionamide. 2. The combination of ethionamide/protionamide with PAS is more frequently associated with hypothyroidism than the individual use of each drug.
Nausea and vomiting	**Eto/Pto**, **PAS**, H, E, Z	1. Assess for dehydration; initiate dehydration if indicated. 2. Initiate antiemetic therapy. 3. Lower dose of suspected agent if this can be done without compromising regimen. 4. Discontinue suspected agent if this can be done without compromising regimen – rarely necessary.	1. Nausea and vomiting universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy. 2. Electrolytes should be monitored and repleted if vomiting is severe. 3. Reversible upon discontinuation of suspected agent. 4. Severe abdominal distress and acute abdomen have been reported with the use of clofazimine. Although these reports are rare, if this effect occurs, clofazimine should be suspended.

TABLE 11.3 *(continued)*

ADVERSE EFFECT	SUSPECTED AGENT(S)[a]	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Gastritis	**PAS**, **Eto/Pto**	1. H2-blockers, proton-pump inhibitors, or antacids. 2. Stop suspected agent(s) for short periods of time (e.g, one to seven days). 3. Lower dose of suspected agent, if this can be done without compromising regimen. 4. Discontinue suspected agent if this can be done without compromising regimen.	1. Severe gastritis, as manifested by haematemesis, melaena or haematechezia, is rare. 2. Dosing of antacids should be carefully timed so as to not interfere with the absorption of antituberculosis drugs (take 2 hours before or 3 hours after antituberculosis medications). 3. Reversible upon discontinuation of suspected agent(s).
Hepatitis	**Z**, **H**, **R**, Eto/Pto, PAS, E, fluoro-quinolones	1. Stop all therapy pending resolution of hepatitis. 2. Eliminate other potential causes of hepatitis. 3. Consider suspending most likely agent permanently. Reintroduce remaining drugs, one at a time with the most hepatotoxic agents first, while monitoring liver function.	1. History of previous hepatitis should be carefully analysed to determine most likely causative agent(s); these should be avoided in future regimens. 2. Generally reversible upon discontinuation of suspected agent.
Renal toxicity	**S**, **Km**, **Am**, **Cm**, **Vm**	1. Discontinue suspected agent. 2. Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen. 3. Consider dosing 2–3 times a week if drug is essential to the regimen and patient can tolerate (close monitoring of creatinine). 4. Adjust all antituberculosis medications according to the creatinine clearance.	1. History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these co-morbidities may be at increased risk for developing renal failure. 2. Renal impairment may be permanent.
Electrolyte disturbances (hypoka-laemia and hypomagne-saemia)	**Cm**, **Vm**, Km, Am, S	1. Check potassium. 2. If potassium is low, also check magnesium (and calcium if hypocalcaemia is suspected). 3. Replace electrolytes as needed.	1. If severe hypokalaemia is present, consider hospitalization. 2. Amiloride 5–10 mg QD or spironolactone 25 mg QD may decrease potassium and magnesium wasting and is useful in refractory cases. 3. Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhoea.

Optic neuritis	**E**, Eto/Pto	1. Stop E. 2. Refer patient to an ophthalmologist.	1. Usually reverses with cessation of E. 2. Rare case reports of optic neuritis have been attributed to streptomycin.
Arthralgias	**Z**, fluoro-quinolones	1. Initiate therapy with non-steroidal anti-inflammatory drugs. 2. Lower dose of suspected agent if this can be done without compromising regimen. 3. Discontinue suspected agent if this can be done without compromising regimen.	1. Symptoms of arthralgia generally diminish over time, even without intervention. 2. Uric acid levels may be elevated in patients on pyrazinamide. Allopurinol appears not to correct the uric acid levels in such cases.

[a] See list of drug abbreviations, page vi.

Note: Drugs in bold type are more strongly associated with the adverse effect than drugs not in bold.

in treating the adverse effects. It is rarely necessary to suspend antituberculosis drugs completely. Ancillary drugs for the management of adverse effects should be available to the patient and without charge. Despite the many challenges, programmes in resource-poor areas can successfully monitor and manage large cohorts of patients when appropriate human and financial resources are available, and DOT workers and health-care workers are properly trained.

TABLE 11.4 **Commonly used ancillary medications**

INDICATION	DRUG
Nausea, vomiting, upset stomach	Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, bismuth subsalicylate
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 flouroquinolones
Oral candidiasis (non-AIDS patient)	Fluconazole, clotrimazole lozenges
Diarrhoea	Loperamide
Depression	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)
Severe anxiety	Lorazepam, diazepam, clonazepam
Insomnia	Dimenhydrinate
Psychosis	Haloperidol, thorazine, risperidone (consider benzotropine or biperiden to prevent extrapyramidal effects)
Seizures	Phenytoin, carbamazepine, valproic acid, phenobarbital
Prophylaxis of neurological complications of cycloserine	Pyridoxine (vitamin B_6)
Peripheral neuropathy	Amitriptyline
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, dexamethasone)
Bronchospasm	Inhaled beta-agonists (albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisone), injectable steroids (dexamethasone, methylprednisolone)
Hypothyroidism	Levothyroxine
Electrolyte wasting	Potassium and magnesium replacement

References

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CHAPTER 12

Treatment delivery and community-based DR-TB support

12.1 Chapter objectives

This chapter outlines the strategies for treatment delivery that will improve adherence among patients receiving treatment for DR-TB. The same strategies can also be used for any patient with TB, including drug-susceptible TB. The main adherence promotion strategies include DOT, socioeconomic support, emotional support and management of adverse effects.

The chapter devotes a section to community-based DR-TB care and support. It includes examples to illustrate that even in resource-constrained areas, engaging the community can contribute substantially to mitigating the problem of DR-TB.

Key recommendations (* indicates updated recommendation)

- Use disease education, DOT, socioeconomic support, emotional support, management of adverse effects and monitoring systems to improve adherence to treatment.
- NTPs are encouraged to incorporate community-based care and support into their national plans.*

12.2 Treatment delivery settings

There are several strategies for the delivery of DR-TB treatment, including community-based care, clinic-based treatment and hospitalization (*1*, *2*).

Regardless of the mode of delivery, the management of DR-TB depends on a steady supply of medicines provided to patients free of charge through a reliable network of educated providers.

- **Community-based care.** Although early in the history of DR-TB treatment, strict hospitalization of patients was considered necessary, community-based care provided by trained lay and community health workers (CHWs) can achieve comparable results and, in theory, may result in decreased nosocomial spread of the disease (*1*, *2*). In each setting, care should be delivered by a multidisciplinary team of providers, including physicians, nurses, social workers and CHWs. The roles and responsibilities of each of these groups of providers will vary depending on the needs and resources available in specific settings. A more detailed description of community-based care and support is given in section 12.10.
- **Clinic-based treatment.** Some DR-TB treatment strategies involve the patient travelling to a clinic each day to receive DOT. This system works provided there is no barrier to travel or if the patient lives near a facility offering DOT of DR-TB; the patient should be given an enabler for travel in situations other than these. The patient should be smear-negative if travelling on public transportation or waiting in common waiting rooms. Some facilities have a separate area with infection control measures for smear-positive patients. Special early morning appointments can be made for patients who need to get to work. An alternative version of this strategy is to have the clinic act as a "day hospital" where patients can rest or get a meal as an incentive for coming each day. Special attention must be taken in clinic-based programmes so that HIV-infected patients are not exposed to smear-positive patients.
- **Hospitalization.** Hospitals should provide acceptable living conditions, sufficient activities so that patients avoid boredom, adequate food, a heating system in cool areas, fans or cooling systems in hot climates and proper infection control measures. Infection control requirements are described in Chapter 15. Prisons require specific measures to improve adherence, which are described in detail in the WHO guidelines for TB control in prisons (*3*).

12.3 Adherence to therapy

Patients with DR-TB are more likely to have had problems with non-adherence in the past (*4*). Adherence to DR-TB therapy is particularly difficult because of its prolonged treatment regimens with larger numbers of drugs

that have more serious adverse effect profiles (*5*). Thus, DR-TB patients are at increased risk of non-adherence to treatment. Adherence is an essential element in preventing the generation of pan-resistant strains capable of community-wide spread that leave virtually no possibility of cure for the patient (*6*).

DR-TB treatment can be successful, with high overall rates of adherence, when adequate support measures are provided (*1*). These measures include enablers and incentives for delivery of DOT to ensure adherence to treatment and may include the following: disease education, DOT, socioeconomic support, emotional support, management of adverse effects and monitoring systems to improve adherence.

12.3.1 Disease education

Patients and their families should receive education about DR-TB, its treatment, potential adverse drug effects and the need for adherence to therapy. Educational interventions should begin at the start of therapy and continue throughout the course of treatment. Education can be provided by physicians, nurses, lay and CHWs and other health-care providers. Materials should be appropriate to the literacy levels of the population and should be culturally sensitive as well.

12.3.2 Directly observed therapy (DOT)

Because DR-TB treatment is the last therapeutic option for many patients, and because there is a serious public health consequence if therapy fails in a patient with DR-TB, it is recommended that all patients receiving treatment for DR-TB receive DOT either in the community, at health centres or posts, or within the hospital setting. DOT should be provided in a way that does not place undue burdens on patients and their families. Long transportation times and distances, short clinic operation hours and difficulty in accessing services may all reduce the efficacy of DOT.

- **Who can deliver DOT?** When human and financial resources permit, the first choice for DOT delivery is to use health-care workers. Otherwise, trained community members can serve as effective DOT workers. With appropriate training and support, they can visit patients in their homes or workplaces. Receiving DOT from a community member is often a convenient alternative to the health centre and can result in excellent treatment adherence (*7*). However, community members need more intensive training, ongoing supervision by health professionals and support to deliver DOT for DR-TB than those who deliver DOT for drug-susceptible TB. It is recommended that the patient's DOT worker should not be a family member. Family relationships are often complicated for the DR-TB patient, and a family observer could be subject to subtle manipulation by the patient, relatives, employers, etc.

- **Maintaining confidentiality.** The DOT worker should explore the need to maintain strict confidentiality regarding the patient's disease. In some cases, this may entail working out a system whereby the patient can receive medication without the knowledge of others.

12.3.3 Socioeconomic interventions

Socioeconomic problems, including hunger, homelessness and unemployment, should be addressed to enable patients and their families to adhere to treatment. These problems have been successfully tackled through the provision of "incentives" and "enablers". Enablers are goods or services that make it easier for patients to adhere to treatment, such as the provision of transportation vouchers. Incentives are goods or services that are used to encourage patients to adhere to therapy, such as the provision of clothing. Maximal interventions should be given to patients with the most need. Programmes should benefit from professional social workers who can assess the need for such socioeconomic interventions and monitor their delivery. Socioeconomic interventions have included:

- health care free of charge;
- food parcels for DR-TB patients and their dependents;
- temporary shelter in a housing facility or in a rented home for DR-TB patients;
- school fees for dependent children;
- transportation fees;
- advice and assistance in administrative matters relating to the treatment;
- assistance in defending rights and/or reinforcing the responsibilities of patients;
- providing skills training and livelihood to patients both while on treatment as well as to prepare them with skills that can support them as they reintegrate into the community upon treatment completion.

12.3.4 Psychosocial and emotional support

Having DR-TB can be an emotionally devastating experience for patients and their families. Considerable stigma is attached to the disease and this may interfere with adherence to therapy. In addition, the long nature of DR-TB therapy combined with the adverse effects of the drugs may contribute to depression, anxiety and further difficulty with treatment adherence. The provision of emotional support to patients may increase the likelihood of adherence to therapy. This support may be organized in the form of support groups or one-to-one counselling by trained providers. Informal support can also be provided by physicians, nurses, DOT workers and family members. Most programmes use a multidisciplinary "support to adherence" team (social worker, nurse, health educator, companion and doctor).

12.3.5 Early and effective management of adverse drug effects

Although rarely life-threatening, the adverse effects of second-line drugs can be debilitating for patients. Patients experiencing high rates of adverse effects may be at increased risk of non-adherence. Therefore, early and effective management of adverse effects should be part of adherence-promotion strategies in the management of DR-TB. In most cases, management of adverse effects can be accomplished using relatively simple and low-cost interventions without compromising the integrity of the DR-TB treatment regimen (*8*). Management of adverse effects is addressed in more detail in Chapter 11.

12.3.6 Monitoring and follow-up of the non-adherent patient

A strong system of monitoring that allows the patient to be followed throughout treatment must be in place. The forms in Chapter 18 are designed to assist the care provider in follow-up. When a patient fails to attend a DOT appointment, a system should be in place that allows prompt patient follow-up. Most often, this involves a DOT worker visiting the patient's home the same day to find out why the patient has missed an appointment and to ensure that treatment is resumed promptly and effectively. The situation should be addressed in a sympathetic, friendly and non-judgemental manner. Every effort should be made to listen to reasons for the patient missing a dose(s) and to work with patient and family to ensure continuation of treatment. Transportation problems should be addressed.

12.4 Community-based care and support

Community-based care and support is any action or help provided *by, with or from* the community, including situations in which patients are receiving ambulatory treatment. This support contributes to, and may even be necessary to, patient recovery. Political will from the health and local community authorities is vital to these efforts, and in settings with no tradition of community participation, it may help to involve organizations that have expertise in social mobilization and community organizing (*9*).

- **Community care supporters.** There are numerous potential supporters who can be brought into the effort to address programmatic needs on a local level (*9–13*). These include local health centre nurses, paid (and in some cases volunteer) CHWs, former and current patients, affected families, associations, cooperatives, grassroots organizations, local NGOs, community volunteers and many more.
- **Function of the community care supporters.** Community care supporters can provide assistance in clinical management, DOT, contact tracing, infection control, recording and reporting, training, advocacy and social support.

— *Clinical management.* This can come in the form of: (i) early detection of potentially serious adverse reactions and prompt referral of such reactions to health workers; (ii) provision of simple, non-medical measures to manage adverse reactions, e.g. oral hydration in mild diarrhoea, or counselling on the avoidance of alcohol while taking drugs that have hepatic effects, etc; and (iii) psychological encouragement. This can often be most effective when coming from patients and former patients who endured the same adverse effects while on treatment.

— *DOT.* Community-based support in DOT can be highly effective, especially if provided by former patients acting as treatment partners for daily DOT, who are living proof that adherence to daily DOT pays and that there is hope for cure if they persevere with their treatment. Former patients also show better understanding, having gone through the same treatment themselves. Even when DOT is not provided by a former patient but by a local community member, it is a powerful act of solidarity. This solidarity is vital to new patients, who often feel isolated and vulnerable.

— *Contact tracing.* New cases can be discovered by community-care supporters through contact tracing. Early diagnosis of new cases may improve cure rates and acts as an important infection control measure.

— *Infection control.* Community-based support in infection control includes providing health education to patients on simple infection control practices that can be done in the home, such as observing cough etiquette (covering the mouth and nose when coughing, or sneezing), keeping one's room well ventilated by opening windows or staying outdoors as much as possible while visiting others.

— *Recording and reporting.* Data obtained within the family and community can contribute to better comprehensive management. This can include documenting processes occurring outside the health centre and closer to the patient's home. Recording certain variables during a home visit can better assess risks for the patient and family (such as leaky roofs, insufficient living space or poor sanitary conditions). Community-based support in recording and reporting may require close supervision and validation by health facility staff, and should be done in a manner that underlines "partnership".

— *Training/education.* Community-based training and education can come in the form of peer educators (i.e. former patients) or trained advocates. Topics can include general information on TB, how DR-TB develops, the treatment of DR-TB and the importance of adherence and infection control. Training and education on DR-TB will be most effec-

tive with the aid of materials written in lay language. WHO has issued guidelines for the development of teaching materials under strategies referred to as advocacy, communication and social mobilization (ACSM) (*14–16*). These materials will be more effective if they contain input from patients. Patients can become part of a team that designs the text and visuals of materials for DR-TB patients. Topics such as the rights and responsibilities of patients as stated in the *Patients' charter for tuberculosis care* (*17*) should also be included. When former patients and care supporters participate in this health education process, it is more credible locally and serves also to raise awareness of TB in the wider community, strengthening basic TB control and care.

— Advocacy and decreasing stigma. Community-based supporters, often in the form of patients, give a voice and face to TB. The establishment of patient peer groups (community care club) and perhaps eventually a local organization or association can help reduce stigma and dispel inaccurate information about the disease. The groups can often influence decision-makers for policy change either in the clinics that they attend or in the wider community where they live.

— Social support. Community care supporters help identify socioeconomic and psychosocial needs and help channel support in a timely and more effective manner. They also help develop community resources that may provide useful support, and encourage patients to contribute to the community by upholding their responsibilities (see also sections 12.3.3 and 12.3.4 above on socioeconomic and psychosocial interventions).

- **The relationship of community-based support and hospitalization for DR-TB.** CHWs and community-based support can facilitate timely access to the hospital, as hospitals and emergency services sometime reject DR-TB patients, making advocacy necessary. During hospitalization, the community-based network can continue to accompany patients and provide additional support as needed. With an efficient network for community-based care, the patient will be able to return to ambulatory treatment sooner, resulting in less nosocomial transmission, reduced hospitalization costs and more hospital beds available for other patients. Understanding and compassion are often lacking in hospitals that cater to general diseases because of health workers' fear of contracting DR-TB, as well as lack of experience in dealing with DR-TB.

- **Costs and sustainability.** When care is rooted in the community, ownership by the community supporters will make the support more sustainable. The CHW is often the backbone of a community-based support network. These guidelines advocate for trained CHWs who are a certified part of the health system and who receive a regular stipend that is a reasonable

compensation for the amount of time that they spend each day participating in community-based care. The added cost of a strong CHW network is often cost effective because it contributes to lower rates of failure and prevention of further drug resistance.

- **Monitoring the CHW.** As stated, the CHW is often the backbone of the community-based network. Monitoring of the CHW can involve supervisors who perform unannounced or ad hoc visits to the patient. At these visits, they can perform pill counts, examinations of the treatment card and assess how activities are being carried out. Whenever a patient is doing poorly, a home visit and assessment of DOT should be performed. It is important to monitor the health status of CHWs and teach them how to protect themselves against TB transmission as well to ensure that they themselves do not develop disease. Weekly/monthly reports from the CHWs or those providing care in the community should be required. A communication network should be clear and in place, making sure that community volunteers have easy access to professional health staff should there be problems that arise in the community, e.g. adverse events or questions asked by patients that the CHWs cannot answer.

12.5 Conclusion

Treatment delivery to patients with DR-TB can be accomplished in even the most resource-poor settings. It may be carried out using a hospital-, clinic- or community-based approach, depending on the programme's organization and resources. Trained community members who are closely supervised on an ongoing basis can play an important role in the management of DR-TB in the NTP. Therefore, NTPs should be encouraged to incorporate community-based care and support into their national plans. Non-adherence to treatment is one of the primary factors leading to poor outcomes for patients with DR-TB. There are many reasons why patients may not adhere to therapy, and many of these stem from socioeconomic constraints. Higher rates of adherence can be achieved if patients are offered a comprehensive package of services, including disease education, DOT, socioeconomic support, emotional support, management of adverse effects and monitoring systems to improve adherence. The human resources required to deliver the proper support should not be underestimated (see Chapter 16). Provision of the services and strategies discussed in this chapter should be viewed as an essential part of DR-TB treatment programmes worldwide, not only as a method of improving clinical and epidemiological outcomes but also in solidarity with each member of the community, especially those in greatest need. The political will needed to ensure integration of community initiatives with local and national TB programme activities demonstrates a commitment to the right to health and promotes participation in activities promoting the common good. Empower-

ing the community and the individual recognizes and reinforces the dignity of each person.

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CHAPTER 13

Management of patients after MDR-TB treatment failure

13.1 Chapter objectives

The objectives of this chapter are:

- To describe the clinical approach in suspected MDR-TB treatment failure.
- To discuss indications for suspending treatment for patients in whom a Category IV regimen has failed.
- To outline the supportive care options for patients in whom all the possibilities of MDR-TB treatment have failed.

13.2 Assessment of patients at risk for treatment failure

Patients who do not show signs of improvement after four months of treatment are at risk for treatment failure. All patients who show clinical, radiographical or bacteriological evidence of progressive active disease, or reappearance of disease after month 4 of treatment, should be considered as being at high risk for treatment failure.

The following steps are recommended in such patients:

- The treatment card should be reviewed to confirm that the patient has adhered to treatment.
- The treatment regimen should be reviewed in relation to medical history, contacts and all DST reports. If the regimen is deemed inadequate, a new regimen should be designed.

- The bacteriological data should be reviewed. Often, the smear and culture data are the strongest evidence that a patient is not responding to therapy. 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, or in which the number of colonies is decreasing, may 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. Repeated culture- and smear-negative results in a patient with clinical and radiographical deterioration may indicate that the patient has a disease other than MDR-TB.
- The health-care worker should confirm that the patient has taken all the prescribed medicines. A non-confrontational interview should be undertaken without the DOT worker present.
- A non-confrontational interview of the DOT worker alone should also be carried out. Questions should be asked to rule out the possible manipulation of the DOT worker by the patient. If manipulation is suspected, the DOT worker should be switched to another patient, and the patient with suspected treatment failure should be assigned to a new DOT worker.
- Other illnesses that may decrease absorption of medicines (e.g. chronic diarrhoea) or may result in immune suppression (e.g. HIV infection) should be excluded.
- If surgical resection is feasible, it should be considered.

MDR-TB treatment often consists of a treatment cycle; if no response is seen, reassessment of the regimen and treatment plan and formulation of a new plan of action are necessary. Patients who have persistent positive smears or cultures at month 4 but who are doing well clinically and radiographically may not require a regimen change. Whenever a regimen change is indicated because of treatment failure, a new regimen is started (with at least four effective drugs) and options for adjunctive treatment – most commonly surgery – can be considered. Adding one or two drugs to a failing regimen should be avoided. Changes in treatment can be made as early as 4–6 months if conversion is not seen and if there is clinical deterioration.

13.3 Indications for suspending treatment

It takes 3–4 months to evaluate whether a change in treatment plan has been effective. If the patient continues to deteriorate despite the measures described in the previous section, treatment failure should be considered. There is no single indicator to determine whether a treatment regimen is failing. Although there is no simple definition for treatment failure, there often comes a point

during the treatment when it becomes clear that the patient is not going to improve. Signs indicating treatment failure include:

- persistent positive smears or cultures past month 8–10 of treatment;
- progressive extensive and bilateral lung disease on chest X-ray, with no option for surgery;
- high-grade resistance (often XDR-TB), with no option to add two additional agents;
- overall deteriorating clinical condition that usually includes weight loss and respiratory insufficiency.

It is not necessary for all of these signs to be present to identify failure of the treatment regimen. However, a cure is highly unlikely when they are all present.

The epidemiological definition of treatment failure for recording outcomes (see Chapter 4) is often different from that used in the process of suspending therapy in a patient when the therapy is failing. The epidemiological definition is an outcome to account for the patient in a treatment cohort analysis, while the clinical decision to suspend therapy is made after the clinical search for all other options has been exhausted and cure of the patient is considered to be highly unlikely.

13.4 Suspending therapy

Treatment can be considered to have failed and suspension of therapy is recommended in cases where the medical personnel involved are confident that all the drugs have been ingested and there is no possibility of adding other drugs or carrying out surgery.

There are two important considerations in suspending therapy or changing it to a supportive care regimen. The first is 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 suffering. The second is the public health concern: continuing a treatment that is failing can amplify resistance in the patient's strain, resulting in highly resistant strains such as XDR-TB that may cause subsequent infection of others.

13.5 Approach to suspending therapy

The approach to suspending therapy should start with discussions among the clinical team, including all physicians, nurses and DOT workers 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 takes place over 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.

13.6 Supportive care for patients in whom all the possibilities of MDR-TB treatment have failed

A number of supportive measures can be used once the therapy has been suspended. It is very important that medical visits continue and that the patient is not abandoned. The supportive measures are described in detail in the Integrated Management of Adolescent and Adult Illness guidelines produced by WHO in a booklet titled *Palliative care: symptom management and end-of-life care* (*1*). The supportive measures are summarized in Box 13.1.

BOX 13.1 END-OF-LIFE SUPPORTIVE MEASURES

- **Pain control and symptom relief.** Paracetamol, or codeine with paracetamol, gives relief from moderate pain. Codeine also helps control cough. Other cough suppressants can be added. If possible, stronger analgesics, including morphine, should be used when appropriate to keep the patient adequately comfortable.
- **Relief of respiratory insufficiency.** Oxygen can be used to alleviate shortness of breath. Morphine also provides significant relief from respiratory insufficiency and should be offered if available.
- **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 therapy stops, regular visits by the treating physician and support team should not be discontinued.
- **Continuation of ancillary medicines.** All necessary ancillary medications should be continued as needed. Depression and anxiety, if present, should be addressed.
- **Hospitalization, hospice care or nursing home care.** Having a patient die at home can be difficult for the family. Hospice-like care should be offered to families who want to keep the patient at home. Inpatient end-of-life care should be available to those for whom home care is not available.
- **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.
- **Infection control measures.** The patient who is taken off antituberculosis treatment because of failure often remains infectious for long periods of time. Infection control measures should be continued (see Chapter 15).

13.7 Conclusion

Suspension of therapy should be considered only after all other options for treatment have been explored. Suspending therapy in a patient who has failed MDR-TB treatment is a delicate situation and difficult for family members and caregivers; but it is especially difficult for the patient as treatment is often viewed as his or her only hope. Strong support, care and sympathy must be given to the patient and family.

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CHAPTER 14

Management of contacts of MDR-TB patients

14.1 Chapter objective

This chapter outlines the management of symptomatic adults and children who have or have had a known contact with an MDR-TB patient.

Key recommendations (* indicates updated recommendation)

- DR-TB contact investigation should be given high priority, and NTPs should consider contact investigation of XDR-TB as an emergency situation.*
- Close contacts of DR-TB patients should receive careful clinical follow-up.

14.2 General considerations

Opportunities to halt the transmission of resistant mycobacteria in communities and to treat MDR-TB in a timely fashion are often squandered. The main reasons are lack of investigation of contacts of MDR-TB patients, failure to ask patients presenting with active TB disease about any history of exposure to MDR-TB, and lack of access by national treatment programmes to second-line regimens and/or DST.

Close contacts of MDR-TB patients are defined as people living in the same household, or spending many hours a day together with the patient in the same indoor living space. The available data indicate that close contacts of MDR-TB patients who develop active TB most commonly have drug-resistant disease (*1–5*).

While all contacts of TB require investigation, DR-TB requires the most

vigilance. Because of the severe risk of morbidity and mortality of XDR-TB, contact tracing of cases of XDR-TB should be given the highest level of alertness and priority. **NTPs should consider contact investigation of XDR-TB as an emergency situation**.

14.3 Management of symptomatic adult contacts of patients with MDR-TB

All close contacts of MDR-TB cases should be identified through contact tracing and evaluated for active TB by a health-care provider. If the contact appears to have active TB disease, culture and DST should be performed. If DST is not available, or while DST results are awaited, an empirical regimen based either on the resistance pattern of the index case or on the most common resistance pattern in the community may be started. Delay in the diagnosis of MDR-TB and start of appropriate treatment can lead to increased morbidity and mortality as well as unchecked amplification and transmission of drug-resistant strains of TB.

When investigation of a symptomatic adult contact yields no evidence of TB, a trial of a broad-spectrum antibiotic, particularly one that is not active against TB, such as trimethoprim/sulfamethoxazole, can be used. If the patient continues to have symptoms, chest computed tomography and/or directed bronchoscopy for smear and culture should be considered if available. Where these diagnostic tools are not available or the results are not conclusive, a diagnosis should be based on the clinical information at hand. If the initial investigation is not suggestive of active TB but the contact remains symptomatic, repeat physical examinations, smears and cultures should be performed monthly with repeat chest X-ray as needed.

14.4 Management of symptomatic paediatric contacts of patients with MDR-TB

MDR-TB should be suspected in children with active TB in the following situations:

- A child who is a close contact of an MDR-TB patient.
- A child who is a contact of a TB patient who died while on treatment when there are reasons to suspect that the disease was MDR-TB (i.e. the deceased patient had been a contact of another MDR-TB case, had poor adherence to treatment or had received more than two courses of antituberculosis treatment).
- Children with bacteriologically proven TB who are not responding to first-line drugs given with direct observation.

The diagnosis of TB is more difficult in children than in adults. Symptoms of TB in young children can be nonspecific, e.g. chronic cough or wheeze, failure

to thrive and recurrent fevers. Bacteriological confirmation may be difficult to obtain because of the inability of children to generate a sputum sample, as well as the paucibacillary nature of paediatric TB and the increased likelihood of extrapulmonary TB in children. While every effort should be made to establish a bacteriological diagnosis (and obtain DST) in a child with suspected MDR-TB, in practice paediatric cases are often not confirmed bacteriologically. Use of scoring systems that have been produced to aid screening and diagnosis of active TB is strongly recommended (see *Guidance for national tuberculosis programmes on the management of tuberculosis in children* (*6*)).

Symptomatic paediatric household contacts should receive:

- An evaluation by a physician, including history and physical examination.
- Tuberculin skin testing with purified protein derivative (PPD).
- A chest X-ray examination (computerized tomography is helpful especially in documenting hilar adenopathy but this is often not available in low-resource areas).
- Sputum smear, culture and DST: every effort should be made to establish a bacteriological diagnosis (and obtain DST) in a child with suspected DR-TB. Bacteriological confirmation may include more aggressive measures such as induced sputum, gastric aspirate, lymph node aspirate or other relevant sample, plus culture and DST. (Note: gastric aspiration should only be undertaken where culture facilities are available due to the low yield from microscopy and the distress involved for the child. Culture specimens need to be processed within the hour because the acidic juices will kill the bacteria relatively quickly) (*6*).
- HIV counselling and testing (in areas of high HIV prevalence or if parent(s) known, or suspected to be, HIV-infected).When the tuberculin (PPD) skin test result is >5 mm but the chest radiograph and gastric aspirate or sputum smear are negative, the symptomatic child can be treated with a broad-spectrum antibiotic that is not active against TB, such as trimethoprim/sulfamethoxazole. The child should be followed closely, with evaluations including smear test and culture on samples from induced sputum or gastric aspirates, or sputum samples whenever possible, as well as chest X-rays. The optimal frequency of these evaluations has not yet been determined. It is not clear whether the frequency of evaluation recommended for adults can be applied to children. If a child's clinical condition is highly suggestive of TB, or progressively deteriorates, empirical therapy designed according to the DST pattern of the strain from the index case can be started.

Children with MDR-TB who are incorrectly entered in SCC may suffer significant and protracted morbidity as a result of ongoing active disease, with the possibility of lifelong disability or even death. Because children with TB

may never become sputum smear-positive, it is reasonable to initiate empirical MDR-TB therapy based on the DST pattern of the contact. If DST of the contact is not available, therapy can be based on the common DST patterns of resistance in the community.

14.5 Chemoprophylaxis of contacts of MDR-TB index cases

The only chemoprophylaxis regimens to have been studied are based on isoniazid and, to a lesser extent, rifampicin. Since by definition MDR-TB is resistant to both of these drugs, it is unlikely that use of these drugs to treat latent infection caused by an MDR-TB strain will prevent the development of active TB disease.[1]

Contacts of MDR-TB patients in whom latent infection is diagnosed may not be infected with the same strain; some may be infected with isoniazid-susceptible strains, particularly in high-burden areas where many different strains of TB may circulate in homes, schools, workplaces, etc. Studies from high-burden TB areas have shown that approximately one-half to two-thirds of household members had the same strain of TB, as determined by genetic testing (*7–9*). (The degree of strain concordance could be higher in contacts who are children aged under 5 years because they have less exposure to strains circulating outside the household.)

Close contacts of DR-TB patients should receive careful clinical follow-up for a period of at least two years. If active disease develops, prompt initiation of treatment with a regimen designed to treat MDR-TB is recommended. On the basis of the currently available evidence, WHO does not recommend the universal use of second-line drugs for chemoprophylaxis in MDR-TB contacts.

More information on contract tracing can be found in other WHO documents (*10*).

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[1] Tuberculin skin tests become positive in most patients infected with TB irrespective of whether the strain is susceptible or resistant.

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CHAPTER 15

Drug resistance and infection control

15.1 Chapter objectives

This chapter addresses special considerations for reducing transmission of DR-TB through infection control measures. Infection control practices are discussed in more detail in other WHO documents (1). Since every instance of transmission averted represents one less potential DR-TB case, infection control needs to be a leading programmatic priority. It is equally important to protect health workers in the setting of DR-TB.

Key recommendations (* indicates updated recommendation)

- Infection control, including administrative and engineering controls and personal protection, should be made a high priority in all DR-TB control programmes.
- XDR-TB patients should be placed in isolation until no longer infectious.*
- DR-TB patients should receive routine care outside of normal HIV care settings.*

15.2 The priorities of infection control

DR-TB is transmitted in the same manner as drug-susceptible TB. Well-documented outbreaks of highly drug-resistant strains of TB constitute convincing evidence that DR-TB is transmissible, especially among highly vulnerable populations and in institutional settings. Moreover, because DR-TB patients may respond to treatment slowly and remain sputum smear-positive longer than other TB patients, they may infect more contacts.

The management of DR-TB does not significantly alter the basic TB infec-

tion control strategies. However, in view of its seriousness, every programme attempting to treat DR-TB should also undertake a systematic review of current practices and ensure that everything possible is done to prevent transmission among patients and to staff.

Recommendations for infection control to prevent DR-TB are essentially the same as those to prevent the spread of drug-susceptible TB, with only minor differences in emphasis. Further information is provided in the WHO/CDC/IUATLD *Guidelines for prevention of tuberculosis in health care facilities in resource-limited settings* (*1*). This chapter reviews briefly the recommendations that have a specific focus on DR-TB. (Additional recommendations for areas with high HIV prevalence are in preparation.) TB infection control has three components. By order of importance, they are: administrative controls, environmental or engineering controls, and personal respiratory protection. The administrative controls are the most effective and least expensive and therefore have highest priority in resource-constrained settings.

15.2.1 Administrative controls

Administrative controls include policies and procedures intended to promptly identify infectious cases so that additional precautions can be taken. They necessitate the appointment of a director of infection control for the institution, and an infection control committee representing key departments of the facility. The initial task of the committee is the formulation of a comprehensive infection control plan for the institution, including a programme for the education of all staff on infection control policies and procedures.

An important aspect of administrative control measures is the physical separation of patients known or suspected to have TB or DR-TB (especially smear-positive cases) from other patients, especially those who are immunocompromised. In many resource-limited settings, however, isolation rooms are not available and patients are mixed together in open wards. A second, less satisfactory but practical, solution is to separate rather than isolate patients. In this approach, patients with TB are grouped together and apart from those with suspected DR-TB, who are grouped together. This separation may be difficult as wards are usually separated by sex, which increases the number of different areas required. The presence of a substantial number of HIV-infected patients further complicates separation as they are not only potentially infectious but also highly vulnerable to intercurrent infection and reinfection from others. Placing HIV-infected patients on wards with known or suspected TB together with other TB or MDR-TB patients should always be avoided.

Infectious patients with XDR-TB, whether infected with HIV or not, should not be placed on general wards. Given the high mortality associated with XDR-TB, isolation until the patient is no longer infectious is recommended. Forced isolation and human rights are discussed more in Chapter 19 and Annex 4. Another administrative issue is the length of time patients

spend in the hospital. In many resource-limited countries, patients are traditionally treated for prolonged periods in the hospital, particularly when they come from great distances. However, this practice involves an increased risk of nosocomial transmission. The risk of transmission to patients and health-care workers decreases when community-based ambulatory treatment is established and hospital stays are reduced. Although most transmission is likely to have occurred before the diagnosis and start of treatment, ambulatory patients should be advised to avoid contact with the general public and with particularly susceptible people, such as young children or individuals with HIV infection. Health-care workers visiting TB patients at home before treatment is well established should wear properly fitted personal respirator masks.

Attention should also be paid to outpatient clinical settings. Because of the risk of severe morbidity and mortality in HIV-infected persons from DR-TB, persons with known DR-TB should receive routine care outside of normal HIV care settings (*2*).

15.2.2 Environmental controls

Environmental (or engineering) controls assume that unsuspected, untreated TB patients will enter hospitals despite all efforts to identify them. In addition, there are certain high-risk settings, such as sputum induction rooms, bronchoscopy rooms and rooms for the evaluation of newly admitted patients who may have untreated TB or DR-TB, where engineering interventions are necessary to reduce risk. Engineering controls attempt to reduce the concentration of infectious droplet nuclei in the air. They include natural and/or mechanical ventilation, ultraviolet germicidal irradiation (UVGI) and high-efficiency particulate air filtration. Environmental methods should never replace administrative controls; in fact, they work together.

In warm climates, infection control often depends on natural ventilation. The efficacy of natural ventilation has not been studied, but it probably depends heavily on climatic conditions. In warm climates, patients spend much of their time outdoors where transmission is highly unlikely. However, at night, for security and warmth, patients stay indoors with doors and windows usually closed tightly. Thus, patients in sub-Saharan Africa (warm climate) and in Siberia (cold climate) may endure similar high-risk conditions, at least some of the time.

The use of extraction fans to improve ventilation in closed rooms through wall vents can be extremely useful. Mechanical ventilation systems are uncommon in resource-poor settings and, when present, are often poorly maintained. However, a little ventilation is better than none, and in facilities with mechanical ventilation systems, efforts should be made to ensure that they function correctly. Clinics in warm climates should be designed without interior hallways, which tend to trap air and with waiting areas that are open on at least three sides.

Ventilation can be supplemented with upper-room UVGI. This has long been known to be extremely effective in inactivating infectious particles in the air above people's heads, while not exposing them to skin or eye irritation, which is the only practical safety concern. Normal convection currents or low-velocity ceiling fans usually ensure good room air mixing, thereby decontaminating air in the breathing zone. Upper-room UVGI is intended for use while rooms are occupied, but not to sterilize empty rooms as is commonly done in some parts of the world. It is much more important to decontaminate air while the infectious source and other occupants are present, and upper-room UVGI is designed to do so without significant radiation risks.

A growing number of manufacturers of fixtures designed for upper-room use are established in low-income countries and can provide products at relatively low cost. However, there are currently no standards for these products; the buyer should obtain advice from an engineer knowledgeable in the field.

In addition to UVGI designed for upper-room use, germicidal UV is sometimes used in ventilation ducts or in fan-driven air sterilizing devices mounted on ceilings or walls, or portable units that can be moved from room to room. However, the efficacy of these systems is limited by the number of air turnovers they can produce, especially in large spaces. By irradiating large volumes of upper-room air at one time, upper-room systems have a quantitative advantage, especially when combined with low-velocity ceiling fans to ensure room air mixing.

Laboratories that process specimens that may be DR-TB require particularly strict environmental controls. These aspects are addressed in other WHO documents (*3*) and in Chapter 6 of these guidelines.

15.2.3 Personal respiratory protection (special masks)

Because administrative and engineering controls cannot provide complete protection, the third line of defence against nosocomial TB transmission is the use of personal respirators.

Personal respirators are fundamentally different from, and more expensive than, the more familiar surgical masks which they resemble. Surgical masks are designed to protect the operating field from relatively large respiratory droplets generated by surgeons and surgical nurses. They are relatively loose-fitting and made of paper or cloth; they are not adequate for prevention of TB infection.

Masks that prevent TB transmission are known as "particulate respirators" or simply "respirators". They are designed to protect the wearer from tiny (1–5 μm) airborne infectious droplets. The filtration media through which air passes must capture these minute particles; most importantly, the respirator must fit tightly on the face, especially around the bridge of the nose. Ideally, respirators should be "fit tested" for individual wearers. In addition to choosing the proper model for each worker, this process serves to educate workers

on how to put on their respirators correctly to minimize face-seal leakage. Men with beards cannot be properly fitted with personal respirators. Institutions purchasing respirators are advised to look for models that are specifically designed to protect against TB and that meet international standards of quality.

Because they are visible and relatively expensive, it is sometimes assumed that personal respirators alone will prevent TB transmission. However, they cannot be worn continuously and are likely not to be in use when unsuspected TB cases, or unsuspected DR-TB, are encountered. For these reasons, administrative controls that aim to detect and separate cases, and engineering controls that can reduce the risk even for unsuspected cases, are more important.

15.3 Role of rapid tests in infection control

The use of a rapid test for rifampicin or other drugs is an excellent method of distinguishing those who may have DR-TB from others. Patients who are identified by rapid tests can be properly separated or isolated immediately (in addition to starting proper empirical regimens). Chapters 5 and 6 provide further information on the use of rapid tests.

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CHAPTER 16

Human resources: training and staffing

16.1 Chapter objectives

This chapter considers the development of human resources for DR-TB control programmes within the national programme, addressing a broad agenda that includes the overall management of training and issues related to staffing.

16.2 General considerations

The development of human resources for DR-TB control programmes requires specific planning within the national TB control plan. A programme that correctly implements and manages Category IV regimens cannot simply be added to the responsibilities of staff currently implementing the DOTS strategy. As well as the organization of special training courses, the availability of sufficient staff in all categories of personnel involved in the programme at all levels (clinical, laboratory, pharmaceutical and managerial) must be ensured to reach a specific long-term goal for professional competence in programme implementation.

Ensuring competent and sufficient human resources for the implementation of a DR-TB control programme of high quality requires ongoing management. As programme implementation expands, the management of human resources will become more complex because of the continued and diversified demands on staff at all levels.

16.3 Human resource development plan for DR-TB control programmes

There are numerous constraints to the effective performance of the health workforce, as indicated in Table 16.1. In many instances, additional staff with appropriate expertise have to be recruited to manage the activities of the

programme at the central and other levels. Central management should estimate staff requirements for the implementation of all aspects of the programme. Realistic projections, based on task analysis, revision of job descriptions and estimation of workloads for concerned staff form the basis of a plan for human resource development (HRD plan) to support the programme. Issues to be addressed include the level of effort and support systems (e.g. transportation) required for prolonged DOT, for health-care worker visits, for social support and for clinical and laboratory personnel.

The HRD plan for the DR-TB control programme should be part of the national HRD plan. The plan should include all staff involved in the diagnosis and treatment of DR-TB, patients and national authorities responsible for overseeing the programme, and include the proper regulatory documents.

The objectives of the human resource development component of the DR-TB control programme are twofold:

- To ensure the availability of sufficient staff (clinical and managerial) at all levels to implement the plan without detriment to other areas of work of the NTP.
- To ensure that all staff involved in the programme (at all service levels, and both public or private) are competent (have the required knowledge, skills and attitudes) and motivated for implementation.

To prepare the HRD plan for implementation by the DR-TB control programme, the following 10 steps are recommended:

1. Assign a focal point for human resources development for the DR-TB control programme within the NTP.
2. Assess the human resource requirements of the DR-TB control programme and their implications for the existing workforce (clinical, managerial, laboratory, pharmaceutical):
    - Define tasks to be performed at each level of the system to implement the DR-TB control programme.
    - Assign tasks to specific categories of health workers.
    - Assess the time needed to implement those tasks, particularly at peripheral level (where changes in the number and type of cases diagnosed and treated have the most impact on the workload).
    - Assess how many staff of the respective categories are needed to maintain the current service delivery level and include treatment of DR-TB.
3. Assess the current human resources situation of the NTP/health system and determine the number of staff of the relevant categories available at each programme level.

TABLE 16.1 **Human resource constraints to programme implementation**

TRAINING/COMPETENCE	STAFFING/MOTIVATION
■ Inadequate skills of existing staff: — Many staff involved in TB control in general are not trained — Suboptimal training (in-service training): lack of specific measurable learning objectives, lack of training materials, inadequate length of training, poor use of adequate training methodologies, lack of learning evaluation — An assumption by trainers and control managers that everything taught is learnt and will lead to competent performance — Lack of attention to other factors influencing behaviour change of health-care providers — Training is seen as a time-limited activity that is no longer needed when the treatment strategy has reached 100% coverage – "all have been trained" — Inadequate pre-service training	■ Imbalances in human resources for TB control: — Imbalances in overall numbers — Imbalances in distribution — Urban/rural imbalance — Imbalances in skills or skill-mix (a mismatch between the type or level of training and the skills required by the health system) ■ Shortages of human resources for TB control ■ Increased demand on existing staff – not only by national TB control programmes: — Impact of AIDS — Low staff retention — Low staff motivation • under-skilled (inadequate/infrequent training) • unsupported/lack of supervision • poor work environment • poor career structure • underpaid • overburdened • morale problems • sick or caring for sick family members — Insufficient number of posts — Increased "brain drain" — High staff turnover

4. Identify the gaps in human resources in terms of both the numbers required (increased numbers, additional roles and responsibilities, such as a coordinator for treatment of DR-TB or a laboratory focal point) and the quality of staff (additional knowledge and skills needed) to implement the DR-TB control programme.

5. Prepare short- and medium-term plans including how to ensure adequate staffing and preparation of training programmes based on the task analysis. The following options can be considered:

   • In-service training (clinical and managerial):
   — initial training in basic implementation of treatment for DR-TB,
   — retraining (major performance problems need more time than a supervisory visit to solve, e.g. a formal training course),
   — on-the-job training (refresher: small performance problems that can be addressed during a supervisory visit),

  - — continuing training (to gain more skills and knowledge without repeating previous training).
- Coordination with other in-service training programmes/training institutions and departments (in particular, measures to retain trained staff, interventions to stop unnecessary rotation of staff and support for career paths).
- Pre-service training (basic training in skills needed before entering in-service training).

6. Develop training programmes to ensure that:

   - Job descriptions are based on task analysis.
   - Training courses/programmes have learning objectives based on the task analysis and the job descriptions.
   - Training courses/programmes use methods and time allocation that allow participants to meet the learning objectives.
   - The participants:facilitators ratio in each course allows participants to meet the learning objectives.
   - The learning objectives have been met.

7. Consider the following issues in planning and implementing evaluation:

   - Evaluation during training courses:
     - — by participants to determine whether the course met their needs,
     - — of participants to determine whether their skills met the learning objective(s).
   - Evaluation in the field:
     - — supervision (post-training evaluation) to identify performance problems and determine whether problems are caused by "lack of skill or lack of will",
     - — specific follow-up immediately after training.

8. Ensure monitoring and supervision to:

   - Detect performance deficiencies in newly trained staff.
   - Identify new staff in need of training (additional staff needs, staff vacancies).

9. Carry out timely implementation of the HRD plan with regular monitoring of the implementation.
10. Carry out periodic evaluation of the implementation of the HRD plan, with revision as necessary.

Note: More information on human resource development can be found in the WHO document *Training for better TB control. Human resource development for TB control: a strategic approach within country support* (*1*) and other sources (*2*–*3*).

References

1. *Training for better TB control. Human resource development for TB control: a strategic approach within country support*. Geneva, World Health Organization, 2002 (WHO/CDS/TB/2002.301).
2. *Human resources development for TB control. Report of a Consultation held on 27 and 28 August 2003*. Geneva, World Health Organization, 2003.
3. Harries AD et al. Human resources for control of tuberculosis and HIV-associated tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 2005, 9(2):128–137.

CHAPTER 17

Management of second-line antituberculosis drugs

17.1 Chapter objectives

This chapter provides information on the procedures for procurement and management of the second-line drugs used in the treatment of DR-TB. Information is included on procurement of drugs through the GLC mechanism.

17.2 WHO Model List of Essential Medicines: second-line antituberculosis drugs

Essential medicines are those that satisfy the health-care needs of the majority of the population. The drug selection is based on the development of treatment guidelines and on the evidence underlying the development of those treatment guidelines. The current version of the WHO Model List of Essential Medicines, the 14th list, dates from March 2005 and includes nine second-line drugs (see Box 17.1). This Model List does not imply that no other drugs could be useful for management of DR-TB, but simply that these basic drugs, when used in accordance with appropriate therapeutic guidelines, cost-effectively meet the needs of an important proportion of the population.

17.3 Drug management cycle of second-line antituberculosis drugs

The management cycle of drugs comprises six elements: drug selection, quantitative assessment of drug requirements, management of procurement, distribution, assurance of drug quality and ensuring rational drug use.

BOX 17.1

Second-line antituberculosis drugs included in the WHO Model List of Essential Medicines[a]

kanamycin	levofloxacin	ofloxacin
cycloserine	amikacin	capreomycin
	ethionamide	*p*-aminosalicylic acid

[a] Note. While ciprofloxacin has not yet been removed from the WHO Model List of Essential Medicines and second-line antituberculosis drugs, it is no longer recommended for the treatment of any forms of TB (see Chapter 7).

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 the treatment (see Chapter 7).

Accurate demand forecasting for second-line drugs, i.e. correct quantification of the drug needs for a specific period of time, is one of the elements that guarantees an uninterrupted drug supply. There are two main approaches for demand forecasting:

- The most precise method is usually the consumption-based approach, with projections of future needs based on records of past consumption of individual drugs. This method assumes that the data are complete, accurate, and properly adjusted for stock-outs and expected changes in demand and use. However, this method is recommended only for an established programme managing DR-TB.
- The morbidity-based approach method is recommended for new projects. 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 the drugs. Shelf-lives of second-line drugs are longer than those of first-line drugs, ranging from 18 to 36 months. It is recommended that stock should be sufficient for a period of 2–3 times the delivery delay.

An inventory management system needs to be set up to ensure a safety stock and optimal stock movement, and to provide an accurate source of information for drug demand forecasting.

Effective management of procurement ensures the availability of the drugs selected, in the right quantities, at the right time, at affordable prices and of acceptable standards of quality. For more information see the manual *Operational principles for good pharmaceutical procurement* (*1*).

Management of drug importation and distribution requires that all port and customs clearance forms are duly completed. The formalities involved depend on whether the drugs have been registered in the importing country.

In many countries, it is possible to obtain an exemption on the basis of the public health interest, allowing the NTP to import drugs that are not locally registered.

To preserve quality, the drugs should be stored and transported by the supplier and the NTP following "good storage practices" and the recommendations of the manufacturer regarding temperature and humidity.[1]

The quality assurance component of a drug supply system makes certain that each drug used by a patient is safe, efficacious and of appropriate quality. All drugs used in a regimen for DR-TB should meet the WHO recommended standards for safety, efficacy and quality. The WHO prequalification project[2] aims at producing a list of second-line drugs and manufacturers that meet specific approved standards. The manufacturers selected to supply second-line antituberculosis drugs should be (as a minimum) compliant with the WHO standards of "good manufacturing practices".[3]

Access to second-line drugs must be accompanied by measures to ensure rational drug use. Misuse of the drugs will result in loss of susceptibility to the second-line agents, producing circulating strains that will be extremely difficult to cure with currently available medicines. Box 17.2 lists the most important elements to consider when preparing a plan to procure second-line drugs for the management of MDR-TB.

BOX 17.2

Main elements to consider when planning procurement of second-line antituberculosis drugs

- Drug forecast based on treatment regimen, cohort size and pace of patient enrolment
- Drug registration status of products selected
- Drug labelling
- Customs regulations for importing drugs
- Shelf-life of the products
- Lead-time for delivery of the drug request
- Estimated size of buffer stock (2–3 times the delivery delay)

17.4 The WHO Green Light Committee mechanism

NTPs have had to face several obstacles in the area of drug procurement, including the high cost of second-line drugs, the lack of local capacity to apply a stringent quality assessment of drug manufacturers and their products, inconsistent availability and the lack of guidelines on the proper use of second-line

[1] For a more detailed discussion see "Guide to good storage practices for pharmaceuticals" of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, Annex 9 (*2*).

[2] http://mednet3.who.int/prequal/

[3] As defined in "Good Manufacturing Practices for pharmaceutical products: main principles" of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, Annex 4 (*2*).

drugs. In order to tackle these obstacles, the GLC mechanism was set up in 2000 by WHO and its partners in the Stop TB Working Group on DOTS-Plus. GLC-approved projects purchase directly from agent(s) contracted by WHO to procure the drugs. By utilizing the GLC mechanism, a DR-TB control programme benefits from access to quality-assured drugs at concessionary prices and a continuous drug supply to the approved cohorts of patients. For further information, including details of technical assistance offered by the GLC, see Chapter 1 and Annex 1. The most up-to-date information is available on the WHO web page.[1] For approved projects, additional information is provided on drug procurement through the *Procurement manual for DOTS-Plus projects approved by the Green Light Committee* (*3*).

References

1. *Operational principles for good pharmaceutical procurement*. Geneva, World Health Organization, 1999 (WHO/EDM/PAR/99.5).
2. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Thirty-seventh report. Geneva, World Health Organization, 2003 (Technical Report Series No. 908).
3. *Procurement manual for DOTS-Plus projects approved by the Green Light Committee*. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2003.328 Rev.2).

[1] http://www.who.int/tb/challenges/mdr/greenlightcommittee/en/index.html

CHAPTER 18

Category IV recording and reporting system

18.1 Chapter objectives

This chapter describes the information system for Category IV patients, with the objective of recording information needed to monitor programme performance and treatment outcomes. It presents the instruments and minimum variables necessary to implement and monitor Category IV treatment. Tools are also introduced to track screening and enrolment efforts. Lastly, the chapter presents additional optional components (see Box 18.1) that programmes should use when it is feasible and relevant.

BOX 18.1 OPTIONAL RECORDING AND REPORTING COMPONENTS

Some programmes may want to include additional recording and reporting components than those described in Chapter 18. These guidelines recommend going beyond basic recording and reporting whenever it is feasible and relevant.

Optional indicators and analysis include:

- **MDR-TB treatment coverage:** the proportion of patients started on Category IV treatment among the total number patients detected with MDR-TB during a defined period. This indicator can be calculated from the Quarterly report on MDR-TB detection and Category IV treatment start (Form 05). The same analysis can also be done for XDR-TB.
- **Delay between MDR-TB detection and Category IV treatment start.** This indicator may be analysed separately for each treatment history group and for XDR-TB. This indicator can be calculated from the Laboratory Register for culture and DST (Form 04) and the Category IV Register (Form 02).
- **DST coverage in patient groups targeted for DST.** This assessment requires comparing the number of patients in the target groups for DST. For example, a programme may aim at having all patients who start Category II have DST and, by comparing the names of patients who started Category II with the names in the laboratory register for DST, determine the coverage of obtaining DST in this patient group.
- **The number of failures of Category I treatment.** Routine information from the quarterly reports from most NTP systems.
- **The number of failures of Category II treatment.** Routine information from the quarterly reports from most NTP systems.
- **Percentage of MDR-TB in different patient groups.** This information may be collected from the District TB Registers (if DST data are included), from the Laboratory Register for culture and DST (Form 04) or through surveys. For example, the percentage of MDR-TB in failures of Category I vs failures of Category II vs default vs relapse.

Key recommendations (* indicates updated recommendation)

- A standardized method of recording and reporting should be implemented in DR-TB control programmes.
- DR-TB treatment cards should have an expanded section for information on patients with HIV.*
- International Health Regulations should be followed.*

18.2 Aims of the information system and performance indicators

The aims of the information system are twofold:

- To allow NTP managers at different levels to monitor overall programme performance (such as patients started on treatment and treatment results), to follow trends in the number of cases notified, to plan drug supply, and to provide the basis for programme and policy developments.

- To aid clinical providers in management of individual patients.

The performance indicators include:

- The number of patients in whom MDR-TB is detected in the laboratory (Form 05).
- The number of MDR-TB patients started on treatment (Form 05).
- Interim treatment outcome at 6-months of MDR-TB cases (Form 06).
- Final outcome of MDR-TB treatment (Form 07).

18.3 Scope of the information system

The information system for treatment of DR-TB is based upon, and is an extension of, the basic DOTS information system (*1–5*). The forms have therefore been designed to be as similar as possible to the standard forms used in DOTS programmes.

The core information system should be consistent across settings to permit comparison. The forms may be modified as necessary to suit the local context. For instance, additional variables that are considered valuable in specific situations can be included.

The core system does not include all of the detailed information that treatment units may need to manage individual patients; that information should be contained in clinical records and other special forms used in the wards or clinics, and depends on local requirements and practices.

18.4 Main forms/registers and flow of information

The forms and registers include the following:

- Category IV Treatment Card (Form 01);
- Category IV Register (Form 02);
- Request for sputum examination (Form 03);
- Laboratory Register for culture and DST (Form 04).

Reports include:

- Quarterly report on MDR-TB detection and Category IV treatment start (Form 05);
- Six-month interim outcome assessment of confirmed MDR-TB cases (Form 06);
- Annual report of treatment result of confirmed MDR-TB patients starting Category IV treatment (Form 07).

Chapter 4 defines patient registration groups and treatment outcomes useful for the completion of these forms.

18.4.1 Category IV Treatment Card (Form 01)

When the relevant health authority (such as a review panel) decides that a patient should start Category IV treatment, the health staff in the treatment unit should enter the patient in the Category IV Register (see section 18.4.2). The staff should complete the Category IV Treatment Card when the patient is actually starting treatment.

This card is a key instrument for DOT workers who administer drugs to patients on a daily basis. The card should be updated daily by ticking off the supervised administration of drugs. The card represents the primary source of information to complete and periodically update the Category IV Register. The card, or a copy of the card, must always follow the patient (e.g. from a specialized hospital to an ambulatory facility). A copy of the card may be used as a notification form and later also to report the final outcome of treatment.

The Category IV Treatment Card contains the following sections:

Page 1

- **Basic demographic and clinical information**. Records name, address, sex, age, weight and site of disease.
- **Category IV registration number.** This is a new unique identification number assigned when the patient is entered in the Category IV Register.
- **Date of Category IV registration.** Provides registration date in the Category IV Register.
- **Previous district TB registration number and date of registration.**
- **Registration group according to result of previous antituberculosis treatment.** See Chapter 4, section 4.5 for definitions.
- **Previous TB treatment episodes.** Lists and describes any previous antituberculosis treatment and outcomes. Start with the earliest treatment and label it number 1. Use the drug abbreviations given on the front of the treatment card. Also note here the outcome of any previous treatment.
- **Previous use of second-line antituberculosis drugs.** Documents use of any of the second-line drugs listed at the front of the chart for antituberculosis treatment for more than one month.
- **Meetings of review panel (medical commission, selection committee, concilium).** These guidelines promote periodic meetings with the group of caregivers involved with Category IV patients. This section provides a space to record major decisions by the panel.

Page 2

- **HIV testing information.** This section is filled in for all patients. If tested for HIV, include date of testing and results. If HIV-infected, indicate whether patient is on ART and/or CPT.
- **HIV flow sheet.** This section is only filled in for HIV-infected patients.
- **Monitoring of weight.** Weight should be recorded at least monthly.

- **Monitoring of laboratory data** including creatinine, potassium, liver function tests, and thyroid tests. Recommendations regarding the interval for monitoring these indicators can be found in Chapter 11.

Page 3

- **Medical diagnoses other than TB.** All other important medical diagnoses are recorded here, including diabetes, hypertension, cardiomyopathy, HIV, opportunistic infections, etc.
- **Monitoring and recording adverse effects.** Record date, adverse effects and suspected drug(s).

Page 4

- **DST results.** Record the date of sputum collection and results of all DST performed.
- **Monitoring of chest X-ray.**
- **Monitoring of smear and culture.** Record date of sputum collection, sample number in the laboratory register and result of smear and culture. "Prior" refers to the sample used to indicate Category IV registration; include the date and result of that sample. Month "0" is the time of specimen collection at the start of the Category IV regimen. Requirements for monitoring of smear and culture are described in Chapter 11.

Pages 5 and 6

- **Regimen.** Record the initial Category IV regimen and later changes. Use one line for each date on which a drug(s) is changed. If drug dosage is progressively increased (e.g. starting 250 mg of ethionamide daily and increasing by 250 mg over 2–3 days until the full dose is reached), record this in the patient's medical record (not on the treatment card).
- **Record of daily observed administration of drugs.** This is constructed with one line per month to facilitate assessment of adherence. Mark one box for each day the entire treatment is administered. Additionally, if dosing is twice daily, one slash mark could be made for the A.M. dose and a second, intersecting mark could be made for the P.M. dose; if both are received, the box would contain an "x". An alternative is a more detailed system containing one box for each drug prescribed daily, since there may be some inconsistency in administration among drugs.
- **Outcome of treatment.** Chapter 4, Section 4.6 provides definitions. Record the outcome of treatment when the final bacteriology results become available.

18.4.2 Category IV Register (Form 02)

The NTP should have two TB registers: a District Tuberculosis Register and a Category IV Register. The Category IV Register is the record of all patients who start Category IV treatment (see Chapter 4, section 4.1 for a general definition of Category IV patients). This register allows quick assessment of the implementation of Category IV, facilitating quarterly reporting and analysis of treatment start and outcomes.

The District Tuberculosis Register is the traditional register used by DOTS programmes in which all TB patients are first registered. In order to integrate the treatment of Categories I, II, III and IV, this register should be modified in three ways:

1. If culture is being done in addition to smear examination in a substantial number of cases, dates of collection and results should be added to both the initial testing and the follow-up areas.
2. Capability to record DST should be added, including the date of collection of the sample and the drugs that are being tested.
3. Any patient who is switched to a Category IV regimen because of resistance (without meeting the formal criteria of failure) should have the outcome category "Change to Category IV" entered in the District Tuberculosis Register.

When a patient is starting Category IV treatment, the health staff in the treatment unit should enter the patient in the Category IV Register and indicate in the District Tuberculosis Register that the patient has entered Category IV. The date of registration should be the day when the health staff enters the patient in the Category IV Register. In some countries, it may be the date of the review panel meeting. The Category IV Register should be updated regularly from the Category IV Treatment Card and from the laboratory registers. Patients should be recorded consecutively by their date of registration. There should be a clear separation (extra line) when a new quarter is started.

These guidelines recommend that patients infected with strains with relatively simple resistance patterns (H, HS, HE and HZ) stay in the District Tuberculosis Register, where adjustment of their regimen should be recorded, including any second-line agents used (see Chapter 8). Patients infected with more complicated mono- and poly-resistance strains (involving R or HEZ resistance) or any mono- and poly-resistant strains that may have developed into MDR-TB should be entered into the Category IV Register.

Some patients started on Category IV regimens may be found to have drug-susceptible disease. Patient in this situation can be removed from Category IV treatment and placed on appropriate first-line therapy. The patient should be crossed out of the Category IV Register (but the name still left legible) and a comment noted in the last column that s/he has drug-susceptible disease. *All*

patients who are switched should be registered in the District Tuberculosis Register (if they are already registered in the district register, the final outcome should be documented in the original line of registration (do not create a new registration). These patients do not need to appear in Forms 05, 06 and 07 of the DR-TB reporting forms as they do not have MDR-TB.

Any patient with mono- or poly resistance whom it has been determined should stay in the DR-TB programme should not be crossed out of the Category IV Register. Whether the patient continues on the same Category IV regimen (often done in programmes using standardized regimens) or gets an individualized regimen based on DST can be documented on the treatment card and the final outcome reported in the Category IV Register. *These patients do not need to appear in Forms 05, 06 and 07 of the DR-TB reporting forms as they do not have MDR-TB.*

The following information is recorded in the Category IV Register (for explanation see also section 18.4.1):

- **Category IV registration number.**
- **Date of Category IV registration.**
- **Name, sex, date of birth, address (from treatment card, p. 1).**
- **District TB registration number.** All patients should have been entered in a District Tuberculosis Register. A patient who for any reason has never been registered in the District Tuberculosis Register should be registered there and the number transferred to the Category IV Register.
- **Site of disease (from treatment card, p. 1).** Pulmonary, extrapulmonary or both. Patients with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.
- **Registration group (from treatment card, p. 1).** Described in Chapter 4, section 4.5.
- **Second-line drugs received for more than one month prior to registration (from treatment card, p. 1).**
- **DST (from treatment card, p. 4).** Date sample taken, date of DST result and the results. Enter the DST that resulted in the patient being registered as a Category IV patient. Follow-up DSTs are not recorded in the register. If the patient has more than one DST, results are recorded on the treatment card. If DST is performed in a staged fashion (e.g. of rifampicin and isoniazid first, followed by other first-line drugs, and then of second-line drugs) all results from the same sample should be recorded in the register.
- **Category IV regimen (from treatment card, p. 5).** Record the initial Category IV regimen using the drug abbreviations. Include milligram doses and number of tablets.

- **Date of start of Category IV treatment (from treatment card, p.5).**
- **Smear and culture monitoring results (from treatment card, p.4).** Record all smear and culture results, even if done more often than the recommended frequency.
- **Final outcome (from treatment card, p.6).** See Chapter 4, section 4.6 for definitions.
- **HIV status (from treatment card, p.2).** Testing results, CPT and ART treatment information.
- **Comments.**

18.4.3 Request for sputum examination (Form 03)

Form 03 is the same as that recommended for DOTS programmes in the *Revised TB recording and reporting forms and registers – version 2006* (*5*); the upper portion is for requesting smear microscopy, the middle portion for culture and the lower portion for DST; the last section is used for reporting the results. When DST is requested, the registration group should be added. Results should be sent stepwise as they become available.

18.4.4 Laboratory Register for culture and DST (Form 04)

Laboratories will have separate registers for sputum smear microscopy and culture (*5*), while reference laboratories carrying out DST should have additional space in the culture register for DST results (see Form 04). The Laboratory Register for culture and DST should contain samples from all MDR-TB suspects, indicating the registration group (including if positive smear at 3 or 4 months), and be filled in from the request form.

The Laboratory Register should be compared regularly with the Category IV Register to ensure that all confirmed MDR-TB cases are entered in the Category IV Register.

18.4.5 Quarterly report on MDR-TB detection and Category IV treatment start (Form 05)

This report is used to assess the number of MDR-TB cases detected (distribution and trends) and the number of MDR-TB cases who start treatment. The report should be made quarterly in line with the routines of the NTP. The report should be made by the unit managing MDR-TB. The quarterly report includes:

- The number of patients, with date of result showing MDR-TB during the relevant quarter taken from the Laboratory Register (Form 04). Optionally, the patients could be split by registration group (see Box 18.1).
- The number of MDR-TB patients started on Category IV treatment during the quarter, taken from the Category IV Register (Form 02).

If relevant, the number of XDR-TB cases registered (after cross-checking DST results with type of resistance) and the number of XDR-TB cases started on XDR-TB treatment should be added.

Since there may be a considerable delay between Category IV registration and the start of Category IV treatment, patients who start treatment during the quarter may not be the same as those detected with DR-TB. The information provides an approximation of treatment coverage. These guidelines encourage programmes to calculate the average delay between detection of DR-TB and treatment start (see Box 18.1).

18.4.6 Six-month interim outcome assessment of confirmed MDR-TB cases (Form 06)

Since treatment takes on average two years before final results are known, the TB control programme needs more updated information on treatment outcome. Form 06 can be used to report bacteriological status (negative, positive or no information) of those still on treatment at 6 months, and for those who have already defaulted, died or transferred out, this can be recorded as the final outcome. Bacteriological results are based on the smear and culture data during months 5 and 6 of treatment. Consider the 6-month outcome assessment unknown for a particular patient if a culture or smear result is unknown for either month 5 or 6.

All cases from the Category IV Register should be included in this report.

The form should be completed 9 months after the closing day of the cohort. This allows culture information at month 6 of treatment to be included for all patients in the cohort. For instance, TB patients who started treatment during the first quarter of a year (1 January to 31 March), should have the form filled in from 1 January of the following year.

18.4.7 Annual report of treatment result of confirmed MDR-TB patients starting Category IV treatment (Form 07)

This report is made by the central unit and shows the final result of treatment by year of treatment start. All the patients are classified by previous use of antituberculosis drugs (none, only first-line drugs, also second-line drugs). If relevant, results for patients with XDR-TB could be added. All data can be extracted from treatment cards and Category IV Register. Form 07 is first completed at 24 months after the last patient in the cohort started treatment. Most of the patients will have finished treatment by 24 months, allowing preliminary assessment of cure rates. Since a few patients may be on treatment for longer than 24 months, the form may be completed again at 36 months, which will then be considered the final result.

18.5 Addressing the backlog of patients who failed Category II treatment in the past

When Category IV treatment is being introduced, there may be a large group of patients who are still sputum smear-positive after supervised Category II treatment from previous years. There may also be patients who have received several unsuccessful treatments, are considered incurable by health staff and who have lived with active TB disease with no or inadequate treatment for a period of time. While preparing for Category IV treatment, TB control programmes should keep a list of these patients. When Category IV treatment becomes available, such cases with evidence of active disease should follow the national protocol for Category IV treatment start, ideally having a DST done at the start to confirm MDR-TB.

The number of patients waiting for Category IV treatment should be estimated in all programmes, as this will facilitate planning of drug and other resource needs. As the Category IV treatment programme progresses, the list of chronic cases will become smaller and eventually include only patients who have failed Category IV treatment.

18.6 Assuring the quality of the recording and reporting system

In order for the information system for DR-TB to function well, adequate training and supervision are needed. The staff require basic knowledge of the DOTS information system, with additional training on the specifics of the Category IV forms.

Regular supervisory visits by a central unit to the units using the information system are fundamental to maintain good quality of the information. Regular meetings with staff from different levels may also be very helpful in updating information.

The person responsible for Category IV management should regularly (at least weekly) compare the Category IV Register with the DST register in all the laboratories performing DST to ensure that all patients in whom MDR-TB is diagnosed are started on Category IV treatment. The inclusion of MDR-TB patients from the Laboratory Register should take into consideration the quality of the DST performed in the laboratory. Patients diagnosed with MDR-TB in laboratories without proper quality assurance (i.e. in many private laboratories, the quality of DST is completely unknown) should not be included in the Laboratory Register for Culture and DST (Form 04) until their DST has been confirmed in a qualified laboratory.

18.7 Computerized systems

The recording and reporting system can be managed by hand. However, an electronic system is highly desirable since it facilitates better quality of information as well as data analysis; it will also obviate the need for transcrip-

tion and repeated entry into different forms. Patient data may be entered in a format similar to the Category IV Treatment Card, and lists similar to the Category IV Register can then be generated. Print-outs of the list may be compared with the handwritten Category IV Register to ensure completeness of the system. The corrected database may then be used to generate quarterly and annual reports.

Even if a computerized system is in place, a handwritten Category IV Register should be maintained, since otherwise corrections cannot be seen.

18.8 International Health Regulations (IHR)

The IHR (2005) entered into force on 15 June 2007 and are legally binding upon all WHO Member States. Their purpose and scope are "to prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade." The scope of diseases covered is extremely broad but can include DR-TB. For more information on the IHR (2005) see the WHO web site: http://www.who.int/ihr.

References

1. *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003.313) (with revision 2005).
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3. *Management of tuberculosis: training for district TB coordinators. How to organize training for district TB coordinators*. Geneva, World Health Organization, 2005 (WHO/HTM/TB/2005.353).
4. Enarson DA et al. *Management of tuberculosis: a guide for low-income countries*, 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.
5. *Revised TB recording and reporting forms and registers – version 2006*, Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.373).

CHAPTER 19

Managing DR-TB through patient-centred care

19.1 Chapter objectives

Any patient in whom DR-TB is suspected or diagnosed should be provided with high-quality patient-centred care, as outlined in the *International standards for tuberculosis care* (*1*) and the *Patients' charter for tuberculosis care* (*2*). This new approach identifies certain rights and responsibilities of both providers and patients, and facilitates a mutual collaboration to achieve cure with dignity. This chapter provides guidance on how this "partnership" can be forged, in common cause.

19.2 General considerations

The programmatic management of MDR-TB is extremely challenging even in the best of circumstances, demanding substantial efforts from a team of health professionals and the patient to reach a successful outcome. The long duration of complicated treatment and often difficult adverse effects require a joint commitment to complete the process, and this is best practiced in an environment of mutual respect and consideration. Certain basic steps should be taken to ensure this, and some of these are made by changing attitudes, perceptions and behaviours while others may require refining existing management practices and service delivery systems.

19.3 Understanding patient-centred care

All health workers involved with the management of DR-TB should be made familiar with the International Standards and the Patients' Charter. Copies of these documents should be made available in local languages, and staff should review their content as part of continuing education. Training materials are available upon request from WHO, the Tuberculosis Coalition for Technical Assistance and the World Care Council, and technical assistance can also be provided. An understanding of patient-centred care provides the basis to build better patient–provider relations, and can contribute to improved adherence to treatment, reduced stigmatization and better treatment outcomes. It also sends a message to the wider effective community that DR-TB can be successfully treated within a dignified framework of mutual respect, thus facilitating case-finding and community participation.

19.4 Dignity, from Day One

People suspected of having DR-TB should begin what may be a long march towards a cure in a manner to encourage their willful participation. From the first consultation or examination, the patient should be accorded the understanding of innocence, that it is not the fault of the person that bacteria are resistant to certain drugs. Offering solidarity and compassion initially, instead of reproach, will begin the process in a "healthy" way, which the patient will remember during the many months of treatment that follow.

To grow this initial expression of respect into a sustained programmatic management tool, at the first consultation patients should be provided with a copy of the short version of the Patients' Charter in their local language. This charter outlines the rights and responsibilities for patients, and its distribution will assist the provider with educating the patient about the disease and treatment as a basis for reaching better final outcomes. It is a key element of the Stop TB Strategy under component five (empowering people with TB, and communities).

The socioeconomic impact of both the physical aspects of TB and of its long-treatment can be extremely difficult for patients and their families. 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. Although food packages and transport vouchers may be useful in mitigating some of the difficulties, providing a minimum revenue for all patients may be a worthy investment to ensure adherence and willful participation.

In settings where many months of isolation are mandated by the state or programme, financially supporting the patient and their family with a minimum "living-allowance" would not only be a proactive step under the patient-centred care approach and an effective incentive but also a clear sign of respect for human dignity.

19.5 Staff as stakeholders, patients supporting peers

Programmes for DR-TB control should identify a member of staff who will serve as the focal point for developing patient-centred care, and to identify a number of patients who could be initiated in ways to encourage their peers to embrace this new approach. This lays the groundwork for the development of a social network within the clinical facility, which can play an essential role in galvanizing adherence and decreasing default. Working together, a health worker and a patient can facilitate a wider participation, foster a spirit of collaboration and take an innovative step to reduce stigma. This dynamic relationship facilitates gaining further support from the community and authorities to raise the standards of care.

The human resource component, specifically that of health-care workers, is an important aspect of the patient-centred approach and an essential factor in achieving a favorable response to treatment. CHWs should be trained appropriately in communicating and interacting "positively" with both patients and families. The attitudes and interpersonal skills of health workers are tools for better outcomes, as patients default from treatment if dissatisfied with the way they are treated as human beings, and this echoes throughout the wider affected community. Furthermore, among patients in many countries, it is commonly understood that stigma, like water, flows downward, not upwards from the bottom. Health-care workers can thus play a leading role in diminishing stigma by seeing the patient–provider relationship with an appreciation of the challenges each other faces, and viewing the process to cure DR-TB as a joint endeavour.

Providing on-site social support for patients and their families through peer counselling has shown itself to be highly effective in controlling TB in a number of communities and is a key element of scaling-up the response to HIV. MDR-TB control programmes should develop a comprehensive component that identifies a cured patient ("community champion"), and provides training and employment to function as a peer supporter. This worker engages in support, treatment literacy and communicating with peers under treatment. These "champion counsellors" would follow each patient from diagnosis through to cure, and 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. As it professionalizes the role of local "MDR-TB champions", it also serves to counter the systematic stigma that many patients perceive accompanies TB. Training modules and materials for the development and implementation of peer counsellor services are becoming available through the World Care Council and the Stop TB Partnership's Working Group on MDR-TB.

19.6 Communicating "cure"

Although implementing patient-centred high-quality care, as outlined in the International Standards, will often require resources to scale up programmatic infrastructure and services, part of the process requires simple adjustments in the attitudes and language of health-care providers. Programmes that seek to manage DR-TB should appreciate the fundamental human resistance to being controlled. Although the term "TB control" is still used by many health professionals, people with the disease are much more responsive, and more responsible if the term "TB care" is emphasized. This seemingly small change in language speaks volumes to the people who must struggle to "win" the challenge of a long and difficult treatment. The word "prevention" is also seen to be more user-friendly for families and communities, which strengthens their participation in supporting patients and the programme.

Programmes should adopt methods of "communicating with" and not "talking at" patients and their families, in a manner that builds a positive partnership towards successful treatment completion. For patients with literacy limitations, efforts should be undertaken to provide audio or visual supports, such as information by recorded cassette or graphic illustrations. Staff acting as focal points for patient-centred care and peer supporters can also play an important role as "communicators".

During all phases of care, patients should be provided with appropriate and understandable information about the disease and its treatment. An informed patient can better assist health workers in caring for patients. Peer support groups, champions and trained health workers can offer information-sharing sessions to educate patients, and for better detecting risk factors for default (e.g. understanding adverse effects) and other warning signs that can affect treatment outcome. These discussion sessions should be two-way communications, mutually deciding on interventions for problems, for example, on how to handle drug side-effects.

19.7 Forced isolation and respect for human rights

Management of DR-TB, which can be a threat to public health, must be balanced with a consideration of the human rights and dignity of the patient. Guided by the Siracusa Principles (*3*), WHO states that forcibly isolating people with DR-TB must be used only as the last possible resort when all other means have failed, and only as a temporary measure.

Health authorities and providers choosing the extreme measure of involuntary treatment should do so only if they can ensure it is done in a transparent and accountable manner. If it can be proved, through evidence-based analysis, that forced isolation is temporarily required, patients must be provided with the high-quality care that includes, among other rights, free access to second-line drugs, laboratory support including effective DST and social support, and be treated with respect and dignity. Patients should be informed clearly, in

their language, of the decision and its details, and of their rights and responsibilities, as outlined in the Patients' Charter, accompanied by a peer supporter and/or family member.

The fear of forced isolation without consideration of patients' dignity creates a negative perception of TB control within an affected community, discouraging people from being tested for TB testing and raising the stigma attached to the disease. If the conditions of isolation are equated with punishment, efforts to stop transmission of the disease will be made more difficult.

Certain restrictions on liberties may be determined to be necessary on a case-by-case basis, but these should not be prescribed unless clinically evidenced, and with the information communicated in a clear and understandable manner to the patient, accompanied by a peer supporter and/or a family member. Independent monitoring should be welcomed by the programme to reassure families and the community that the human rights of the person are being respected. In the extreme case of XDR-TB, where cure is no longer a possibility, extra steps should be taken by programmes to ensure that palliative care is extremely patient-centred and extra measures of social support are provided to patients and their families. Although infection control remains essential and isolation may be needed, facilitating additional compassionate human contact permits the patient and his or her family the dignity to better deal with the reality. For more information on human and patients' rights, see Annex 4.

19.8 Civil society

The involvement of civil society, such as patient support groups, nongovernmental organizations, community or faith-based organizations, in various aspects of the programmatic management of DR-TB is strongly recommended. These organizations can assist the programme through diverse but important actions, including providing social support services, case-finding, prevention campaigns and advocating for greater resources for local services. DR-TB is a problem for the affected community, and welcoming the participation and building working relations with civil society organizations not only brings new resources to confront the problem but also can serve as a dynamic link between patient and care provider (also see Chapter 12).

19.9 Conclusion

Successful management of DR-TB requires putting the patient at the centre of a comprehensive programme of care that includes allows patients to exercise their rights. This, in turn, enables patients to fulfill their responsibilities and assist in the treatment success. The process of adopting the patient-centred care approach is essential both for good programmatic management practices and for scaling up the response to the growing threat of DR-TB.

References

1. *International standards for tuberculosis care*. The Hague, Tuberculosis Coalition for Technical Assistance, 2006 (available at http://www.who.int/tb/publications/2006/istc_report.pdf; accessed May 2008).
2. *The Patients' charter for tuberculosis care*. Geneva, World Care Council, 2006 (available at http://www.who.int/tb/publications/2006/istc_charter.pdf; accessed May 2008).
3. *Siracusa principles on the limitation and derogation provisions in the International Covenant on civil and political rights*. New York, United Nations Economic and Social Council, 1985; available at http://www1.umn.edu/humanrts/instree/siracusaprinciples.html; accessed May 2008).

Annexes

ANNEX 1

Drug information sheets

Adapted from *Drug-resistant tuberculosis: a survival guide for clinicians*. San Francisco, Francis J. Curry National Tuberculosis Center and California Department of Health Services, 2004.

Common presentations of the drugs are described; actual preparations may vary depending on manufacturer.

AMIKACIN (Am)	
DRUG CLASS: AMINOGLYCOSIDE	
Activity against TB, mechanism of action, and metabolism	**Bactericidal**: aminoglycosides inhibit protein synthesis through disruption of ribosomal function; less effective in acidic, intracellular environments; polypeptides appear to inhibit translocation of the peptidyl-tRNA and the initiation of protein synthesis; aminoglycosides are not metabolized in the liver, they are excreted unchanged in the urine.
Preparation and dose	Amikacin sulfate, colourless solution; 250 mg/ml (2 or 4 ml vials) and 50 mg/ml (2 ml vial). The optimal dose is 15–20 mg/kg body weight, usually 750 mg to 1 g given daily or 5–6 days per week, by deep intramuscular injection. Rotation of injection sites avoids local discomfort. When necessary, it is possible to give the drug at the same total dose 2 or 3 times weekly during the continuation phase, under close monitoring for adverse effects.
Storage	Solution is stable at room temperature (15–25 °C); diluted solution is stable at room temperature for at least 3 days or in the refrigerator for at least 60 days.
Oral absorption	There is no significant oral absorption. Intramuscular absorption may be delayed if the same site is used consistently.
CSF penetration	Penetrates inflamed meninges only.
Special circumstances	**Pregnancy/breastfeeding**: safety class D. No reports linking the use of amikacin to congenital defects have been located. Ototoxicity has not been reported as an effect of in utero exposure to amikacin; however, eighth cranial nerve toxicity in the fetus is well known following exposure to other aminoglycosides (kanamycin and streptomycin) and could potentially occur with amikacin. Only a trace amount of amikacin was found in some nursing infants. Given the poor absorption of aminoglycosides, systemic toxicity should not occur, but alteration in normal bowel flora may occur in nursing infants. **Renal disease**: use with caution. Levels should be monitored for patients with impaired renal function. Interval adjustment (12–15 mg/kg 2 or 3 times per week) is recommended for creatinine clearance <30 ml/min or haemodialysis.

AMIKACIN (Am)	
DRUG CLASS: AMINOGLYCOSIDE	
Special circumstances	**Hepatic disease**: drug levels 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 effects	**Frequent**: pain at injection site, proteinuria, serum electrolyte disturbances including hypokalaemia and hypomagnesaemia. **Occasional**: cochlear ototoxicity (hearing loss, dose-related to cumulative and peak concentrations, increased risk with renal insufficiency, may be irreversible), nephrotoxicity (dose-related to cumulative and peak concentrations, increased risk with renal insufficiency, often irreversible), peripheral neuropathy, rash, vestibular toxicity (nausea, vomiting, vertigo, ataxia, nystagmus), eosinophilia. Ototoxicity potentiated by certain diuretics (especially loop diuretics), advanced age, and prolonged use. The effect of non-depolarizing muscle relaxants may be increased. Penicillins: in vitro antagonism.
Drug interactions	**Loop diuretics** (bumetanide, furosemide, etacrynic acid, torasemide). Co-administration of aminoglycosides with loop diuretics may have an additive or synergistic auditory ototoxicity. Ototoxicity appears to be dose-dependent and may be increased with renal dysfunction. Irreversible ototoxicity has been reported. Avoid concomitant administration; if used together, careful dose adjustments in patients with renal failure and close monitoring for ototoxicity are required. **Non-depolarizing muscle relaxants** (atracurium, pancuronium, tubocurarine, gallamine triethiodide): possible enhanced action of non-depolarizing muscle relaxants resulting in possible respiratory depression. Nephrotoxic agents (amphotericin B, foscarnet, cido-fovir): additive nephrotoxicity. **Penicillins**: in vitro inactivation (possible). Do not mix together before administration.
Contraindications	Pregnancy (congenital deafness seen with streptomycin and kanamycin use in pregnancy). Hypersensitivity to aminoglycosides. Caution with renal, hepatic, vestibular, or auditory impairment.
Monitoring	Monthly creatinine and serum potassium in low-risk patients (young with no co-morbidities), more frequently in high-risk patients (elderly, diabetic, or HIV-positive patients, or patients with renal insufficiency). If potassium is low, check magnesium and calcium. Baseline audiometry and monthly monitoring in high-risk patients. For problems with balance, consider increasing dosing interval.
Alerting symptoms	— Problems with hearing, dizziness or balance — Rash or swelling of the face — Trouble breathing — Decreased urination — Swelling, pain or redness at IM site — Muscle twitching or weakness

CAPREOMYCIN (CM)

DRUG CLASS: CYCLIC POLYPEPTIDE

Activity against TB, mechanism of action, and metabolism	**Bactericidal:** capreomycin has a different chemical structure from the aminoglycosides, but the mechanism of antibacterial activity is similar. Polypeptides appear to inhibit translocation of the peptidyl-tRNA and the initiation of protein synthesis. No cross-resistance with the aminoglycosides. 50–60% excreted via glomerulofiltration. Small amount of biliary excretion.
Preparation and dose	Capreomycin sulfate is supplied as a sterile white powder for intramuscular injection in sealed vials each containing 1000 units, approximately equivalent to 1 g capreomycin base. This should be dissolved in 2 ml of 0.9% sodium chloride in water; 2–3 minutes should be allowed for complete solution. Dose: 15–20 mg/kg daily. The usual dose is 1 g in a single dose daily. When necessary, it is possible to give the drug at the same dose 2 or 3 times weekly during the continuation phase, under close monitoring for adverse effects.
Storage	Reconstituted capreomycin can be stored in the refrigerator for up to 24 hours before use.
Oral absorption	There is no significant oral absorption. Intramuscular absorption may be delayed if the same site is used consistently.
CSF penetration	Penetrates inflamed meninges only.
Special circumstances	**Pregnancy/breastfeeding**: less ototoxicity reported in adults with capreomycin than with aminoglycosides; unknown if these data can be extrapolated to the developing fetal ear. Category C animal studies show teratogenic effect ("wavy ribs" when given 3.5 times the human dose). Avoid in pregnancy. Concentrations in breast milk unknown. **Renal disease**: use with caution. Levels should be monitored for patients with impaired renal function. Interval adjustment (12–15 mg/kg 2 or 3 times per week) is recommended for creatinine clearance <30 ml/min or haemodialysis.
Adverse effects	**Frequent**: nephrotoxicity (20–25%), tubular dysfunction, azotaemia, proteinuria, urticaria or maculopapular rash. **Occasional**: ototoxicity (vestibular>auditory); electrolyte abnormalities (decreased blood levels of calcium, magnesium, and potassium); pain, induration and sterile abscesses at injection sites.
Drug interactions	Avoid co-administration of non-depolarizing muscle relaxants. If concurrent administration is needed, titrate the non-depolarizing muscle relaxant slowly and monitor neuromuscular function closely. Though not reported with capreomycin, neuromuscular blockade has been reported with other polypeptide antibiotics when administered with non-depolarizing muscle relaxants. Avoid use with other nephro- or ototoxic agents because of the additive effect.
Contraindications	Patients with hypersensitivity to capreomycin. Great caution must be exercised in patients with renal insufficiency or pre-existing auditory impairment.

CAPREOMYCIN (CM)

DRUG CLASS: CYCLIC POLYPEPTIDE

Monitoring	Monthly creatinine and serum potassium in low-risk patients (young with no co-morbidities), more frequently in high-risk patients (elderly, diabetic, or HIV-positive patients, or patients with renal insufficiency). If potassium is low, check magnesium and calcium. Electrolyte disturbances are more common with capreomycin than other injectable agents. Baseline audiometry and monthly monitoring in high-risk patients. For problems with balance, consider increasing dosing interval.
Alerting symptoms	— Rash — Decreased urination — Fever or chills — Trouble breathing — Bleeding or bruising — Muscle weakness — Problems with hearing, dizziness or balance — Bleeding or lump at IM injection site

CIPROFLOXACIN (Cfx)

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 bacterial DNA. There is no cross-resistance with other antituberculosis agents, but near complete cross-resistance between ofloxacin and ciprofloxacin and high in vitro cross-resistance with moxifloxacin and gatifloxacin. Ciprofloxacin is eliminated principally by urinary excretion, but non-renal clearance may account for about one-third of elimination and includes hepatic metabolism, biliary excretion, and possibly transluminal secretion across the intestinal mucosa.
Preparation and dose	Tablets (250, 500, 1000 mg). Vials (20 and 40 ml) or flexible containers (200 and 400 ml) with aqueous or 5% dextrose IV solutions equivalent to 200 and 400 mg. Usual dose: 1000–1500 mg/day.
Storage	Room temperature (15–25 °C), airtight containers protected from light.
Oral absorption	Well absorbed (70–85%) from the gastrointestinal tract and may be taken with meals or on an empty stomach. Should not be administered within 2 hours of ingestion of milk-based products, antacids, or other medications containing divalent cations (iron, magnesium, zinc, vitamins, didanosine, sucralfate).
Distribution, CSF penetration	Widely distributed to most body fluids and tissues; high concentrations are attained in kidneys, gall bladder, gynaecological tract, liver, lung, prostatic tissue, phagocytic cells, urine, sputum, and bile, skin, fat, muscle, bone and cartilage. CSF penetration is 5–10% and with inflamed meninges 50–90%.
Special circumstances	**Pregnancy/breastfeeding**: safety class C. Ciprofloxacin levels in amniotic fluid and breast milk almost as high as in serum. Fluoroquinolones are not recommended during breastfeeding because of the potential for arthropathy. Animal data demonstrated arthropathy in immature animals, with erosions in joint cartilage. **Renal disease**: doses of ciprofloxacin should be reduced in patients with severe renal impairment. When the creatinine clearance is less than 30 ml/min, the recommended dosing is 1000–1500 mg 3 times per week.
Adverse effects	Generally well tolerated. **Occasional**: gastrointestinal intolerance; CNS-headache, malaise, insomnia, restlessness, and dizziness. **Rare**: allergic reactions; diarrhoea; photosensitivity; increased liver function tests (LFTs); tendon rupture; peripheral neuropathy.
Drug interactions	**Sucralfate**: decreased absorption of fluoroquinolones caused by the chelation by aluminium ions contained in the sucralfate. **Antacids** (magnesium, aluminium, calcium, Al-Mg buffer found in didanosine): binding to fluoroquinolone antibiotics resulting in decreased absorption and loss of therapeutic efficacy. **Probenecid**: interferes with renal tubular secretion of ciprofloxacin; this may result in 50% increase in serum level of ciprofloxacin. **Milk or dairy products**: decrease the gastrointestinal absorption of ciprofloxacin by 36–47%. **Vitamins and minerals** containing divalent and trivalent cations such as zinc and iron: formation of fluoroquinolone-ion complex results in decreased absorption of fluoroquinolones.

CIPROFLOXACIN (Cfx)	
DRUG CLASS: FLUOROQUINOLONE	
Drug interactions	**Mexiletine**: fluoroquinolones may inhibit cytochrome P450 1A2 resulting in increased mexiletine concentration. **Warfarin**: case reports of ciprofloxacin enhancing anticoagulation effect of warfarin.
Contraindications	Pregnancy, intolerance of fluoroquinolones.
Monitoring	No specific laboratory monitoring requirements.
Alerting symptoms	— Pain, swelling or tearing of a tendon or muscle or joint pain — Rashes, hives, bruising or blistering, trouble breathing — Diarrhoea — Yellow skin or eyes — Anxiety, confusion or dizziness

CLOFAZIMINE (Cfz)

DRUG CLASS: PHENAZINE DERIVATIVE

Activity against TB, mechanism of action, and metabolism	**Bacteriostatic** against *M. leprae*, active in vitro against *M. tuberculosis*. Clinical effectiveness against *M. tuberculosis* not well established. Clofazimine appears to bind preferentially to mycobacterial DNA (principally at base sequences containing guanine) and inhibit mycobacterial replication and growth. Excreted in faeces as unabsorbed drug and via biliary elimination. Little urinary excretion.
Preparation and dose	Capsules (50 and 100 mg).
Storage	Store below 30 °C, in airtight containers.
Oral absorption	20–70% absorbed from from gastrointestinal tract.
Distribution, CSF penetration	Widely distributed principally to fatty tissue, reticuloendothelial system and macrophages. High concentrations found in mesenteric lymph nodes, adipose tissue, adrenals, liver, lungs, in gall bladder, bile and spleen.
Special circumstances	**Pregnancy/breastfeeding**: safety class C. Animal studies demonstrated teratogenicity (retardation of fetal skull ossification). Crosses placenta and is excreted in milk. Not recommended during breastfeeding. **Renal disease**: usual dose. **Hepatic disease**: dose adjustments should be considered in patients with severe hepatic insufficiency.
Adverse effects	**Frequent**: ichthyosis, and dry skin; pink to brownish-black discoloration of skin, cornea, retina and urine; anorexia and abdominal pain.
Drug interactions	May decrease absorption rate of rifampicin. Isoniazid increases clofazimine serum and urine concentrations and decreases skin concentrations. Ingestion of clofazimine with orange juice resulted in a modest reduction in clofazimine bioavailability.
Contraindications	Pregnancy, severe hepatic insufficiency, hypersensitivity to Cfz.
Monitoring	No specific laboratory monitoring requirements.
Alerting symptoms	— Nausea and vomiting — Abdominal pain/distress (caused by crystal depositions and can present as an acute abdomen)

CYCLOSERINE (Cs) [AND TERIZIDONE (Trd)]

DRUG CLASS: ANALOG OF D-ALANINE

Activity against TB, mechanism of action, and metabolism	**Bacteriostatic:** competitively blocks the enzyme that incorporates alanine into an alanyl-alanine dipeptide, an essential component of the mycobacterial cell wall. No cross-resistance with other antituberculosis drugs. 60–70% excreted unchanged in the urine via glomerular filtration; small amount excreted in faeces; small amount metabolized.
Preparation and dose	Capsules (250 mg). 10–15 mg/kg daily (max. 1000 mg), usually 500–750 mg per day given in two divided doses. (Some producers of terizidone make 300 mg capsule preparations, while others make 250 mg.)
Storage	Room temperature (15–25 °C) in airtight containers.
Oral absorption	Modestly decreased by food (best to take on an empty stomach); 70–90% absorbed.
Distribution, CSF penetration	Widely distributed into body tissue and fluids such as lung, bile, ascitic fluid, pleural fluid, synovial fluid, lymph, sputum.
	Very good CSF penetration (80–100% of serum concentration attained in the CSF, higher level with inflamed meninges)
Special circumstances	**Pregnancy/breastfeeding**: safety class C. Breastfeeding with B_6 supplement to the infant. **Renal disease**: doses of cycloserine should be reduced in patients with severe renal impairment. When the creatinine clearance is less than 30 ml/minute, the recommended dosing is 250 mg/day, or 500 mg/dose 3 times per week. The appropriateness of 250 mg/day doses has not been established. There should be careful monitoring for evidence of neurotoxicity; if possible, measure serum concentrations and adjust regimen accordingly.
Adverse effects	**Frequent**: neurological and psychiatric disturbances, including headaches, irritability, sleep disturbances, aggression, and tremors, gum inflammation, pale skin, depression, confusion, dizziness, restlessness, anxiety, nightmares, severe headache, drowsiness. **Occasional**: Visual changes; skin rash; numbness, tingling or burning in hands and feet; jaundice; eye pain. **Rare**: seizures, suicidal thoughts.
Drug interactions	**Ethionamide**: additive nervous system side-effects. **Isoniazid**: additive nervous system side-effects. **Phenytoin**: may increase phenytoin levels. Toxic effect if combined with alcohol, increases risk of seizures. Vitamin B_6 decreases CNS effect.
Contraindications	Hypersensitivity to cycloserine. Epilepsy. Depression, severe anxiety or psychosis. Severe renal insufficiency. Excessive concurrent use of alcohol.
Monitoring	When available, serum drug monitoring to establish optimal dosing (not higher than 30 µg/ml).
Alerting symptoms	— Seizures — Shakiness or trouble talking — Depression or thoughts of intentional self-harm — Anxiety, confusion or loss of memory — Personality changes, such as aggressive behaviour — Rash or hives — Headache

ETHIONAMIDE (Eto)
PROTIONAMIDE (Pto)

DRUG CLASS: CARBOTHIONAMIDES GROUP, DERIVATIVES OF ISONICOTINIC ACID

Activity against TB, mechanism of action, and metabolism	**Bacteriostatic:** the mechanism of action of thionamides has not been fully elucidated, but they appear to inhibit mycolic acid synthesis. Resistance develops rapidly if used alone and there is complete cross-resistance between ethionamide and protionamide (partial cross-resistance with thioacetazone). Ethionamide is extensively metabolized, probably in the liver, to the active sulfoxide and other inactive metabolites and less than 1% of a dose appears in the urine as unchanged drug.
Preparation and dose	Ethionamide and protionamide are normally administered in the form of tablets containing 125 mg or 250 mg of active drug. The maximum optimum daily dose is 15–20 mg/kg/day (max. 1 g/day), usually 500–750 mg.
Storage	Room temperature (15–25 °C), in airtight containers.
Oral absorption	100% absorbed but sometimes erratic absorption caused by gastrointestinal disturbances associated with the medication.
Distribution, CSF penetration	Rapidly and widely distributed into body tissues and fluids, with concentrations in plasma and various organs being approximately equal. Significant concentrations also are present in CSF.
Special circumstances	**Pregnancy/breastfeeding**: safety class C. Animal studies have shown ethionamide to be teratogenic. Newborns who are breastfed by mothers who are taking ethionamide should be monitored for adverse effects. **Renal disease**: doses of the thionamides are only slightly modified for patients with severe renal impairment. When the creatinine clearance is less than 30 ml/minute, the recommended dosing is 250–500 mg daily. **Hepatic disease**: thionamides should not be used in severe hepatic impairment. **Porphyria**: ethionamide is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in animals and in vitro systems.
Adverse effects	**Frequent:** severe gastrointestinal intolerance (nausea, vomiting, diarrhoea, abdominal pain, excessive salivation, metallic taste, stomatitis, anorexia and weight loss). Adverse gastrointestinal effects appear to be dose-related, with approximately 50% of patients unable to tolerate 1 g as a single dose. Gastrointestinal effects may be minimized by decreasing dosage, by changing the time of drug administration, or by the concurrent administration of an antiemetic agent. **Occasional**: allergic reactions; psychotic disturbances (including depression), drowsiness, dizziness, restlessness, headache, and postural hypotension. Neurotoxicity (administration of pyridoxine has been recommended to prevent or relieve neurotoxic effects); transient increases in serum bilirubin; reversible hepatitis (2%) with jaundice (1–3%); gynaecomastia; menstrual irregularity, arthralgias, leukopenia, hypothyroidism especially when combined with PAS. **Rare**: reports of peripheral neuritis, optic neuritis, diplopia, blurred vision, and a pellagra-like syndrome, reactions including rash, photosensitivity, thrombocytopenia and purpura.

ETHIONAMIDE (Eto) PROTIONAMIDE (Pto) DRUG CLASS: CARBOTHIONAMIDES GROUP, DERIVATIVES OF ISONICOTINIC ACID	
Drug interactions	**Cycloserine**: potential increase incidence of neurotoxicity. **Ethionamide** has been found to temporarily raise serum concentrations of isoniazid. Thionamides may potentiate the adverse effects of other antituberculosis drugs administered concomitantly. In particular, convulsions have been reported when ethionamide is administered with cycloserine. Excessive ethanol ingestion should be avoided because of possible psychotic reaction. **PAS:** possible increase in liver toxicity, monitor liver enzymes; hypothyroidism in case of combined administration.
Contraindications	Thionamides are contraindicated in patients with severe hepatic impairment and in patients who are hypersensitive to these drugs.
Monitoring	Ophthalmological examinations should be performed before and periodically during therapy. Periodic monitoring of blood glucose and thyroid function is desirable. Diabetic patients should be particularly alert for episodes of hypoglycaemia. Liver function tests should be carried out before and during treatment with ethionamide.
Alerting symptoms	— Any problems with eyes: eye pain, blurred vision, color blindness, or trouble seeing — Numbness, tingling, or pain in hands and feet — Unusual bruising or bleeding — Personality changes such as depression, confusion or aggression — Yellowing of skin — Dark-coloured urine — Nausea and vomiting — Dizziness

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 bacterial DNA. It undergoes limited metabolism and is excreted largely unchanged in the urine with less than 1% as metabolites. A small amount (5%) is also excreted unchanged in the faeces.
Preparation and dose	Tablets, 200 or 400 mg. Vials (20 and 40 ml) or flexible containers (200 and 400 ml) with aqueous or 5% dextrose IV solutions equivalent to 200 and 400 mg. Usual dose: 400 mg/day.
Storage	Room temperature (15–25 °C), airtight containers protected from light.
Oral absorption	Gatifloxacin is readily absorbed from the gastrointestinal tract with an absolute bioavailability of 96%. Should not be administered within 4 h of other medications containing divalent cations (iron, magnesium, zinc, vitamins, didanosine, sucralfate). No interaction with milk or calcium.
Distribution, CSF penetration	Widely distributed in body fluids, including the CSF; tissue penetration is good and approximately 20% appears to be bound to plasma proteins. It crosses the placenta and is distributed into breast milk. It also appears in the bile. Kidney and lung tissue levels exceeded those in serum.
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 the creatinine clearance is less than 30 ml/min, the recommended dosing is 400 mg 3 times per week.
Adverse effects	Generally well tolerated. **Occasional**: gastrointestinal intolerance; CNS-headache; malaise; insomnia; restlessness; dizziness; allergic reactions; diarrhoea; photosensitivity; increased LFTs; tendon rupture (increased incidence seen in older men with concurrent use of corticosteroids).
Drug interactions	As gatifloxacin may have the potential to prolong the QT interval, it should not be given to patients receiving class Ia antiarrhythmic drugs (such as quinidine and procainamide) or Class III antiarrhythmics (such as amiodarone and sotalol). In addition, caution should be exercised when gatifloxacin is used with other drugs known to have this effect (such as the antihistamines astemizole and terfenadine, cisapride, erythromycin, pentamidine, phenothiazines, or tricyclic antidepressants). **Sucralfate**: decreased absorption of fluoroquinolones caused by the chelation by aluminium ions contained in the sucralfate. **Antacids** (magnesium, aluminium, calcium, Al-Mg buffer found in didanosine): antacid binding to fluoroquinolone antibiotics resulting in decreased absorption and loss of therapeutic efficacy. **Probenecid**: probenecid interferes with renal tubular secretion of ciprofloxacin; this may result in 50% increase in serum level of ciprofloxacin. **Vitamins and minerals** containing divalent and trivalent cations such as zinc and iron: formation of fluoroquinolone-ion complex results in decreased absorption of fluoroquinolones.

GATIFLOXACIN (Gfx)	
DRUG CLASS: FLUOROQUINOLONE	
Drug interactions	**Mexiletine**: fluoroquinolones may inhibit cytochrome P450 1A2, resulting in increased mexiletine concentration. **Warfarin**: case reports of gatifloxacin enhancing anticoagulation effect of warfarin.
Contraindications	Pregnancy, intolerance of fluoroquinolones.
Monitoring	No laboratory monitoring requirements.
Alerting symptoms	— Pain, swelling or tearing of a tendon or muscle or joint pain — Rashes, hives, bruising or blistering, trouble breathing — Diarrhoea — Yellow skin or eyes — Anxiety, confusion or dizziness

KANAMYCIN (Km)

DRUG CLASS: AMINOGLYCOSIDE

Activity against TB, mechanism of action, and metabolism	**Bactericidal:** aminoglycosides inhibit protein synthesis by irreversibly binding to 30S ribosomal subunit; aminoglycosides are not metabolized in the liver, they are excreted unchanged in the urine.
Distribution	0.2–0.4 l/kg; distributed in extracellular fluid, abscesses, ascitic fluid, pericardial fluid, pleural fluid, synovial fluid, lymphatic fluid and peritoneal fluid. Not well distributed into bile, aqueous humour, bronchial secretions, sputum and CSF.
Preparation and dose	Kanamycin sulfate, sterile powder for intramuscular injection in sealed vials. The powder needs to be dissolved in water for injections before use. The optimal dose is 15 mg/kg body weight, usually 750 mg to 1 g given daily or 5–6 days per week, by deep intramuscular injection. Rotation of injection sites avoids local discomfort. When necessary, it is possible to give the drug at the same total dose 2 or 3 times weekly during the continuation phase, under close monitoring for adverse effects.
Storage	Powder stable at room temperature (15–25 °C), diluted solution should be used the same day.
Oral absorption	There is no significant oral absorption.
CSF penetration	Penetrates inflamed meninges only.
Special circumstances	**Pregnancy/breastfeeding**: safety class D. Eighth cranial nerve damage has been reported following in utero exposure to kanamycin. Excreted in breast milk. The American Academy of Paediatrics considers kanamycin to be compatible with breastfeeding. **Renal disease**: use with caution. Levels should be monitored for patients with impaired renal function. Interval adjustment (12–15 mg/kg 2 or 3 times per week) is recommended for creatinine clearance <30 ml/minute or haemodialysis. **Hepatic disease**: drug levels 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 effects	**Frequent**: pain at injection site, renal failure (usually reversible). **Occasional**: vestibular and auditory damage – usually irreversible; genetic predisposition possible (check family for aminoglycoside ototoxicity), nephrotoxicity (dose-related to cumulative and peak concentrations, increased risk with renal insufficiency, often irreversible), peripheral neuropathy, rash. Ototoxicity potentiated by certain diuretics (especially loop diuretics), advanced age, and prolonged use. The effect of non-depolarizing muscle relaxants may be increased. Penicillins: in vitro antagonism.
Drug interactions	**Loop diuretics** (bumetanide, furosemide, etacrynic acid, torasemide). Co-administration of aminoglycosides with loop diuretics may have an additive or synergistic auditory ototoxicity. Ototoxicity appears to be dose-dependent and may be increased with renal dysfunction. Irreversible ototoxicity has been reported. Avoid concomitant administration; if used together, careful dose adjustments in patients with renal failure and close monitoring for ototoxicity are required.

KANAMYCIN (Km)

DRUG CLASS: AMINOGLYCOSIDE

Drug interactions	**Non-depolarizing muscle relaxants** (atracurium, pancuronium, tubocurarine, gallamine triethiodide): possible enhanced action of non-depolarizing muscle relaxant resulting in possible respiratory depression. Avoid co-administration; if concurrent administration is needed, titrate the non-depolarizing muscle relaxant slowly and monitor neuromuscular function closely. **Nephrotoxic agents** (amphotericin B, foscarnet, cidofovir): additive nephrotoxicity. Avoid co-administration; if used together, monitor renal function closely and discontinue if warranted. **Penicillins**: in vitro inactivation (possible). Do not mix together before administration.
Contraindications	Pregnancy (congenital deafness seen with streptomycin and kanamycin use in pregnancy). Hypersensitivity to aminoglycosides. Caution with renal, hepatic, vestibular or auditory impairment.
Monitoring	Monthly creatinine and serum potassium in low-risk patients (young with no co-morbidities), more frequently in high-risk patients (elderly, diabetic, or HIV-positive patients, or patients with renal insufficiency). If potassium is low, check magnesium and calcium. Baseline audiometry and monthly monitoring in high-risk patients. For problems with balance, consider increasing dosing interval.
Alerting symptoms	— Problems with hearing; dizziness — Rash — Trouble breathing — Decreased urination — Swelling, pain or redness at injection site — Muscle twitching or weakness

LEVOFLOXACIN (Lfx)

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 bacterial DNA. Levofloxacin is generally considered to be about twice as active as its isomer, ofloxacin. Minimal hepatic metabolism; 87% of dose excreted unchanged in the urine within 48 h via glomerular filtration and tubular secretion.
Preparation and dose	Tablets (250, 500, 750 mg). Aqueous solution or solution in 5% dextrose for IV administration – vials (20, 30 ml) 500 or 750 mg and flexible containers (50, 100, 150 ml) 250; 500 or 750 mg. Usual dose: 750 mg/day.
Storage	Tablets: room temperature (15–25 °C), airtight containers protected from light.
Oral absorption	Levofloxacin is rapidly and essentially completely absorbed after oral administration. Orally, should not be administered within 4 h of other medications containing divalent cations (iron, magnesium, zinc, vitamins, didanosine, sucralfate). No interaction with milk or calcium.
Distribution, CSF penetration	Distributes well in blister fluid and lung tissues, also widely distributed (kidneys, gall bladder, gynaecological tissues, liver, lung, prostatic tissue, phagocytic cells, urine, sputum and bile). 30–50% of serum concentration is attained in CSF with inflamed meninges.
Special circumstances	**Pregnancy/breastfeeding**: safety class C. There are no adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal data demonstrated arthropathy in immature animals, with erosions in joint cartilage. Because of the potential for serious adverse effects from levofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Renal disease**: doses of levofloxacin should be reduced in patients with severe renal impairment. When the creatinine clearance is less than 30 ml/minute, the recommended dosing is 750–1000 mg 3 times per week. **Hepatic disease**: given the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.
Adverse effects	Generally well tolerated. **Occasional**: gastrointestinal intolerance; CNS-headache; malaise; insomnia; restlessness; dizziness; allergic reactions; diarrhoea; photosensitivity. **Rare**: QT prolongation; tendon rupture; peripheral neuropathy.
Drug interactions	Should not be given to patients receiving class Ia antiarrhythmic drugs (such as quinidine and procainamide) or Class III antiarrhythmics (such as amiodarone and sotalol). **Sucralfate**: decreased absorption of fluoroquinolones caused by the chelation by aluminium ions contained in the sucralfate. **Antacids** (magnesium, aluminium, calcium, Al-Mg buffer found in didanosine): antacid binding to fluoroquinolone antibiotics resulting in decreased absorption and loss of therapeutic efficacy.

LEVOFLOXACIN (Lfx) DRUG CLASS: FLUOROQUINOLONE	
Drug interactions	**Probenecid**: probenecid interferes with renal tubular secretion of fluoroquinolones, which may result in 50% increase in serum level of levofloxacin. **Vitamins and minerals** containing divalent and trivalent cations such as zinc and iron. Formation of fluoroquinolone-ion complex results in decreased absorption of fluoroquinolones. **Mexiletine**: fluoroquinolones may inhibit cytochrome P450 1A2 resulting in increased mexiletine concentration.
Contraindications	Pregnancy; hypersensitivity to fluoroquinolones; prolonged QT.
Monitoring	No specific laboratory monitoring requirements.
Alerting symptoms	— Pain, swelling or tearing of a tendon or muscle or joint pain — Rashes, hives, bruising or blistering, trouble breathing — Diarrhoea — Yellow skin or eyes — Anxiety, confusion or dizziness

MOXIFLOXACIN (Mfx)

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 bacterial DNA. The cytochrome P450 system is not involved in moxifloxacin metabolism, and is not affected by moxifloxacin. Approximately 45% of an oral or intravenous dose of moxifloxacin is excreted as unchanged drug (~20% in urine and ~25% in faeces).
Preparation and dose	Tablets 400 mg and intravenous solution 250 ml–400 mg in 0.8% saline. Usual dose: 400 mg/day.
Storage	Tablets: room temperature (15–25 °C), airtight containers protected from light.
Oral absorption	Moxifloxacin, given as an oral tablet, is well absorbed from the gastro-intestinal tract. The absolute bioavailability of moxifloxacin is approximately 90%. Co-administration with a high fat meal (e.g. 500 calories from fat) does not affect the absorption of moxifloxacin.
Distribution, CSF penetration	Moxifloxacin has been detected in the saliva, nasal and bronchial secretions, mucosa of the sinuses, skin blister fluid, and subcutaneous tissue, and skeletal muscle following oral or intravenous administration of 400 mg.
Special circumstances	**Pregnancy/breastfeeding**: safety class C. Since there are no adequate or well-controlled studies in pregnant women, moxifloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because of the potential for serious adverse effects in infants nursing from mothers taking moxifloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Renal disease**: no dosage adjustment is required in renally impaired patients, including those on either haemodialysis or continuous ambulatory peritoneal dialysis. **Hepatic disease**: no dosage adjustment is required in patients with mild or moderate hepatic insufficiency.
Adverse effects	Generally well tolerated. **Occasional**: gastrointestinal intolerance; CNS-headache; malaise; insomnia; restlessness; dizziness; allergic reactions; diarrhoea; photosensitivity. Moxifloxacin has been found in isolated cases to prolong the QT interval.
Drug interactions	Should not be given to patients receiving class Ia antiarrhythmic drugs (such as quinidine and procainamide) or class III antiarrhythmics (such as amiodarone and sotalol). **Sucralfate**: decreased absorption of fluoroquinolones caused by the chelation by aluminium ions contained in the sucralfate. **Antacids** (magnesium, aluminium, calcium, Al-Mg buffer found in didanosine): antacid binding to fluoroquinolone antibiotics resulting in decreased absorption and loss of therapeutic efficacy. **Vitamins and minerals** containing divalent and trivalent cations such as zinc and iron: formation of fluoroquinolone-ion complex results in decreased absorption of fluoroquinolones.
Contraindications	Pregnancy; hypersensitivity to fluoroquinolones; prolonged QT.
Monitoring	No specific laboratory monitoring requirements.

MOXIFLOXACIN (Mfx)

DRUG CLASS: FLUOROQUINOLONE

Alerting symptoms	— Pain, swelling or tearing of a tendon or muscle or joint pain — Rashes, hives, bruising or blistering, trouble breathing — Diarrhoea — Yellow skin or eyes — Anxiety, confusion or dizziness

OFLOXACIN (Ofx)

DRUG CLASS: FLUOROQUINOLONES

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 bacterial DNA. There is no cross-resistance with other antituberculosis agents, but complete cross-resistance between ofloxacin and ciprofloxacin. There is limited metabolism to desmethyl and N-oxide metabolites; desmethylofloxacin has moderate antibacterial activity. Ofloxacin is eliminated mainly by the kidneys. Excretion is by tubular secretion and glomerular filtration and 65–80% of a dose is excreted unchanged in the urine over 24–48 hours, resulting in high urinary concentrations.
Preparation and dose	Tablets (200, 300 or 400 mg). Vials (10 ml) or flexible containers (50 and 100 ml) with aqueous or 5% dextrose IV solutions equivalent to 200 and 400 mg. Usual dose: 400 mg twice daily.
Storage	Room temperature (15–25 °C), airtight containers protected from light.
Oral absorption	90–98% oral absorption.
Distribution, CSF penetration	About 25% is bound to plasma proteins. Ofloxacin is widely distributed in body fluids, including the CSF, and tissue penetration is good. It crosses the placenta and is distributed into breast milk. It also appears in the bile.
Special circumstances	**Pregnancy/breastfeeding**: usually compatible with breastfeeding. **Renal disease**: doses of ofloxacin should be reduced in patients with severe renal impairment. When the creatinine clearance is less than 30 ml/minute, the recommended dosing is 600–800 mg 3 times per week.
Adverse effects	Generally well tolerated. **Occasional**: gastrointestinal intolerance; CNS-headache, malaise, insomnia, restlessness, and dizziness. **Rare**: allergic reactions; diarrhoea; photosensitivity; increased LFTs; tendon rupture; peripheral neuropathy.
Drug interactions	Fluoroquinolones are known to inhibit hepatic drug metabolism and may interfere with the clearance of drugs such as theophylline and caffeine that are metabolized by the liver. Cations such as aluminium, magnesium or iron reduce the absorption of ofloxacin and related drugs when given concomitantly. Changes in the pharmacokinetics of fluoroquinolones have been reported when given with histamine H2 antagonists, possibly due to changes in gastric pH, but do not seem to be of much clinical significance. The urinary excretion of ofloxacin and some other fluoroquinolones is reduced by probenecid; plasma concentrations are not necessarily increased.
Contraindications	Pregnancy, intolerance of fluoroquinolones.
Monitoring	No specific laboratory monitoring requirements.
Alerting symptoms	— Pain, swelling or tearing of a tendon or muscle or joint pain — Rashes, hives, bruising or blistering, trouble breathing — Diarrhoea — Yellow skin or eyes — Anxiety, confusion or dizziness

P-AMINOSALICYLIC ACID (PAS)

DRUG CLASS: SALICYLIC ACID; ANTI-FOLATE

Activity against TB, mechanism of action, and metabolism	**Bacteriostatic:** disrupts folic acid metabolism. Acetylated in the liver to *N*-acetyl-*p*-aminosalicylic acid and *p*-aminosalicylic acid, which are excreted via glomerular filtration and tubular secretion.
Preparation and dose	Tablets, sugar-coated, containing sodium salt: sodium *p*-aminosalicylate, 0.5 g of PAS. Granules of PAS with an acid-resistant outer coating rapidly dissolved in neutral media, 4 g per packet. 150 mg/kg or 10–12 g daily in 2 divided doses. Children: 200–300 mg/kg daily in 2–4 divided doses.
Storage	Packets should be kept in the refrigerator or freezer. Other formulations may not require refrigeration (consult manufacturer's recommendations).
Oral absorption	Incomplete absorption (usually 60–65%): sometimes requires increased doses to achieve therapeutic levels.
Distribution, CSF penetration	Distributed in peritoneal fluid, pleural fluid, synovial fluid. Not well distributed in CSF (10–15%) and bile.
Special circumstances	**Pregnancy/breastfeeding**: safety class C. Congenital defects in babies have been reported with exposure to PAS in the first trimester. PAS is secreted into human breast milk (1/70th of maternal plasma concentration). **Renal disease**: no dose adjustment is recommended. However, PAS can exacerbate acidosis associated with renal insufficiency and if possible should be avoided in patients with severe renal impairment due to crystalluria. Sodium PAS should also be avoided in patients with severe renal impairment.
Adverse effects	**Frequent**: gastrointestinal intolerance (anorexia and diarrhoea); hypo-thyroidism (increased risk with concomitant use of ethionamide). **Occasional**: hepatitis (0.3–0.5%); allergic reactions; thyroid enlargement; malabsorption syndrome; increased prothrombin time; fever. Careful use in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.
Drug interactions	**Digoxin**: possible decrease in digoxin absorption; monitor digoxin level – may need to be increased. **Ethionamide**: possible increase in liver toxicity, monitor liver enzymes; hypothyroidism in case of combined administration. **Isoniazid**: decreased acetylation of isoniazid resulting in increased isoniazid level. Dose may need to be decreased.
Contraindications	Allergy to aspirin; severe renal disease; hypersensitivity to the drug.
Monitoring	Monitor TSH, electrolytes, blood counts, and liver function tests.
Alerting symptoms	— Skin rash, severe itching, or hives — Severe abdominal pain, nausea or vomiting — Unusual tiredness or loss of appetite — Black stools as a result of intestinal bleeding

ANNEX 2

Weight-based dosing of drugs for adults

The table below shows the suggested dosing of antituberculosis drugs for adults based on body weight. For paediatric doses, see Chapter 9, section 9.5. While antituberculosis drugs are traditionally grouped into first-line and second-line drugs, the drugs in the table are divided into five groups based on drug efficacy and drug properties (or drug classes). Detailed information on drug groups 1–4 is given in Annex 1.

Weight-based dosing of antituberculosis drugs in the treatment of drug-resistant TB

MEDICATION (DRUG ABBREVIATION), (COMMON PRESENTATION)	WEIGHT CLASS			
	<33 KG	33–50 KG	51–70 KG	>70 KG (ALSO MAXIMUM DOSE)
GROUP 1: FIRST-LINE ORAL ANTITUBERCULOSIS DRUGS				
Isoniazid (H) (100, 300 mg)	4–6 mg/kg daily or 8–12 mg 3 x wk	200–300 mg daily or 450–600 mg 3 x wk	300 mg daily or 600 mg 3 x wk	300 mg daily or 600 mg 3 x wk
Rifampicin (R) (150, 300 mg)	10–20 mg/kg daily	450–600 mg	600 mg	600 mg
Ethambutol (E) (100, 400 mg)	25 mg/kg daily	800–1200 mg	1200–1600 mg	1600–2000 mg
Pyrazinamide (Z) (500 mg)	30–40 mg/kg daily	1000–1750 mg	1750–2000 mg	2000–2500 mg
GROUP 2: INJECTABLE ANTITUBERCULOSIS DRUGS				
Streptomycin (S) (1 g vial)	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg
Kanamycin (Km) (1 g vial)	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg
Amikacin (Am) (1 g vial)	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg
Capreomycin (Cm) (1 g vial)	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg

MEDICATION (DRUG ABBREVIATION), (COMMON PRESENTATION)	WEIGHT CLASS			
	<33 KG	33–50 KG	51–70 KG	>70 KG (ALSO MAXIMUM DOSE)
GROUP 3: FLUOROQUINOLONES				
Ofloxacin (Ofx) (200, 300, 400 mg)	15–20 mg/kg daily	800 mg	800 mg	800–1000 mg
Levofloxacin (Lfx) (250, 500 mg)	7.5–10 mg/kg daily	750 mg	750 mg	750–1000 mg
Moxifloxacin (Mfx) (400 mg)	7.5–10 mg/kg daily	400 mg	400 mg	400 mg
GROUP 4: ORAL BACTERIOSTATIC SECOND-LINE ANTITUBERCULOSIS DRUGS				
Ethionamide (Eto) (250 mg)	15–20 mg/kg daily	500 mg	750 mg	750–1000 mg
Protionamide *(Pto)* (250 mg)	15–20 mg/kg daily	500 mg	750 mg	750–1000 mg
Cycloserine (Cs) (250 mg)	15–20 mg/kg daily	500 mg	750 mg	750–1000 mg
Terizidone (Trd) (300 mg)	15–20 mg/kg daily	600 mg	600 mg	900 mg
P-aminosalicylic acid (PAS) (4 g sachets)	150 mg/kg daily	8 g	8 g	8–12 g
Sodium PAS	Dosing can vary with manufacture and preparation: check dose recommended by the manufacturer.			
Thioacetazone (Thz)	Usual dose is 150 mg for adults			
GROUP 5: AGENTS WITH UNCLEAR ROLE IN DR-TB TREATMENT (NOT RECOMMENDED BY WHO FOR ROUTINE USE IN MDR-TB PATIENTS). OPITMAL DOSES FOR DR-TB ARE NOT ESTABLISHED				
Clofazimine (Cfz)	Usual adult dose is 100 mg to 300 mg daily. Some clinicians begin at 300 mg daily and decrease to 100 mg after 4 to 6 weeks.			
Linezolid (Lzd)	Usual adult dose is 600 mg twice daily. Most reduce the dose to 600 mg once a day after 4 to 6 weeks to decrease adverse effects.			
Amoxicillin/ Clavulanate (Amx/Clv)	Dosages for DR-TB not well defined. Normal adult dose 875/125 mg twice a day or 500/125 mg three times a day. Dosages of 1000/250 have been used but adverse side-effects may limit this dosing.			
Thioacetazone (Thz)	Usual adult dose is 150 mg			
Imipenem/cilastatin (Ipm/Cln)	Usual adult dose is 500–1000 mg IV every 6 hours.			
Clarithromycin (Clr)	Usual adult dose is 500 mg twice daily			
High-dose isoniazid (High-dose H)	16–20 mg/kg daily			

ANNEX 3

Suggestions for further reading

Policy issues

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2. *Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach*. Geneva, World Health Organization, 2003.
3. *The PIH guide to the community-based treatment of HIV in resource-poor settings*. Boston, Partners In Health, 2004.
4. Bartlett JG. *The Johns Hopkins Hospital 2003 guide to medical care of patients with HIV infection*, 11th ed. Philadelphia, Lippincott Williams & Wilkins, 2003.
5. *Interim policy on collaborative TB/HIV activities*. Geneva, World Health Organization, 2004 (WHO/HTM/TB/2004.330; WHO/HTM/HIV/2004.1).
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ANNEX 4

Legislation, human rights and patients' rights in tuberculosis prevention and control

Objectives

This annex provides information regarding legislation, human rights and patients' rights in prevention and control of TB. Legislation should be placed in the context of a comprehensive strategy political, health and social action needed to strengthen TB prevention and control.

Legislation of communicable diseases

Legislation is an expression of national political commitment to prevent and control TB. Government commitment to sustained TB control is one of the key components of the national TB prevention and control strategy. This should be manifest in national legislation and regulations relating to all aspects of a national TB control strategy, and in financial and technical support to national TB control programmes (NTPs). The Stop TB Initiative addresses ways of strengthening health legislation and regulations in order to better support the vital efforts to develop and expand TB prevention and control, particularly extensively drug-resistant TB (XDR-TB).

- **The role of legislation and regulations in TB control.** Legislation expresses and formulates health policy, supports the implementation of public health goals and sets the foundation for executive action. Legislation also formulates patients' rights and duties, helping them to realize the right to health in terms of health protection and access to health care.
- **Scope and purpose of communicable diseases legislation.** The scope of the communicable disease acts and legislation should cover all communicable diseases. A distinction should be made between communicable diseases that are hazardous to public health and other infections that are non-hazardous. Its purpose should be:
  - — to protect the population from communicable diseases by preventing their occurrence or spread;
  - — to ensure that health authorities and other authorities implement the measures necessary to control communicable diseases and to coordinate their efforts;

— to safeguard the rights of individuals who are affected by measures to control communicable diseases pursuant to the legislation.

The legislation should provide the legal basis for the implementation of the various measures proven effective in combating communicable diseases and for the continuous and systematic prevention and control of outbreaks. These measures must:

— be necessary to prevent the transmission of a disease;
— be justifiable from a medical point of view;
— not cause needless or unreasonable harm to those affected.

Human rights and patients' rights in respect to TB

The voluntary participation in communicable disease legislation of affected citizens should always be sought. If needed, participation can be made compulsory to prevent the spread of a communicable disease that is hazardous to public health. In extreme situations, measures may also be made compulsory. Such compulsory measures should be limitedly enumerated in the law and provisions must be made for such decisions to be appealed in court.

- **The need for up-to-date legislation to support an effective national TB prevention and control strategy.** Provisions that have been in force for many years may need to be updated to reflect current public health approaches; many of the older communicable disease laws pre-date modern methods of prevention and control. Legislation has also often been allowed to grow in a complex way, and thus measures on TB control appear in various statutes but their relationship may not be clear or effective. Appropriate legislation and regulations help ensure that policies and strategies are effective and sustainable. They must give strong backing to programmes that produce results through a clear definition of duties and responsibilities at local, regional and national levels. Provisions must also seriously consider the human, technical and financial resources necessary for TB prevention and control programmes.
- **Basic values in the foundations of public action.** Health policy decisions are also considered with regard to basic human values that both motivate and constrain our actions. The following values, which serve as the cornerstones of health-care systems, require careful consideration before effecting TB prevention and control legislation.

  — *Respect for the person.* Respect for people is the most essential value in a society professing to adhere to the principles of human rights. It requires acknowledgement and protection of the dignity and autonomy of each individual. Each individual's interests and aspirations should be regarded as worthy of protection, except insofar as they violate the rights

of others. The right to self-determination and privacy and the right to informed consent to medical treatment flow from this principle.

— *Justice.* Justice mandates that, as respecting people, all people should be respected equally. Equity in all actions is required by the value of justice.

— *Equity.* Equity refers to both fairness and justice. Equity in health implies that everyone can attain their full health potential and that no one should be disadvantaged from achieving this potential because of any socially determined circumstances. Equity calls for the recognition of differential needs, requiring that equal rights are recognized and that equal needs are met. Because resources are finite, this has to be understood in relative terms; it becomes a matter of prioritization in selecting those activities that would best reduce inequities in health. Equity involves the fair distribution of resources needed for health, fair access to the opportunities available and fairness in the support offered to people when ill. A variation or difference in health becomes a social inequity when it is systematic and socially produced, therefore modifiable and unfair.

— *Beneficence.* Beneficence is the value of doing good and of meeting the needs and interests of others. Our constant efforts to relieve suffering, to meet human needs and to enhance the human condition are rooted in this value.

— *Non-malfeasance.* Similarly, we seek to advance the cause of mankind without causing harm along the way. The value of non-malfeasance is an aspect of respect for people. It permits limitations on an individual's liberty to pursue personal goals and choices when others will be injured by those activities.

— *Responsibility and accountability.* Because people are autonomous agents worthy of respect, they also bear responsibility for their actions, in addition to enjoying fundamental human rights.

This set of rights, principles and values provides the justification for the obligation placed on individuals to act in the interest of others in the control of communicable diseases.

- **Normative principles that govern public action.** In order to be sound, legislation on TB prevention and control must be based on solid scientific and epidemiological evidence but also on the following normative principles:

— *Equality of treatment (before the law and public regulation).* Prescriptions cannot be imposed arbitrarily on some people and not on others. If one is to request duties from one group and not from another, there must be strong and compelling reasons.

— *Relevance.* Public action should be directly relevant to the policy objectives and the management of the problem to which the policy is addressed.

— *Proportionality and least infringement.* The duty that may be imposed must be commensurate with the benefit it brings. When considering a compulsory public health measure, it is necessary to weigh carefully the human rights and liberties limitations that it would introduce as compared with the advantages it is supposed to bring and the consequential damage of negligence or inaction.

— *Effectiveness.* There must be a reasonable expectation that the provisions will result in effective action. It is not sufficient that a provision appears logical or has a scientific basis to be useful in reality.

— *Feasibility.* It follows that all actions envisaged must be feasible and capable of being implemented in the real world given the actual cultural, social, political and material circumstances and constraints.

— *Social acceptability.* The advocacy of morals is not a major role of the State, which usually only halts what clearly offends it. When dealing with communicable diseases, the authorities have to take into account what is socially acceptable in the community concerned.

Human rights in legislation and regulation for TB prevention and control

The promotion of health requires the protection of human rights of vulnerable individuals and populations; indeed, safeguarding human rights empowers individuals and enables them to take steps to improve their own health. This is especially important with respect to communicable diseases and in particular TB, for instance in encouraging self-reporting to health services and compliance with treatment.

- **The right to the highest attainable standard of health.** The right to the highest attainable standard of health is a claim to a set of social arrangements – norms, institutions, laws, an enabling environment – that can best secure the enjoyment of this right. Other key human rights relevant to health include freedom from discrimination and the right to participation, education and information. Human rights are grounded in concrete governmental obligations and generate entitlements on individuals and groups, with a particular emphasis on those considered most vulnerable.
- **The tension between public health and civil rights in communicable disease legislation/TB regulations.** Two distinct areas of human rights are protected under international law: civil and political rights on the one hand; and social, cultural and economic rights on the other. Civil and

political rights aim to protect both the individual sphere and an individual's liberties. They safeguard individuals from restraint, loss of freedom and discrimination; whereas the goal of social rights is to safeguard a just participation of people in social goods. While individual rights are inherent to the individual as a human being, social rights, among them the right to health care, are actually conditioned by the resources of a country. In the field of TB control, the balance between individual civil rights and societal obligations is crucial when drafting legislation that specifies the circumstances in which it is permitted to apply involuntary measures. Communicable disease legislation and TB regulations have intervened to mediate the tension between public health and individual civil rights. In this respect, the role of communicable disease legislation consists of both defining and limiting government authority to constrain, on behalf of public health, the civil rights of individuals. It empowers the public health authorities to:

— test and screen;
— require notification and reporting of cases;
— mandate medical examinations, vaccinations and treatment;
— isolate patients with infectious conditions;
— trace and quarantine contacts.

For instance, communicable disease legislation can:

— limit the right to freedom of movement (in case of isolation of an infectious patient or quarantine of contacts);

— limit the right to autonomy and self-determination (in case of compulsory testing, screening, examination and treatment);

— limit the right to privacy (in case of compulsory contact tracing or patient retrieval).

These are examples of restrictions on rights that may be necessary for the public good and therefore can be considered legitimate under international human rights law.

- **Limiting human rights on grounds of public health.** In fulfilling its duty to protect the public against a communicable disease hazardous to public health such as TB, the government may impose limitations on individual liberty. Where voluntary measures do not work, public health authorities need to be able to ensure compliance. Legislation should make provisions for situations that can range from voluntary to compulsory compliance. Compulsion must always be regarded as a last resort and must respect the human rights of those affected. Before resorting to compulsion, therefore, governments should ensure that public health measures comport with sound science and comprise the least restrictive measures

necessary to prevent and control TB. Circumstances that limit human rights for public health purposes must be:

— strictly provided by the law (hence the importance of proper legislation);
— neither arbitrary nor discriminatory;
— based on objective considerations;
— necessary to respond to a pressing public health need (such as the prevention of TB transmission and the development of the disease following infection);
— proportional to the social aim;
— no more restrictive than necessary to achieve the intended purpose.

Even where such limitations on grounds of protecting public health are permitted, they should be of limited duration and subject to review. In this respect, it is important that countries develop domestic legal standards of due process and equal protection.

Patients' rights in legislation and regulation for TB prevention and control

The rights of patients are central to the proper functioning of a health system. Sick patients are vulnerable and therefore easily subject to a violation of their rights. The recognition of patients' rights in turn makes people more conscious of their *responsibilities* when seeking and receiving health care.

- **Common values and goals in patients' rights.** The underlying values and goals that have supported the evolution of the rights of patients can be summarized as follows:

  — To reaffirm fundamental human rights and values in health care, and in particular to protect the physical and mental integrity, dignity and autonomy of the patient.

  — To help patients obtain the fullest benefit from their use of health services.

  — To promote and sustain a beneficial patient–physician relationship based on trust and marked by mutual support and respect.

  — To ensure high-quality of care and equity of access to scarce and costly health-care resources.

  — To promote humanization of care to the most vulnerable and, in particular, to patients affected by DR-TB.

  The cost of health care places an increasing burden upon national resources and makes the equitable distribution of scarce health-care facilities a major

issue. Social justice and the right to health care are at stake in ensuring this equitable distribution. Decisions made regarding this distribution directly affect the accessibility of patients to health care. These includes issues such as establishing a fair insurance programme or other financing system for the costs of health care, planning health services, setting priorities, managing waiting lists and ensuring quality of care.

- **The rights of patients most often recognized in legislation.** The rights of patients most often recognized in legislation are the rights to:

  — respect for the person;
  — information;
  — informed consent (including the right to refuse or to halt a medical intervention);
  — confidentiality and privacy;
  — autonomy and self-determination;
  — freedom of choice within the functioning of the health-care system;
  — the protection of health as is afforded by appropriate measures for diseases prevention and health care;
  — care and treatment;
  — be treated with dignity in relation to their diagnosis, treatment and care, which should be rendered with respect for the person, culture and values;
  — a quality of care marked by sound professional standards, by a humane relationship between the patient and the health-care providers and by the continuity of care;
  — enjoy the support of their family, and to receive spiritual support;
  — relief of their suffering;
  — humane terminal care and to die with dignity;
  — non-discrimination;
  — the right and the occasion to complain.

  The enjoyment of these rights shall be secured without discrimination; patients should be aware of these rights and be able to assert them.

- **Complementary nature of rights and responsibilities.** It is important to remember the complementary nature of rights and responsibilities and also to keep in mind the perspectives of both health-care providers and patients. It is hoped that the recognition of patients' rights will in turn make people more conscious of their responsibilities when seeking and receiving health care, and that this will ensure that patient–physician relationships are marked by mutual support and respect. Patients have responsibilities both to themselves for their own self-care and to health-care providers. Health-care providers enjoy the same protection of their human rights as all other people. Patients should be aware of the practical contribu-

tions they can make to the optimal functioning of the health system. Their active participation in the diagnosis and treatment process is always desirable and often indispensable. The patient has an essential role, the reciprocal of the physician's, in ensuring that the dialogue between them is carried out in good faith. Indeed, the economic and equitable use of resources allocated to health care is an objective that can be shared together by health professionals and patients.

- **The responsibilities of the patients.** Rights and responsibilities go hand-in-hand. In granting rights to patients, modern laws make the patient more autonomous and therefore also more responsible. Some of the Patients' Right Acts defines the responsibilities of patients. They may be expressed in such terms as "A patient should:

  — take care of his or her health;
  — undertake no action to the detriment of his or her health or the health of others;
  — in case of communicable diseases hazardous to public health, observe precautions during contact with health-care providers and other citizens;
  — undertake the obligatory preventive measures such as immunization;
  — give complete information to the physician about previous and current diseases;
  — follow the treatment given by the physician;
  — refrain from using other medical remedies or drugs than those prescribed or approved by the caring physician;
  — observe the rights and dignity of other patients and other health-care staff;
  — observe the rules of the health-care establishment".

Summary and application to the patient with DR-TB

A patient's right to refuse treatment does not excuse that patient from the duty or responsibility to do nothing that may harm another person or persons. Consequently, patients who refuse to accept that responsibility must expect such curtailment of their liberty or freedom of action as will effectively protect others. The restrictions imposed must be no greater than necessary to protect others, and a patient would have a right of redress if unnecessary restrictions are imposed. A patient who refuses to accept curtailment voluntarily must expect a coercive response from the responsible authorities. However, coercion must always be a last resort and only when all attempts at persuasion and appropriate offers of support and other measures to encourage and facilitate compliance have failed to secure a positive response.

Coercive isolation must never be a substitute for treatment and medical care. All public policies bearing on the well-being of the patient must be com-

patible and reinforcing to give the patient every incentive to seek and comply with treatment. No government policy should deny or limit access to treatment and choose isolation as a solution to decrease transmission over treatment.

No patient should be put at an economic or other disadvantage as a direct consequence of accepting treatment or of complying with curtailments for the purpose of protecting others. Otherwise, the patient may see that the balance of personal advantage lies with refusing treatment or avoiding compliance with treatment or curtailment.

A particular problem arises when DR-TB treatment has failed and no other options exist for treatment. The only course of action may be isolation of the patient to prevent transmission of infection to others, and it is not certain how long the period of isolation will be. It has not been internationally determined what is regarded as reasonable measures to ensure that the patient has an acceptable quality of life, given that the reason for isolation is solely the protection of others. Such end-of-life care must be provided in a dignified, humane manner. Visitation with family and friends is fully possible with infection control measures.

The lack of economic and other resources may put in doubt the feasibility of the policies proposed or implied in the foregoing. The abovementioned descriptions and information are intended to serve as a guide to protect both the health of the general population and the individual's human rights. All countries should strive for the full access to treatment for DR-TB and communicable disease legislation balanced with the full protection of human rights and patients' rights.

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ANNEX 5

Use of experimental drugs outside of clinical trials ("compassionate use")

Objectives

This annex outlines current best practices regarding the use of experimental drugs outside of clinical trials, often referred to as "compassionate use". It aims to encourage national health authorities of countries with a high burden of TB to develop or update the necessary framework (regulation, pharmacovigilance and patient protection mechanisms) to facilitate access to the potential benefit of compassionate use programmes for patients in need and to ensure that adequate precautions exist to protect them from undue risks.

Definitions

The terms "compassionate use," "expanded access" or "special access" programmes have essentially the same meaning. They refer to programmes that are intended to provide potentially lifesaving experimental treatments to patients suffering from a disease for which no satisfactory authorized therapy exists and/or who cannot enter a clinical trial. For many patients, these programmes represent their last hope.

General considerations

Both MDR- TB and XDR-TB can be life-threatening diseases for which approved drugs alone may be ineffective. In some cases, experimental antituberculosis drugs,[1] used in combination with approved drugs, could potentially be effective or lifesaving.

Compassionate use is a well known mechanism for diseases such as cancer, Alzheimer disease and AIDS, and can also be used for TB when other treatment options have been exhausted.

To facilitate access to experimental drugs, countries can ensure that the appropriate framework is in place. The structures that govern compassionate use programmes typically include the following elements:

[1] New drugs currently under clinical testing: diamine (SQ-109), diarylquinoline (TMC-207), nitrodihydroimidazooxazole (OPC-67683), nitroimidazole (PA-284), pyrrole (LL3858).

Regulatory mechanisms

In most countries, only drugs for which a marketing authorization has been granted by the national regulatory agency can be used in humans.

Regulations normally permit use of investigational new drugs (IND) in well-defined circumstances: an IND can only be used through an approved clinical trial in accordance with protocol and inclusion criteria or through a compassionate use programme. Usually the drug must be either the subject of an application for a marketing authorization or the study drug in ongoing clinical trials. The indication for the proposed use of the drug must be within the scope of an IND application or the target label indication.

Some national regulatory agencies have developed additional mechanisms to facilitate the access to new drugs at different stages of development, but before market approval (e.g. single patient and small group access, or continued access to an IND at the end of a clinical trial, for patients enrolled in the trial).

Most extant regulations are based on similar modus operandi:

- The patient must be well-informed about the drug, its intended actions and potential adverse effects and its possible impact on other conditions or treatments. Patients must also consent in writing to be treated with it. It is recommended that an ethical review board (ERB)[1] approve the proposed use of the drug.
- 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 using the IND is no greater than the probable risk from the disease or condition;
  - — must agree to provide the regulatory agency with a report on the results of the use of the drug, including any adverse reactions.
- The sponsor:[2]
  - — 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: GMP certificate for manufacturing site, certificate of analysis, chemical and microbial parameters, stability data, batch number and expiry date;

[1] This refers to the relevant institutions in each setting that provide oversight for protection of human subjects.

[2] An individual, company, institution or organization that 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.

Notes. In some countries, similar mechanisms are in place to give patients access to drugs that are not registered by the national authorities but cannot be considered as IND as they are registered in other countries and are recognized as safe and effective by the international scientific community.

The use of an authorized medicinal product as part of the practice of medicine for an indication different from the one for which the product was approved (i.e. off-label use) is not considered compassionate use and generally does not require the approval of regulatory authorities. This includes the use in MDR TB treatment of drugs such as fluoroquinolones, linezolid, clofazimine, and clarithromycin, imipenem. However, the institution at which the product will be used may require ERB approval.

Patient monitoring and pharmacovigilance

Compassionate use should only be considered if adequate clinical, biological and bacteriological monitoring is in place, including mechanisms for collecting and reporting patient data through specific case report forms. It is of the utmost importance that adverse events are diligently reported by the practitioner within the requested timelines. It is recommended that patients be provided with peer or social support when using an experimental drug to assist in the monitoring of their psycho-social condition and adverse effects.

Patient protection

Although treating a seriously ill patient under compassionate use provisions is motivated by humaneness and compassion, there are several ethical issues to consider regarding the use of experimental drugs.

- *Unproven efficacy.* The lack of approval usually means the safety and/or efficacy have not been scientifically proven. The possible but unproven benefits of the experimental treatment must be weighed against its risks. The risks and benefits of using the experimental treatment should also be weighed against the possible benefits and risks of available alternatives.

- *Informed consent.* The physician should recognize the unique challenge of obtaining valid informed consent for the use of experimental drugs outside of clinical trials. It is critical that the patient is informed of the risks, potential benefits and alternatives, and understands that there is no guarantee of benefit from the experimental drug.
- *Ethical review board approval.* Some regulatory systems require prior approval of an ERB before drugs are provided outside a clinical trial. Even where such a requirement does not exist in government regulations, it is recommended that institutions require the approval of an ERB or other oversight body as a matter of good clinical practice.

Drug developers

Where possible, compassionate use programmes should be incorporated into drug development plans to meet the needs of patients who have exhausted other treatment options and who are not eligible for enrollment in the trials. Such advance planning will facilitate the process of obtaining approvals and making the drugs available in case of a request.

When requests for access to experimental drugs are made, a first analysis of the request should be done by either the medical leader of the compound development team or by the medical affairs department, depending on the status of the compound on the drug development pathway. If medical criteria for the use of the compound are met, an operational team should review the regulatory perspective and logistics.

Indications

In the case of MDR- and XDR TB, compassionate use may be considered for patients with a life-threatening condition (e.g. deteriorating clinical condition due to TB and/or severe immune depression) when available treatments have failed or no authorized drug with bactericidal activity is available, and no other medical or surgical options are appropriate; results of drug susceptibility testing by validated methods would be critical to such decision-making. The experimental drug should never be used in mono-therapy. Instead, it should always be used in conjunction with other drugs with proven or probable efficacy in order to prevent emergence of resistance to the experimental drug.

Cost

The experimental drug should be provided free of charge to the patient.

Scientific benefit

From a methodological point of view, controlled clinical trials are the only means of obtaining reliable and interpretable efficacy and safety data for a medicinal product. Compassionate use programmes are not a substitute for properly conducted trials.

Nevertheless, the experience with antiretroviral treatment has shown that in addition to the benefit to individual patients, these programmes can also generate useful information on safety and effectiveness in different populations than those included in clinical trials.

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ANNEX 6

Methodology

Scoping

WHO first published guidelines that specifically address DR-TB in *Guidelines for establishing DOTS-Plus pilot projects for the management of multidrug resistant tuberculosis* in 2000. As increasing evidence emerged, *Guidelines for the programmatic management of drug-resistance tuberculosis* was published in 2006. This publication had a wider scope and purpose and supported the implementation of the new Stop TB Strategy for 2006–2015.

The recognition that there were strains of TB that had become resistant to some second-line drugs led to the definition of extensively drug-resistant TB (XDR-TB) in 2006, and WHO rapidly organized the first meeting of the Global Task Force on XDR TB in October 2006. This meeting recommended that WHO TB and HIV departments should provide an emergency update to several chapters of the 2006 guidelines in response to the emergence of XDR-TB.

A meeting of the WHO Guidelines Steering Group, together with several WHO advisers who had contributed to the 2006 edition, took place in April 2006. It was agreed that there was an urgent need for guidance on the best response to XDR-TB, based on the emerging evidence. The group identified the chapters to be reconsidered and the gaps to be addressed in this emergency update.

Of the total 18 chapters, eight have been reviewed and substantially changed in response to the emerging evidence about MDR-TB and XDR-TB (chapters 1, 4, 5, 6, 7, 10, 12 and 18). One chapter is new (Chapter 19). The remaining chapters have undergone minor revisions to ensure consistency but have not been rewritten or had any new evidence included.

There was also a decision that a full review of the Guidelines will be started after the emergency update.

The WHO Guidelines Review Committee was in place by January 2008 and had already developed draft Guidance for Emergency Guidelines which was used to guide best practice in the finalization of this emergency update.

Target audience

This document is intended to assist in the development of national policies to improve the diagnosis and management of DR-TB. The guidelines are primarily intended for:

(i) national and regional TB programme managers, managers of nongovernmental organizations and other programme managers who are involved in the scaling up of integrated TB control programmes in resource-limited settings, to be used in conjunction with HIV/AIDS control programmes.
(ii) clinicians in these settings, to enable access to comprehensive, up-to-date, technical and clinical information on the prevention and management of DR-TB and to encourage the implementation of known best practice.

Guidelines Reference Group

The members of the Guidelines Reference Group are listed on pages vi–vii. All made a significant contribution to writing and reviewing particular updated chapters, many of them contributing to several chapters, although only the members of the Steering Group reviewed the whole document.

The Steering Group consisted of two members of the WHO secretariat, and three expert advisers from partner organizations and Member States.

The Steering Group of editors and key authors were Dr Ernesto Jaramillo, Dr Salmaan Keshavjee, Dr Kitty Lambregts, Dr Michael Rich and Dr Karin Weyer.

The first draft of the guidelines was reviewed by the Steering Group at meeting held in February 2008. Other advisers at this meeting were Dr Malgosia Grzemska (WHO), Dr Suzanne Hill (WHO), Dr Tim Holtz (CDC, USA) and Dr Kathrin Thomas (WHO). Any outstanding issues were then resolved by e-mail to agree the final version. Other members of the group were asked to provide reviews at these later stages for particular issues.

Evidence retrieval and synthesis

The nominated lead author for each chapter used a limited evidence retrieval consisting of:

- personal collection of publications and case reports;
- literatures searches using PubMed and other databases and search engines;
- existing guidelines, both from WHO and from other internationally recognized organizations;
- expert consensus during several group meetings for specific topics;
- unpublished data, for example data supplied to the Green Light Committee by their approved MDR-TB management projects.

This evidence was synthesized by each lead author, but a formal quality assessment was not used. Given the relatively small field of experts in managing DR-TB, expert opinion was sought from several of the original researchers in the field. The evidence was not formally assessed or graded and there are no formal evidence summaries.

Peer review

The revised chapters were each reviewed by at least one, and usually several, members of the Guidelines Reference Group, from both within the WHO Stop TB and HIV departments and outside external experts, as appropriate. One of the expert advisers on the Steering Group was commissioned to harmonize and review all the updated chapters (Dr Michael Rich). The reminder of the Steering Group also reviewed the whole document and provided extensive and detailed feedback.

Conflict of interests

All contributors were asked to complete the WHO Declarations of Interest form. A summary is provided on page 4.

Development of recommendations

The 2006 guidelines did not present recommendations in sections separate from the text. The 2008 emergency update kept to this original format to ensure consistency with the non-revised chapters.

The emergency update presents recommendations that were new or considered relevant to the response to XDR-TB or to be of an urgent nature. The Steering Group identified, discussed and finalized the recommendations and established the main new changes from the 2006 guidelines at its final meeting. Key recommendations are placed at the start of each updated chapter with new recommendations indicated by an asterisk.

Cost is not explicitly considered as part of the recommendations, although the realities of human resources, socioeconomic issues and health system infrastructure are taken into consideration throughout the document.

Review date

The process for scoping the *Guidelines for the programmatic management of drug-resistant tuberculosis* has already begun and the next edition is due for publication in 2010, with a rigorous and evidence-based approach following the *WHO guidelines for guidelines 2008*.

Forms

Category IV Treatment Card

Name: _____

Category IV registration number: _____

Date of Category IV registration: ___ /___ /___

District TB registration number: _____

Date of district TB registration: ___ /___ /___

Address: _____

Country/District: _____

Treatment centre: _____

Sex: ❑ M ❑ F

Age: _____ Date of birth: ___ /___ /___

Initial weight (kg): _____ Height (cm): _____

Site: ❑ Pulmonary ❑ Extrapulmonary ❑ Both

If extrapulmonary, specific site: _____

	Registration group	Select one only
1	**New**	
2	**Relapse**	
3	**After default**	
4	**After failure of first treatment**	
5	**After failure of re-treatment**	
6	**Transfer in** (from another Category IV treatment site)	
7	**Other** (previously treated without known outcome status)	

HIV information	
HIV testing done: ❑ Y ❑ N ❑ unknown	
Date of test: ___ /___ /___	Results:
Started on ART: ❑ Y ❑ N	Date: ___ /___ /___
Started on CPT: ❑ Y ❑ N	Date: ___ /___ /___

ART = antiretroviral therapy; CPT = co-trimoxazole preventive therapy

Previous tuberculosis treatment episodes

No.	Start date (if unknown, put year)	Regimen (write regimen in drug abbreviations)	Outcome

Classification of previous drug use:

Used second-line drugs previously? ❑ Yes ❑ No

If Yes, specify: _____

_____

_____

Drug abbreviations

First-line drugs
H = Isoniazid
R = Rifampicin
E = Ethambutol
Z = Pyrazinamide
S = Streptomycin
(Th = Thioacetazone)

Second-line drugs
Am = Amikacin
Km = Kanamycin
Cm = Capreomycin
Ofx = Ofloxacin
Lfx = Levofloxacin
Mfx = Moxifloxacin
Pto = Protionamide
Eto = Ethionamide
Cs = Cycloserine
PAS = *P*-aminosalicylic acid

Review panel meetings: dates and decisions

Date	Decision	Next date

DR-TB Control Programme

FORM 01

Patient name: _____

HIV Information (fill for all patients)

HIV testing done: ❑ Y ❑ N ❑ Unknown

Date of test: ___ /___ /___ Results:

Started on ART: ❑ Y ❑ N Date: ___ /___ /___

Started on CPT: ❑ Y ❑ N Date: ___ /___ /___

ART = antitretroviral therapy;
CPT = co-trimoxazole preventive therapy

Antiretroviral Flow Sheet

Regimen	Start date	Stop date	Reason for stop/change

Reasons for interruption of medications:	1 = Failure 2 = Tuberculosis/ Interaction	3 = Adverse effects 4 = Pregnancy	5 = Stock out 6 = Dose change	7 = Patient refusal 8 = PMTCT ended	9 = Other (specify)
Abbreviations:	INRT 3TC = Lamivudine D4T = Stavudine AZT = ZDV= Zidovudine	INRT ABC = Abacavir DDI = Didanosine TDF = Tenofovir	INNRT NVP = Nevirapine EFV = Efavirenz	IP LOP/R = Lopinavir/ ritonavir	IP NFV = Nelfinavir R = Ritonavir

Weight monitoring

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Date																								
Weight																								

Laboratory monitoring

Date																
ALT/SGPT																
AST/SGOT																
Creatinine																
K																
TSH																
Hemoglobin																
WB count																
CD4																
Lipase																
HIV test																
Pregnancy test																

Patient name: _____

Medical diagnosis other than tuberculosis

Date	**Type** (i.e. diabetes, hypertension, cardiomyopathy, HIV, opportunistic infections)

Adverse effects

Date	**Type** (i.e. neuropathy, hepatitis, rash, etc.)	**Suspected drug**

DR-TB Control Programme

FORM 01

Drug susceptibility testing (DST) results (notation method for DST: r = resistant, s = susceptible, c = contaminated)

Patient name: _____

Date*	S	H	R	E	Z	Km	Am	Cm	Fq	Pto/Eto	PAS	Cs	Other	Other

Chest X-ray

Date	Result

Month #	Sputum smear microscopy		
	Date*	Sample No.	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 #	Culture		
	Date*	Sample No.	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			

Notes:

* All dates in the tables that report smears, culture and DST are dates the specimen was collected from the patient.

** The date the sputum was collected that led to the patient being registered with MDR-TB (if performed).

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 number of colonies
10–100 colonies	+
More than 100 colonies	++
Innumerable or confluent growth	+++

Patient name: _____

CATEGORY IV REGIMEN (date treatment started and dosage (mg), change of dosage, and cessation of drugs):

Date	H	R	Z	E	S	Km	Am	Cm	FQ	Other	Other	Other	Other	Comments

ADMINISTRATION OF DRUGS (one line per month):

Month	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	Weight (kg), Lab, X-ray

Mark in the boxes: **O** = directly observed
N = not supervised
Ø = drugs not taken

Patient name: _____

ADMINISTRATION OF DRUGS (*continued*):

Month	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	Weight (kg), Lab, X-ray

Mark in the boxes: **O** = directly observed
N = not supervised
Ø = drugs not taken

Comments _____

Outcome	Mark one	Date
Cured		
Completed		
Died		
Failed		
Defaulted		
Transferred out		

Category IV Register

Unique Cat. IV Register No.	Date entered in Cat. IV Register	Name (in full)	Sex M or F	Age Date of birth d/m/y	Address	District TB Register number Date of regis-tration	Site of disease (P/EP)	Regis-tration group*	**Result of drug susceptibility testing (DST)** (Enter the DST that resulted in the patient being registered as a Category IV patient. If the DST is pending it should be filled in when the results are known. See treatment card for full history of DST data) R = resistant S = susceptible C = contaminated											Date sample taken for DST	Second-line drugs already received
									H	R	E	S	Km	Cm	Fq	Other	Other	Other	Other		
1				/ /																	
2				/ /																	
3				/ /																	
4				/ /																	
5				/ /																	
6				/ /																	
7				/ /																	
8				/ /																	
9				/ /																	
10				/ /																	

* 1 New
2 Relapse
3 After default
4 After failure of first treatment
5 After failure of re-treatment
6 Transfer in (from another Category IV treatment site)
7 Other

DR-TB Control Programme

FORM 02

			Smear (S) and culture (C) results during treatment (if more than one smear or culture done in a month, enter the most recent positive result)																													
Reasons for entering in Category IV Register		**Category IV 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	
MDR-TB docu-mented	MDR-TB suspected (determined by country protocol)	**Regimen (in drug initials) Date started**	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	
		Date	/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /	
		Date	/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /	
		Date	/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /	
		Date	/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /	
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		Date	/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /		/ /	

Smear (S) and culture (C) results during treatment
(if more than one smear or culture done in a month, enter the most recent positive result)

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		Month 34	
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	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		d/m/y	
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Outcome Cured Completed Failed Died Defaulted Transferred out	**TB/HIV activities**					
	HIV testing					
Date outcome given	Testing done (Y/N/unknown)	Date of test	Result	ART Y/N Start date	CPT Y/N Start date	**Comments**
/ /						
/ /						
/ /						
/ /						
/ /						
/ /						
/ /						
/ /						
/ /						
/ /						
/ /						

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 number of colonies
10–100 colonies	+
More than 100 colonies	++
Innumerable or confluent growth	+++

HPF = high-power field

Drug abbreviations

First-line drugs

H = Isoniazid
R = Rifampicin
E = Ethambutol
Z = Pyrazinamide
S = Streptomycin
(Th = Thioacetazone)

Second-line drugs

Am = Amikacin
Km = Kanamycin
Cm = Capreomycin
Ofx = Ofloxacin
Lfx = Levofloxacin
Mfx = Moxifloxacin
Pto = Protionamide
Eto = Ethionamide
Cs = Cycloserine
PAS = *P*-aminosalicylic acid

DR-TB Control Programme FORM 03

Request for sputum examination (to be completed by treatment centre)

Treatment unit _____ Date _____

Patient name: _____

Age: _____ Date of birth: _____ Sex (mark one) ❑ M ❑ F

Address (in full) _____

_____

Reason for examination (mark one): ❑ diagnosis ❑ follow-up examination

Test request (mark any that are needed): ❑ smear ❑ culture ❑ drug-susceptibility testing

Signature of person requesting examination: _____

RESULTS (to be completed in laboratory)

Smear results

Date collected	Specimen	Laboratory specimen no.	Appearance*	Result (mark one) neg.	1–9	+	++	+++
		1						
		2						
		3						

*visual appearance of sputum (blood-stained, mucopurulent, saliva)

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	+++

Date _____

Examined by (signature) _____

Culture results

Date collected	Specimen	Laboratory specimen no.	Result (mark one) neg.	1–9	+	++	+++	Contaminated
		1						
		2						

No growth reported	0
Fewer than 10 colonies	Report number of colonies
10–100 colonies	+
More than 100 colonies	++
Innumerable or confluent growth	+++

Date _____

Examined by (signature) _____

DST results

Date taken	Laboratory specimen no.	S	H	R	E	Z	Km	Am	Cm	Ofx	Other	Other
	1											
	2											

R = resistant
S = susceptible
C = contaminated

Date _____

Examined by (signature) _____

The completed form (with results) should be sent promptly to the treatment unit

DR-TB Control Programme

Laboratory Register for culture and DST

FORM 04

Date specimen received	Laboratory serial number	Type of specimen received	Referring health facility	Patient name	Patient address if new	Sex M/F	Date of birth	Date specimen collected	Date specimen inoculated

Laboratory Register for culture and DST

Reason for examination		Result of culture***	Result of confirmatory test for *M. tuberculosis* (positive or negative)	Culture sent for DST (Yes or No)	Name of person reporting DST results	Signature	Date results reported	Comments
Diagnosis*	Follow-up**							

* New patients or patients starting a re-treatment regimen.
** Patient on TB treatment, indicate months of treatment at which follow-up examination is performed.
*** Outcome of culture reported as follows:

No growth reported	0
Fewer than 10 colonies	Report number of colonies
10–100 colonies	+
More than 100 colonies	++
Innumerable or confluent growth	+++

Laboratory Register for culture and DST

FORM 04

R	H	E	S	Km	Cm	Fq	Other	Other	Other	DST Results	Name of person reporting DST results	Signature	Comments

Report DST results as s = susceptible, r = resistant, c = contaminated

Quarterly report on MDR-TB detection and Category IV treatment start

FORM 05

Name of area	Name of area coordinator .....
Patients identified during ..... quarter of year	Date .....

1. Number of patients detected with MDR-TB/XDR-TB in the lab (by date of result of MDR-TB/XDR-TB in labortory register) during the quarter:

MDR-TB ☐ **XDR-TB** ☐

2. Number of MDR-TB patients who started Category IV treatment during the quarter

	New case	Previously treated with first-line drugs	Previously treated with second-line drugs
Confirmed cases			
Suspected cases			

1st quarter: 1st January–31 March
2nd quarter: 1er April–30 June
3rd quarter: 1er July–30 September
4th quarter: 1er October–31 December

Signature .....

FORM 06

Six month interim outcome assessment of confirmed MDR-TB cases (to be filled out 9 months after treatment start)

Name of Unit: _____

Date filled in: _____

Quarter treatment was started: _____

Date of the report: _____

Number started on treatment	Bacteriological results at 5 and 6 months of treatment			No longer on treatment		
	Negative (all smears and cultures negative during month 5 and 6, and at least a smear and culture done each month)	Positive (any smear or culture is positive during month 5 and 6)	Culture and smear unknown (Consider unknown if a culture or smear results is not done for either month 5 or 6)	Died	Defaulted	Transferred out

Annual report of treatment result of confirmed MDR-TB patients starting Category IV treatment (to be filled in 24 and 36 months past the closing date of year of treatment)

Year of treatment start: _____

Patient group	Cured	Treatment completed	Failed	Defaulted	Died	Transferred out	Still on treatment	Total
New								
Previously treated with first-line drugs only								
Previously treated with both first- and second-line drugs								
Total								

Index

A full list of abbreviations used in the text appears on pages viii–x.