

Guidelines for the programmatic management of drug-resistant tuberculosis

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Abbreviations and acronyms

AFB	acid-fast bacilli
ART	antiretroviral therapy
CDC	United States Centers for Disease Control and Prevention
CPT	co-trimoxazole preventive therapy
DOT	directly observed therapy
DOTS	internationally recommended strategy for TB control
DRS	drug resistance surveillance
DST	drug susceptibility testing
FIND	Foundation for Innovative New Diagnostics
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GLC	Green Light Committee
HIV	human immunodeficiency virus
HPF	high-power field
HRD	human resource development
IUATLD	International Union Against Tuberculosis and Lung Disease
LFT	liver function test
MDR-TB	multidrug-resistant tuberculosis
NTM	nontuberculous mycobacteria
PIH	Partners In Health
PPD	purified protein derivative
PPM	public-private mix
SCC	short-course chemotherapy
TB	tuberculosis
TSH	thyroid-stimulating hormone
UNAIDS	Joint United Nations Programme on HIV/AIDS
UVGI	ultraviolet germicidal irradiation
WHO	World Health Organization

Antituberculosis drug abbreviations

Am	Amikacin	Lfx	Levofloxacin
Amx/Clv	Amoxicillin/Clavulanate	Lzd	Linezolid
Cfx	Ciprofloxacin	Mfx	Moxifloxacin
Cfz	Clofazimine	Ofx	Ofloxacin
Clr	Clarithromycin	PAS	<i>P</i> -aminosalicylic acid
Cm	Capreomycin	Pto	Protionamide
Cs	Cycloserine	R	Rifampicin
E	Ethambutol	S	Streptomycin
Eto	Ethionamide	Th	Thioacetazone
Gfx	Gatifloxacin	Trd	Terizidone
H	Isoniazid	Vi	Viomycin
Km	Kanamycin	Z	Pyrazinamide

Preface

When, in the early 1990s, the World Health Organization (WHO) resumed leadership in control of tuberculosis (TB) worldwide, the primary focus was to support Member States in setting up proper national TB control programmes. Leadership was crucial at a time when the prospects for TB control were universally bleak in the face of a rampant epidemic. Emphasis was placed on establishment of the key and essential elements of TB control based on current knowledge, and on their assertive promotion. Thus, the DOTS strategy was launched in 1994–1995 and Member States were supported in its implementation. DOTS was, and remains, the most cost-effective approach to detecting and curing cases and to preventing the onset and spread of drug resistance. Prevention was therefore promoted as the main tool for combating drug-resistant TB.

Management of existing cases, especially of the most feared variant, multi-drug-resistant TB (MDR-TB), was left to the individual initiative of national programmes. Best practice guidelines detailing the choice of regimens were published in 1996 to guide clinicians in TB treatment, but no programmatic recommendations were made available by WHO. The focus had to remain on DOTS implementation, since very few countries had an acceptable standard of basic TB control. In essence, the few resources available for TB were prioritized to build, expand and strengthen basic TB control programmes in order to diagnose and cure the majority of TB patients while preventing the emergence of drug resistance. At that time in the mid-1990s, the international community had only just started to become aware of the burden imposed by TB on the societies of developing countries. It was not yet conceivable that already overburdened national programmes could undertake the complex, lengthy and extremely costly (often unaffordable) management of drug-resistant, often chronic, cases of TB. Besides, knowledge about the spread of drug resistance was lacking and there was no standard method of acquiring reliable information.

In 1997, WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) reported for the first time standardized information on drug resistance from surveys or surveillance systems conducted since 1994 in some 35 countries. This information confirmed what many had feared: drug resistance was widespread and MDR-TB was at a critically high level in some

parts of the world, especially in some countries of the former Soviet Union.

Stimulated by this new evidence, many realized that the time had come to address MDR-TB in a more proactive way than previously. WHO, in particular, decided to explore what could be done together with some key partners, such as the Harvard Medical School, the United States Centers for Disease Control and Prevention (CDC) and Médecins Sans Frontières. At two historic meetings – in Cambridge, Massachusetts, in April 1998, during which the term “DOTS-Plus” was coined, and in Geneva, Switzerland, in January 1999 – experts agreed on the need to face MDR-TB programmatically, i.e. no longer solely through individual practitioner’s efforts but through wider DOTS-Plus pilot projects implemented by, or in collaboration with, national TB control programmes. For this purpose, a formal WHO working group, named “DOTS-Plus for MDR-TB”, was established in March 1999 to assist countries and support efforts to assess the feasibility of DOTS-Plus and to produce sound policy recommendations. This working group was later adopted by the Stop TB Partnership in 2001 as its very first “implementation” working group.

While formulating draft guidelines for the management of MDR-TB, the new working group soon encountered an insurmountable obstacle: the price of most second-line antituberculosis drugs recommended for use in the treatment of MDR-TB was unaffordable to countries in need. New frontiers in drug procurement would need to be explored and negotiations with producers embarked upon in order to make these drugs affordable to the poorest countries. The era of a renewed, human rights-based approach to medicine and public health had just begun, and the advent of the principle of access to care for all favourably influenced those discussions. It was decided that a coalition of partners strongly motivated to make MDR-TB treatment affordable would be more effective than any individual group in the negotiations with the pharmaceutical industry.

The Green Light Committee (GLC) was thus born in June 2000: hosted by WHO as a partnership among five categories of participants (governments of resource-limited countries, academic institutions, civil society organizations, bilateral donors and WHO), it successfully negotiated prices of drugs with producers; solicited creation of, and adopted, sound policies for proper management of drug-resistant TB; established strict criteria to review proposals for DOTS-Plus projects; assisted countries in developing such proposals and ensured their proper implementation; and finally, provided access to quality-assured second-line drugs at concessionary prices to those projects 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 to prevent the emergence of

“super”-resistant strains of *Mycobacterium tuberculosis*. In 2002, the GLC was adopted by the newly established Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) as its mechanism for screening proposals for DOTS-Plus financing. This was another historic milestone, and the GFATM is today the leading financial mechanism supporting the management of MDR-TB in resource-constrained settings.

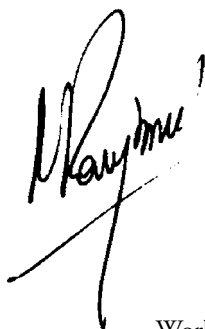
The Scientific Panel of the WHO Working Group on DOTS-Plus for MDR-TB produced its first set of guidelines – *Guidelines for establishing DOTS-Plus pilot projects for the management of multidrug-resistant tuberculosis* – in 2000, following discussions that began at a meeting in Madrid in September 1999. That document was based on the little evidence available at the time, gathered mostly from small-scale projects carried out in previous years and without established standards. Much more evidence has become available in subsequent years. First, the cost-effectiveness of DOTS-Plus has been shown in different settings, including Peru. Second, reasonably high cure rates have been achieved in country-wide programmes to treat MDR-TB, for instance in Latvia. Third, growing favourable evidence of feasibility and cost-effectiveness (still unpublished) has accrued from a number of DOTS-Plus projects in several settings around the world. By September 2005, 35 GLC-approved projects had been implemented in some 29 countries around the world, providing treatment to more than 10 000 cases of MDR-TB in resource-limited settings.

This new evidence mandates a revision of the previous guidelines in order to make available an updated set of recommendations. The new guidelines address this need and provide guidance on current best practice in the management of drug-resistant TB, especially MDR-TB, that should be adopted worldwide. The challenge is huge. WHO estimates that some 300 000–600 000 new cases of MDR-TB may emerge every year, with a global prevalence that may be as high as one million cases. Most of these patients would have no access to proper care and treatment without the existence of the GLC, the DOTS-Plus Working Group and funds made available through the powerful financial mechanisms existing today, such as the GFATM, the World Bank and some bilateral donors.

The new guidelines are also needed in the context of the new Stop TB Strategy, launched in 2005 by WHO and the Stop TB Partnership. This strategy, building on – and enhancing – DOTS, explicitly identifies the management of MDR-TB as a priority. The strategy recognizes the need to provide care to all patients affected by TB, whether the disease is caused by drug-susceptible or drug-resistant bacilli, and the need to avoid jeopardizing TB control efforts where drug-resistant TB is highly prevalent. Therefore, the management of MDR-TB now needs to be integrated into comprehensive national TB control plans in order to comply with the new Stop TB Strategy. Advocacy, built on a solid rationale and the proper demonstration of feasibility

under different programmatic circumstances, is crucial to ensure that the integrated programmes will be fully adopted by all national TB control programmes.

In conclusion, the new guidelines represent the best current knowledge in the management of drug-resistant TB and MDR-TB and offer ample options for tailoring diagnosis and care to different epidemiological and programmatic conditions worldwide. The recommendations, compiled by leading experts, should be followed without hesitation by all national TB control programmes and their partners as the most solid programmatic standards. 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. These guidelines focus on care for MDR-TB patients, in the hope and expectation that, in future, the occurrence of massive numbers of cases can be prevented through sound TB control practices.

A handwritten signature in black ink, appearing to read 'M. Raviglione', with a long, sweeping horizontal stroke extending from the bottom of the signature.

Dr Mario Raviglione
Director
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Introduction

The emergence of resistance to drugs used to treat tuberculosis (TB), and particularly multidrug-resistant TB (MDR-TB),¹ has become a significant public health problem in a number of countries and an obstacle to effective global TB control. In many other countries, the extent of drug resistance is unknown and the management of patients with MDR-TB is inadequate. In countries where drug resistance has been identified, specific measures need to be taken within TB control programmes to address the problem through appropriate management of patients and adoption of strategies to prevent the propagation and dissemination of drug-resistant TB, including MDR-TB.

These guidelines offer updated recommendations for TB control programmes and medical workers in middle- and low-income countries faced with drug-resistant forms of TB, especially MDR-TB. They replace two previous publications by the World Health Organization (WHO) on drug-resistant TB (1–2). Taking account of important developments in recent years, the new guidelines aim to disseminate consistent, up-to-date recommendations for national TB control programmes and medical practitioners on the diagnosis and management of drug-resistant TB in a variety of geographical, political, economic and social settings. The guidelines can be adapted to suit diverse local circumstances because they are structured around a flexible framework approach (see Chapter 2), combining a consistent core of principles and requirements with various alternatives that can be tailored to the specific local situation.

The new guidelines expand upon the most recent general WHO guidelines on TB, *Treatment of tuberculosis: guidelines for national programmes* (3), which includes specific considerations for chronic and MDR-TB cases, classified together under WHO diagnostic Category IV. Detailed strategies are described for the diagnosis of resistant strains of TB and the management of regimens designed to treat Category IV patients.

The term DOTS-Plus has been used recently to refer to piloting of the management of drug-resistant TB within the context of basic DOTS pro-

¹ MDR-TB is defined as tuberculosis 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).

grammes. The integration of management of drug-resistant TB within DOTS programmes is no longer at the pilot stage and is now being integrated under the recommendations set out in this document.

In addition, the guidelines 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).¹ Finally, the guidelines introduce new standards for registering, monitoring and reporting the treatment outcomes of patients with drug-resistant 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.

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3. *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003.313).

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 DOTS-Plus and the Green Light Committee web page at <http://www.who.int/tb/dots/dotsplus/management/en/>

CHAPTER 1

Background information on drug-resistant tuberculosis

1.1 Chapter objectives

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

1.2 Recent developments and the Stop TB Strategy

The original basic package of DOTS provisions for TB control has recently been expanded while retaining the five essential components (see Chapter 2, section 2.2).

The new Stop TB Strategy continues to emphasize the basic package and includes components that tackle additional challenges:

1.2.1 Pursuing high-quality DOTS expansion

- 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 and other challenges by implementing collaborative TB/HIV activities, preventing and controlling MDR-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.

1.2.4 Involving 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 Engaging 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 or 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 tuberculosis

Detection and treatment of all forms of TB, including drug-resistant forms, should be integrated within national TB control programmes. 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 resistant TB are a source of ongoing transmission of resistant strains, resulting in future added costs and mortality. The framework for the management of drug-resistant TB presented in these guidelines can be adapted to all national TB control programmes and integrated within the basic DOTS strategy.

1.4 Causes of drug-resistant tuberculosis

Although its causes are microbial, clinical and programmatic, drug-resistant 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. An inadequate or poorly administered treatment regimen 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 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 short-course chemotherapy.

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

1.5 Addressing the sources of drug-resistant tuberculosis

Any ongoing production of drug-resistant TB should be addressed urgently before embarking on any programme designed for its control. The framework

TABLE 1.1 Causes of inadequate antituberculosis treatment (1)

HEALTH-CARE PROVIDERS: INADEQUATE REGIMENS	DRUGS: INADEQUATE SUPPLY/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

approach described in these guidelines can help to identify and curtail possible sources of drug-resistant TB.

The factors that may be contributing to the development of new drug-resistant cases should be reviewed (see Table 1.1 for a list of possible factors) (1). Well-administered first-line treatment for susceptible cases is the best way to prevent acquisition of resistance. Timely identification of drug-resistant 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 drug-resistant TB works synergistically to eliminate all the potential sources of TB transmission.

1.6 Magnitude of the MDR-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 followed the widespread use of rifampicin since the 1970s.

The WHO Stop TB Department estimates the number of incident cases (including new and re-treatment cases) occurring worldwide in 2003 alone to be 458 000 (95% confidence limits, 321 000–689 000) (2). Prevalent cases worldwide could be two or three times higher than the number of incident cases (3).

The objectives of the WHO/IUATLD Global Project on Antituberculosis Drug Resistance Surveillance are to gather data on drug resistance using a standard methodology and to determine the global magnitude of resistance to four first-line antituberculosis drugs: isoniazid, rifampicin, ethambutol and streptomycin (4). 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. By 2003, three rounds of the global project had been completed

covering 109 countries or regions within large countries (5). Despite these surveillance data, the magnitude of drug resistance is not yet known in many areas of the world with high burdens of TB, such as most of China, India, Indonesia, Nigeria and countries of the former Soviet Union. Nevertheless, evidence from half the world's nations confirms that drug resistance is a serious problem worldwide.

The third global report on antituberculosis drug resistance surveillance has documented that many areas of the world face endemic and epidemic MDR-TB, and in some areas resistance is alarmingly high. In patients never previously treated, the median prevalence of resistance to any of the first-line drugs, most commonly streptomycin and/or isoniazid, was 10.7% (range 0–57.1%); 20 survey sites exceeded 20%. The median prevalence of MDR-TB was 1.2% (range 0–14.2%); 11 sites exceeded the 6.5% threshold for extreme values, including 7 in the former Soviet Union. In patients previously treated, the median prevalence of any resistance was 23.3% (range 0–82.1%) and of MDR-TB, 7.7% (range 0–58.3%).

Drug resistance was 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 more than 20% of sputum smear-positive cases (6).

Many identified MDR-TB cases have resistance to drugs other than both isoniazid and rifampicin. In fact, one third of MDR-TB cases had resistance to all four of the first-line drugs tested in the global survey.

Moreover, MDR-TB patients often live for several years before succumbing to the disease (7). Prevalence of MDR-TB may therefore be three times greater than its incidence (3), suggesting that the true number of MDR-TB cases in the world today may approach or exceed one million.

1.7 Management of drug-resistant tuberculosis, the Green Light Committee and the global response to MDR-TB

The WHO Working Group on DOTS-Plus for 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 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.

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 drug-resistant 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 drug-resistant TB (DR-TB control programmes) and monitors approved projects.

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 (8).

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

Patients who meet WHO diagnostic Category IV criteria (see Chapter 4) are treated with regimens designed to treat MDR-TB. These regimens are referred to as “Category IV regimens” throughout the guidelines.

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CHAPTER 2

Framework for effective control of drug-resistant tuberculosis

2.1 Chapter objectives

This chapter describes the five essential components of the framework approach to management of drug-resistant TB. It also introduces a systematic approach for tailoring these components to the local situation, with integration into a DOTS-based national TB control programme.

2.2 DOTS framework as applied to the management of drug-resistant tuberculosis

The DOTS framework 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 drug-resistant TB usually strengthens the national TB control programme.

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 drug-resistant TB into national TB control programmes. 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 national TB control programme must be strengthened to prevent the emergence of more MDR-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 national TB control programme. Drug-resistant 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 drug-resistant TB are tested (strategies on which risk groups to test are discussed in Chapter 5).

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 national TB control programme 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 supranational TB reference laboratories.

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-centred 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.

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 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 are quality-assured by a stringent drug regulatory authority recognized by WHO. A list of prequalified second-line drugs and manufacturers is in preparation.

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 under the DOTS-Plus strategy. 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 drug-resistant tuberculosis into national programmes

Management of drug-resistant TB should be fully integrated into the national TB control programme. The challenge involved in this integration should not be underestimated. However, the complexity of the process should not deter programmes from taking the necessary steps to allow all patients with drug-resistant TB access to life-saving treatment. If many of the drug-resistant cases 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 drug-resistant TB.

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

BOX 2.1**Key steps for integrating management of drug-resistant 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 drug-resistant TB into national TB control programmes**

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

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 drug-resistant TB can proceed within the national TB control programme. 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 framework approach to management of drug-resistant TB, summarized in Box 2.3, includes five essential components that form the basis for every national TB control programme that includes detection and treatment of drug-resistant TB.

BOX 2.3 FIVE COMPONENTS OF THE DOTS STRATEGY AS APPLIED TO DRUG-RESISTANT 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 drug susceptibility testing (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 performance monitoring and evaluation of treatment outcomes

References

1. *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003.313).
2. *An expanded DOTS framework for effective tuberculosis control*. Geneva, World Health Organization, 2002 (WHO/CDS/TB/2002.297).
3. Laserson KF et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 2005, 9(6):640–645.

CHAPTER 3

Political commitment and coordination

3.1 Chapter objectives

Sustained political commitment is a prerequisite for control of drug-resistant TB. This chapter considers how political commitment can be translated into practical measures to support all aspects of the framework for control of drug-resistant TB, and the practical implications for national TB control programmes. 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 the national TB and DR-TB control programmes. Political commitment is expressed through adequate financial support and appropriate infrastructure, including facilities and trained human resources. Coordination among the different components of public and private health 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 drug-resistant TB.

3.3.1 Sufficient economic support

The national TB control programme budget must be sufficient to develop and retain an adequate workforce with interest and expertise in drug-resistant 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 drug-resistant 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 national TB control programme. 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 inter-departmental agreement should be signed that codifies the mechanism for coordinating services for TB diagnosis and treatment 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 patients will be diagnosed, 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.

3.4 Coordination

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

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

- Background on the DOTS programme and its integration with treatment of drug-resistant 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

- **National TB control programme.** The national TB control programme 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 drug-resistant TB, 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 encourage a feeling of 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.

- **Coordination with prisons (1).** Transmission in prisons is an important source of spread of drug-resistant 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 drug-resistant 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 drug-resistant TB, but they require exceptional coordination.
- **International level.** International technical support through WHO, the GLC, supranational TB reference laboratories and other technical agencies is recommended. The national TB control programme 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, physical infrastructure and 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.

References

1. Bone A et al. *Tuberculosis control in prisons. A manual for programme managers*. Geneva, World Health Organization, 2000 (WHO/CDS/TB/2000.281).
2. *Involving private practitioners in tuberculosis control: issues, interventions and emerging policy framework*. Geneva, World Health Organization, 2001 (WHO/CDS/TB/2001.285).

BOX 3.2 SUMMARY CHECKLIST FOR DR-TB CONTROL PROGRAMME MANAGERS

Laboratory

- ☐ Specimen collection system for smears and cultures
- ☐ Dedicated laboratory space
- ☐ Adequate staffing and training
- ☐ Testing and maintenance of equipment
- ☐ Biosafety measures in place
- ☐ Reagents supply
- ☐ Supervision and quality assurance system (relationship with supranational TB reference laboratory established)
- ☐ Results reporting system to treatment care centre
- ☐ Laboratory for the free monitoring of electrolytes, creatinine, thyroid function and liver enzymes in place
- ☐ HIV testing, 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
- ☐ Adequate DOT in place and plan to ensure case holding
- ☐ System to detect and treat adverse effects including 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 MDR-TB control identified and shut off
- ☐ Legislation for treatment protocols accepted
- ☐ Project manual published and disseminated
- ☐ Strategies for prioritization of patient waiting lists
- ☐ Location of care defined and functional (ambulatory vs. hospitalization)
- ☐ Integration with HIV care
- ☐ Integration of all health-care providers into the DR-TB control programme

Prevention

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

3. *Towards scaling up. Report of the Third Meeting of the PPM Subgroup for DOTS Expansion.* Geneva, World Health Organization, 2005 (WHO/CDS/TB/2005.356).

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, defined as “chronic cases” (still sputum smear-positive after supervised re-treatment; proven or suspected MDR-TB) (1).

For definitions of diagnostic Categories I, II and III, see other WHO documents (1).

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 site, bacteriology and history of treatment,
- cohort analysis of registered Category IV patients and Category IV treatment outcomes.

4.2 General definitions of resistance

A patient is determined to have drug-resistant TB only through laboratory confirmation of in vitro resistance to one or more first-line antituberculosis drugs (see Chapter 6 for further information on laboratory requirements).

Antituberculosis drug resistance is classified according to the following three definitions:

- **Confirmed mono-resistance.** Tuberculosis in patients whose infecting isolates of *M. tuberculosis* are confirmed to be resistant in vitro to one first-line antituberculosis drug.
- **Confirmed poly-resistance.** Tuberculosis in patients whose infecting isolates are resistant in vitro to more than one first-line antituberculosis drug, other than both isoniazid and rifampicin.
- **Confirmed MDR-TB.** Tuberculosis in patients whose infecting isolates are resistant in vitro to at least isoniazid and rifampicin.

While laboratory confirmation of MDR-TB is being obtained, patients may be included in diagnostic Category IV **only** if representative DRS data indicate a very high probability of MDR-TB (see Chapter 5).

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

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

- **Pulmonary tuberculosis.** Tuberculosis involving the lung parenchyma. Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, therefore constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a pulmonary case.
- **Extrapulmonary tuberculosis.** Tuberculosis of organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. The definition of an extrapulmonary case with several sites affected depends on the site representing the most severe form of disease.

4.4 Bacteriology

Bacteriological examinations used in patients with drug-resistant TB include sputum smear microscopy and culture. Sputum smear microscopy and culture should be performed and results reported according to international standards (2). These techniques should be used at the start of treatment to confirm TB disease and to identify the most infectious (sputum smear-positive) patients.

Sputum conversion is defined as two sets of consecutive negative smears and cultures taken 30 days apart. Both bacteriological techniques (smear and culture) are used to monitor patients throughout therapy (see Chapter 11).

Many programmes use the frequency and timing of smear and culture conversion among smear- and/or culture-positive patients receiving Category IV treatment as indicators of programme performance. In order for a patient to be considered culture- or sputum smear-positive at the start of treatment, the following criteria must be met: at least one pretreatment 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.

Alternatively, some programmes will choose not to examine sputum conversion but rather to look at the proportion of patients who are smear- and culture-negative at one point in time (for example, 6 months after the start of treatment) to help in the interim evaluation of programme performance (see Chapter 18 and Form 08).

4.5 Registration based on history of previous antituberculosis treatment

Before enrolling a patient in a Category IV regimen with second-line drugs, it is important to determine whether the patient has previously received antituberculosis treatment and, if so, to record the treatment outcome (see Chapter 18 and Form 01). It is also important to record whether the patient ever previously received second-line drugs. These registration groups are essential for epidemiological monitoring of the TB epidemic at the regional and country level and help to identify patients who may be at risk for failing a Category IV regimen.

The registration groups delineated below refer explicitly to previous treatment and do not purport to explain the reason(s) for resistance.¹ The groups are defined by the treatment history when the sputum was taken that showed MDR-TB or, in cases where MDR-TB is suspected, at the time the patient is registered as Category IV.

- **New Category IV patients.** Category IV patients who have never received antituberculosis treatment or who have received antituberculosis treatment for less than one month. (Note: patients who had DST at the start of a WHO Category I regimen and are then switched to a Category IV regimen because of resistance are placed in this group, even if they received more than one month of Category I treatment.)
- **Category IV patients previously treated with first-line drugs only.** Category IV patients who have been treated for one month or more with first-line drugs only.
- **Category IV patients previously treated with second-line drugs.** Category IV patients who have been treated for one month or more with one or more second-line drugs, with or without first-line drugs.
- **Transfer in.** Category IV patients who have been transferred from another register for treatment of drug-resistant TB to continue Category IV treatment. Their outcomes should be reported to the transferring unit so that it can report their outcomes in the cohort in which they originally started MDR-TB treatment.
- **Other.** Category IV patients who do not fit the above definitions. This group includes Category IV patients who were treated outside DOTS programmes.

¹ These guidelines do not use the terms “primary” and “acquired” drug resistance because these types of resistance cannot be distinguished in most programmes for control of drug-resistant TB. 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.

Patients should be further classified according to the outcome of the most recent previous treatment: failed, defaulted and relapse, as defined in other WHO documents (1). If DST is carried out at the start of Category I, II or III treatment and the patient is later switched to a Category IV regimen because of resistance (without meeting the formal criteria of failure), he or she should be included in the outcome analysis of Category I, II and III – under the category Change to Category IV and noted as such in the District Tuberculosis Register. Programmes should keep track of the number of patients who do not meet the traditional definition of failure and are switched to Category IV regimens because of resistance. The Category IV Treatment Card provides for documentation of history of previous antituberculosis treatment and therefore facilitates the determination of the group registrations as described above (see Chapter 18 and Form 01).

4.6 Treatment outcome definitions for Category IV treatment

The following are mutually exclusive Category IV outcome definitions (3) that rely on the use of laboratory smear and culture as a monitoring tool and will be reported in Forms 01, 02 and 09 (see Chapter 18). The outcomes should be applied to patients who are receiving Category IV regimens. They have been constructed to be parallel to the six DOTS outcomes for drug-susceptible TB (1, 3).

- **Cured.** A Category IV patient who has completed treatment according to the programme's 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 culture¹ 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 the programme's 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

¹ A positive culture requires >10 colonies on solid media; two consecutive positive cultures must be obtained if <10 colonies are detected in the first culture; if the second culture also contains <10 colonies, the culture should be interpreted as positive.

early because of poor response or adverse events. These latter failures can be indicated separately for the purposes of sub-analysis.)

- **Defaulted.** A Category IV patient whose treatment was interrupted for two or more consecutive months for any reason.
- **Transferred out.** A Category IV patient who has been transferred to another reporting and recording unit and whose treatment outcome is unknown.

4.7 Cohort analysis

A Category IV treatment cohort is defined as a group of patients who start Category IV treatment during a defined time period. The Category IV treatment cohort will consist of a subset of patients recorded in the Category IV Register, i.e. those who actually started Category IV treatment during the specified period of time. To allow adequate analysis of all patients who meet the criteria of diagnostic Category IV, three dates should be recorded (these dates are recorded in both Forms 01 and 02; see Chapter 18):

1. **Date of initial registration as a TB case** (most commonly obtained from the District Tuberculosis Register)
2. **Date of registration in Category IV**
3. **Date of starting Category IV treatment**

Treatment cohort analysis focuses on treatment outcomes among patients who actually started Category IV treatment. **Registration cohort analysis** focuses on the number of patients identified and the number who are placed on treatment. Programmes are encouraged to undertake cohort analysis for both treatment and registration.

The recommended time frame for Category IV treatment cohort analysis reflects the long duration of Category IV regimens. Cohort analyses should be carried out at 24 months and repeated at 36 months after the last patient starts treatment (see Chapter 18 and Form 09). The analysis is done at 24 months because most of the patients will have finished treatment, allowing preliminary assessment of cure rates. Since a few patients may be on treatment longer than 24 months, the cohort analysis is repeated at 36 months after the last patient starts treatment. The 36-month evaluation is considered the final treatment cohort analysis result.

All patients should be assigned the first outcome they experience for recording and reporting purposes. Programmes may wish to record subsequent outcomes among patients followed systematically. (For example, a patient defaults on the first Category IV treatment and then 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.) Patients who

remain on treatment at the end of a designated cohort treatment period must be identified as “still on treatment”.

For each cohort, an interim status should be assessed at 6 months after the start of treatment to monitor programme progress (see Chapter 18 and Form 08).

References

1. *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003.313).
2. *Laboratory services in tuberculosis control. Parts I, II and III*. Geneva, World Health Organization, 1998 (WHO/TB/98.258).
3. Laserson KF et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 2005, 9(6):640–645.

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 drug-resistant 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.

5.2 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, the different categories of re-treatment patients (failure after Category I, failure after re-treatment, default and relapse) and 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 for the different groups also enable the number of patients who should enter the programme to be calculated, which in turn greatly facilitates programme planning and drug procurement.

5.3 Targeting risk groups for drug susceptibility testing

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 in patients (or groups of patients, i.e. failures of Category II treatment as listed above) at high risk for drug resistance. These groups should be identified by representative DRS.

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. However, the prevalence of resistance in specific risk groups can vary greatly across different settings. The routine use of DST and the inclusion in Category IV treatment of patients with these risk factors is therefore not recommended for all groups listed. Instead, programmes should examine DRS data in risk groups together with their technical capacity and resources to determine which groups of patients should get routine DST.

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 MDR-TB in Category IV regimens without individual DST. For example, the results of representative DRS surveys may identify a group or groups of patients with a very high percentage of MDR-TB (percentages in these groups can often exceed 80%), 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 failed in sound national TB control programmes often have MDR-TB (1–2). If the quality of DOT is poor or unknown (i.e. if regular ingestions of the medicines during Category II treatment are uncertain), patients may fail Category II treatment for reasons other than MDR-TB.
- **Close contacts of MDR-TB cases.** Category IV regimens for patients who are close contacts of MDR-TB cases are recommended in many, but not all, circumstances (see Chapter 14).
- **Category I failures.** Since the prevalence of MDR-TB in this group of patients may vary greatly, the rate in this group must be documented before deciding whether enrolment in DR-TB control programmes can take place without DST. Programmes should conduct DRS surveys to confirm that the routine use of Category II regimens is justified for patients in whom Category I treatment failed.

The percentage of MDR-TB in these three groups can vary. These guidelines strongly recommend confirming treatment failure by culture and testing for MDR-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.

TABLE 5.1 Target groups for drug susceptibility testing

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 MDR-TB case	Most studies have shown close contacts of MDR-TB patients to have very high rates of MDR-TB. Management of MDR-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 who fail a regimen have MDR-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 MDR-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 MDR-TB. However, certain histories may point more strongly to possible MDR-TB; for example, erratic drug use or early relapses.
Exposure in institutions that have MDR-TB outbreaks or a high MDR-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 MDR-TB.
Residence in areas with high MDR-TB prevalence	MDR-TB rates in new cases in many areas of the world can be high enough to justify routine MDR-TB testing in all new cases.
History of using antituberculosis drugs of poor or unknown quality	The percentage of MDR-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 Target groups for drug susceptibility testing (*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-negative or -positive patients.
HIV in some settings	The 1999–2002 Global Surveillance did not find HIV to be a risk factor. However, numerous MDR-TB outbreaks have been documented in HIV patients, and in some areas of the world HIV is a risk factor for MDR-TB (see Chapter 10).

SCC = short-course chemotherapy

5.5 Information on DST specimen collection

If DST is chosen as part of the case-finding strategy, it is recommended that at least two, and preferably three, 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 have at the time of enrolment in the DR-TB control programme. Programmes that base treatment on DST (individualized treatment) should repeat DST in all patients who have received treatment since the collection of their previous DST specimen.

Paediatric cases require adjustments in diagnostic criteria and treatment. Younger children in particular may not be able to produce sputum specimens on demand. Measures such as nasal gastric aspiration may be considered if this service is available. 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 MDR-TB can be started on Category IV regimens (see Chapter 14).

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

Mono- and poly-drug resistant strains are strains that are resistant to anti-tuberculosis drugs but not to both isoniazid and rifampicin. Most diagnostic strategies used by DR-TB control programmes will also identify cases of

BOX 5.1 COUNTRY EXAMPLES OF CASE-FINDING STRATEGIES

Example 1. Country A has an MDR-TB prevalence of 8% in cases newly diagnosed with the disease without history of previous antituberculosis treatment. 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 of the following drugs in all patients: H, R, E and S. 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 cases newly diagnosed with the disease, 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-controlled 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. Different Category IV regimens are designed for different resistance patterns found (options on how to design these different Category IV regimens and whether to do further DST testing are discussed in Chapters 7 and 8).

Example 3. Country C has made minimal use of second-line drugs for the treatment of TB. There is currently no local laboratory to do DST. A thorough survey has shown that failures of Category I with 4HRZE/6HE (for notation on the standard code on how to write regimens with abbreviations see Chapter 7, section 7.6) have an MDR-TB prevalence of 11%. Return after default and relapse cases have MDR-TB rates below 4%. In the survey, failures of Category II (chronic cases) have an MDR-TB rate of 78%. Patients with MDR-TB are almost all susceptible to Km, Cm, Eto, Cs and PAS (exceeding 95% for each drug).

The survey in Country C was done with a precision of $\pm 4\%$. It is decided that all failures of Category I, relapses and returns after default will enter Category II regimens. Patients who do not respond well to Category II treatment and all failures of Category II will be entered into standardized Category IV regimens without testing for DST (options on how to design the Category IV regimens are described in Chapter 7). Ongoing surveillance data from an external laboratory will be used to evaluate whether the above protocol is adequate for failures of Category I and Category II, relapses and returns after default. Local DST will be built in the country in the coming years and the protocol re-evaluated once it is established.

Example 4. Country D has fairly good access to DST and resources to do testing. Rates of MDR-TB in cases newly diagnosed with the disease without history of previous antituberculosis treatment are low at 1.2%. Country D chooses to do DST on any patient who remains sputum smear-positive after month 2 of SCC. When DST results return, regimens are adjusted if resistance is found.

mono- and poly-drug resistance, in addition to MDR-TB cases. Patients with mono- or poly-drug resistance may require modifications to their short-course chemotherapy regimens or to be moved to Category IV (see Chapter 8).

5.7 Use of second-line DST in case-finding

Not all DR-TB control programmes have the capacity to do DST of second-line drugs. Furthermore, the clinical relevance of second-line DST is not well known (see Chapter 6). Many programmes therefore design diagnostic and treatment strategies that are not dependent on second-line DST. Commonly, programmes will carry out DST of second-line drugs on strains after their identification as MDR-TB. However, some programmes will carry out DST of second-line drugs at the initial evaluation if the suspicion of MDR-TB is very high and if most cases of MDR-TB in the area have shown high rates of resistance to second-line drugs. DST of second-line drugs and the interpretation of the results are discussed in Chapters 6 and 7.

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CHAPTER 6

Laboratory aspects

6.1 Chapter objectives

This chapter describes laboratory services needed to diagnose and treat all forms of drug-resistant TB. It expands on information published in guidelines by WHO (1–3) and the IUATLD (4) on laboratory services for TB control.

6.2 General considerations

Optimal management of drug-resistant TB requires both mycobacterial and clinical laboratory services. At a minimum, the mycobacteriology reference laboratory should provide: culture; confirmation of the species as *M. tuberculosis*, *M. bovis* or nontuberculous mycobacteria (NTM) and testing for susceptibility to isoniazid and rifampicin. Clinical laboratory services, including basic haematology, biochemistry, serology and urine analysis, are required for the proper evaluation and monitoring of patients (see Chapter 11). A comprehensive, routine system of internal quality control and external quality assurance is mandatory.

In addition to diagnostic services, laboratories have a critical role in surveillance of prevailing drug resistance patterns and trends (1). The network of supranational TB reference laboratories provides quality assurance through validation of drug susceptibility data. Central reference laboratories supporting DR-TB control programmes should establish formal links with a supranational TB reference laboratory to help ensure the quality of laboratory services and validation of DST results. Usually, an external quality assurance programme with a supranational TB reference laboratory consists of an initial assessment visit by the laboratory, proficiency testing with a panel of coded isolates and then periodic rechecking of isolates obtained within the programme. This system should be negotiated with the supranational TB reference laboratory before the start of the DR-TB control programme.

Quality assurance goes beyond the relationship with the supranational laboratory and includes good infection control measures and internal methods to document the validity of results. These aspects are discussed below.

6.3 Organization and development of the laboratory network

The laboratory network has a pyramidal structure based on a large number of Level I laboratories accessible to all TB suspects and patients, a moderate number of Level II laboratories located in mid-sized population centres and health facilities and a few (or even a single) apex Level III laboratories at the provincial, state or national level. Table 6.1 describes the different functions and responsibilities of the three different levels of laboratory services. This chapter concentrates on Level III laboratories; the organization and operation of Level I and II laboratories are well described in other publications (1–4).

Each DR-TB control programme must have a rapid, reliable means of collecting and transferring specimens, cultures and information from the patient and physician to each level of the laboratory service and for returning the results. There should be no financial barrier between the patient and the TB diagnostic services at any of these three levels. A country or region can control and prevent drug-resistant TB only if infectious patients are detected and cured without delay. Ready access to microscopy for acid-fast bacilli (AFB), culture and DST free of charge to the patient are essential elements of political commitment to control drug-resistant TB.

DST of at least isoniazid and rifampicin is needed in any programme for control of drug-resistant TB; DST of streptomycin and ethambutol is also desirable, although less essential. In the initial phase of treatment implementation for drug-resistant 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 6.5).

6.4 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).

6.4.1 Microscopy

Microscopy for AFB cannot distinguish between drug-susceptible and drug-resistant *M. tuberculosis* or between different species of mycobacteria. The main uses of microscopy for drug-resistant TB are therefore limited to assessing the infectiousness of patients, triaging specimens to different methods of culture and DST, and confirming that microbes growing on (or in) artificial media are mycobacteria rather than contaminants.

As AFB sputum smear microscopy cannot distinguish between viable and non-viable bacilli, its utility for monitoring patient infectiousness and

TABLE 6.1 **Functions and responsibilities of the different levels of laboratory (2)**

LEVEL I
The peripheral (often district) laboratory <ul style="list-style-type: none"> ■ 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 <ul style="list-style-type: none"> ■ All the functions of Level I laboratory ■ Fluorescence microscopy (optional) ■ Digestion and decontamination of specimens ■ Culture and identification of <i>M. tuberculosis</i> ■ 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 <ul style="list-style-type: none"> ■ All the functions of Level I and II laboratories ■ DST of <i>M. tuberculosis</i> isolates ■ Identification of mycobacteria other than <i>M. tuberculosis</i> ■ 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

response to treatment is also limited. For example, even with adequate treatment, specimens from MDR-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.

6.4.2 Culture

Quality of laboratory processing is of crucial importance. Delays in specimen transport, excessively harsh or insufficient decontamination, poor-quality

ity 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 (<10 colonies) are not well correlated with clinical prognosis (5) 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 (1–4).

6.4.3 Identification of *M. tuberculosis*

In countries with a high burden of TB, most mycobacterial isolates will be *M. tuberculosis*. The prevalence of NTM varies from country to country and can be more common in patients infected with the human immunodeficiency virus (HIV). Unless the species is confirmed as *M. tuberculosis*, mycobacterial isolates appearing phenotypically resistant to first-line drugs may represent not drug-resistant TB but infection with NTM. Treatment of NTM is entirely different from treatment of drug-resistant TB or MDR-TB. As a minimum, laboratories supporting DR-TB control programmes should be able to conduct niacin and nitrate tests (both are positive in most *M. tuberculosis* strains) or at least two other methods that follow international guidelines.

6.5 Drug susceptibility testing

Identification and treatment of patients with, or at high risk of, drug-resistant TB can be based on a range of strategies (see Chapters 5 and 7). In vitro DST plays a key role in all of these strategies. A widely accepted strategy is to decide treatment based on DST results for the individual patient's bacterial isolate. Programmes that do not test each patient's isolate may choose to treat patients based on the prevailing levels of drug resistance in the population or on the previous exposure to antituberculosis drugs, as indicated by case-based clinical data. However, in this latter strategy, the confirmation of MDR-TB with DST of at least isoniazid and rifampicin is recommended.

The drugs used for susceptibility testing should never be taken from those used for treatment. They must come from pure compounds that are available only from the manufacturer.

For diagnosis of suspected MDR-TB, at least two sputum specimens should be submitted to the laboratory for AFB microscopy (smear) and culture. One of the two cultures can then be used for DST. This **indirect method** does DST on a culture grown from the processed sputum specimen. The **direct**

method, which does DST directly from the sputum, requires more sophisticated laboratory expertise, and the sensitivity and specificity are not always as good as for DST done from a culture.

A number of different techniques are available for DST that essentially compare growth of the mycobacterium with a control. Several variations exist for each method. The following is a list of the most common DST techniques:

- proportion method,
- absolute concentration,
- resistance ratio,
- broth (or liquid) methods,
- detection of metabolic changes,
- mycobacteriophage-based,
- molecular.

Several rounds of proficiency testing in the network of supranational TB reference laboratories have shown that the three most commonly used techniques (proportion, absolute concentration and resistance ratio) are highly reliable and reproducible, and that the results do not differ according to the method used.

6.5.1 Limitations of DST

The accuracy of DST (performed under optimal circumstances) varies with the drug tested: it is most accurate for rifampicin and isoniazid and less accurate for streptomycin and ethambutol.

DST of second-line drugs is not as simple as DST of some of the first-line drugs. This is partly because critical drug concentrations defining drug resistance are very close to the minimal inhibitory concentrations (6). The clinical relevance of DST of second-line drugs is less well studied. The calibration of DST methods with representative clinical isolates is in progress. (Better calibration will improve the determination of in vitro test criteria and may improve the ability of second-line DST to predict the clinical effectiveness.)

The clinician needs to understand the limitations of DST and interpret the results accordingly. DST provides an indication of the likelihood of a drug's being effective. Drugs for which the DST results show susceptibility are more likely to be effective than drugs for which the DST shows resistance. When discrepant results are obtained, they must be interpreted with care by a clinician experienced in drug-resistant TB. Chapter 7, section 7.7.3, describes the clinical interpretation of DST.

6.5.2 Choice of drugs used for DST

Each Level III laboratory must decide which drugs to test and how to test them, according to the strategy for designing treatment regimens. Reliable

DST for at least isoniazid and rifampicin is a prerequisite for DR-TB control programmes. Some programmes may choose to have these tests done at a distant laboratory until a local laboratory is able to do them. DST for second-line drugs is not mandatory for such control programmes and is not recommended unless rigorous quality controls are in place, including external proficiency testing by one of the supranational TB reference laboratories. One possible hierarchy of DST capacity is suggested in the following priority-ranked list:

- rifampicin and isoniazid,
- ethambutol, streptomycin,
- pyrazinamide (if broth-based DST systems are available),
- kanamycin (or amikacin) and capreomycin,
- fluoroquinolone (generally, the same fluoroquinolone that is used in treatment),
- ethionamide/prothionamide, PAS, cycloserine.

6.5.3 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 drug-resistant TB, laboratories should define standard turnaround times, which should be strictly followed.

6.6 Rapid tests

The several advantages of rapid testing include screening of patients at risk for MDR-TB, earlier identification of patients on inadequate regimens and prompt ability to isolate MDR-TB patients. The use of rapid DST is encouraged when possible. Rapid tests employ a variety of techniques (some rapid tests are being field-tested by the GLC).

6.7 Infection control and biosafety in the laboratory

Transmission of TB – including drug-resistant forms such as MDR-TB – is a recognized risk for laboratory workers. A well-maintained, properly functioning Class I or Class II biological safety cabinet is an indispensable piece of laboratory equipment for the performance of culture and DST of specimens from MDR-TB patients. Masks designed to protect the wearer from tiny (1–5 µm) airborne infectious droplets should always be used. Instructions on safe handling of specimens (*I*) should be scrupulously followed: the most expensive and sophisticated biological safety cabinet will not provide protection against MDR-TB infection that results from poor laboratory technique. Proper maintenance of such cabinets is an essential component of infection control and biosafety.

Laboratory workers who choose to disclose their HIV-positive status should

be offered safer work responsibilities and should be discouraged from working with MDR-TB specimens. Pregnant women should be reassigned until after childbirth and lactation. Training in laboratory procedures and strict adherence to safety measures should be accompanied by a simple surveillance programme whereby the health status of laboratory staff is monitored regularly.

Routine BCG vaccination is not a substitute for good infection control practices as a means of preventing MDR-TB in laboratory workers. The use of infection control measures is discussed in more detail in Chapter 15.

6.8 Surveillance and surveys using DST

Surveillance of TB antimicrobial resistance is essential for providing information on the magnitude and trends in resistance, for developing treatment guidelines and for monitoring the effect of interventions. WHO and its partners have supported the surveillance of drug-resistant TB in many countries and have provided three global reports (7–9) (see Chapter 1, section 1.7). Surveillance DST of second-line drugs in MDR-TB patients is encouraged provided it is carried out in a quality-assured laboratory. Surveillance systems should be designed according to the needs and capacity of the country. Guidelines for DRS are available from WHO (1).

6.9 Quality control and quality assurance

A comprehensive quality control/quality assurance programme should be developed in each TB laboratory to ensure the accuracy, reliability and reproducibility of the results obtained. Quality control/quality assurance procedures should be performed regularly as an integral part of laboratory operations. Procedures for AFB sputum smear microscopy are described in detail in the WHO manuals *Laboratory services in tuberculosis control. Parts I, II and III* (2). This section will address quality control/quality assurance procedures pertaining to culture and DST.

The procedures for **internal quality control** must be performed during each test round to verify that the test is working correctly. The **external quality control** comprises procedures that are carried out by an external organization to test that the results are correct. **Quality assurance** is control for the entire process of testing, covering all stages from collection of sputum until the result is reported back to the treatment facility.

A manual of standard operating procedures should be available for each of the laboratory operations. Standard operating procedures must be based on precisely how the procedure is carried out in the particular laboratory and incorporate any minor modifications that may have been made when compared with a standard protocol. The manual should also describe a protocol for regular maintenance checks and repairs of equipment.

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CHAPTER 7

Treatment strategies for MDR-TB

7.1 Chapter objectives

Any patient in whom chronic TB or drug-resistant TB is diagnosed requiring treatment with second-line drugs falls under WHO diagnostic Category IV and will need 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. For a description of drugs, doses and coding of treatment regimens used in these guidelines, see Annexes 1, 2 and 5.

7.2 Essential assessments before designing a treatment strategy

Ideally, programmes should design a treatment strategy when both the drug resistance survey data and the availability and use of antituberculosis drugs in the country have been assessed. Programmes that plan to introduce a treatment strategy for drug-resistant TB should be familiar with the prevalence of drug resistance in new patients as well as in different groups of re-treatment cases (failure, relapse, return after default and other cases). It is essential to determine which second-line drugs have been used and the frequency of use in the area served by the DR-TB control programme. Some second-line drugs may have been used only rarely and are likely to be effective in treatment regimens for drug-resistant TB, while others may have been used extensively and are therefore more likely to be ineffective in patients with resistant strains.

7.3 Different programme treatment strategies

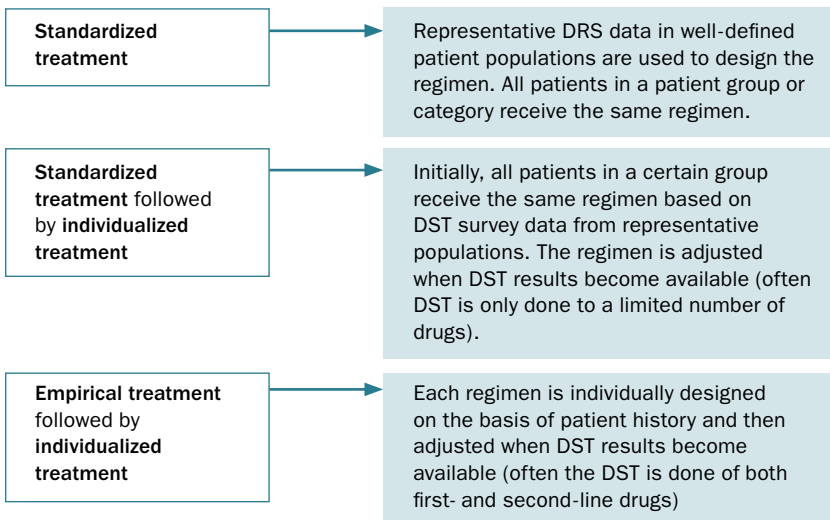
Programmes have different options for treatment strategies. The following are definitions of terms that are often used to describe treatment strategies:

- **Standardized treatment.** Regimens are designed on the basis of representative DRS data of specific treatment categories. However, suspected MDR-TB should always be confirmed by DST results whenever possible. All patients in a defined group or category receive the same treatment regimen (see section 7.7.2 for further details).

- **Empirical treatment.** Each regimen is individually designed on the basis of the previous history of antituberculosis treatment and with the help of representative DRS survey data. Commonly, an empirical treatment is adjusted in each patient when his or her DST results become available (see section 7.7.3 for further details).
- **Individualized treatment.** Each regimen is designed on the basis of previous history of antituberculosis treatment and individual DST results (see section 7.7.3 for further details).

These guidelines recommend using treatment strategies illustrated by Figure 7.1.

Figure 7.1 Recommended treatment strategies for MDR-TB



7.4 Selecting treatment strategies

Treatment strategies involving standardized Category IV regimens offer several advantages. Standardized regimens are based on representative DRS from patient categories or groups. If DST is not available in the country, a supranational TB reference laboratory can perform it to obtain representative patterns. Standardized regimens may enable more patients to access care, while maintaining cure rates comparable to those obtained with individualized treatment strategies. Other advantages include:

- simpler operational aspects of implementation,
- simpler drug ordering,
- easier training,
- less likelihood of mismanagement,
- less dependence on highly technical laboratories.

Individualized treatment strategies require a high degree of laboratory capacity necessary to perform DST of second-line drugs. One advantage of individualized regimens is that they avoid placing patients on toxic and expensive drugs to which the strain is resistant. Individualized regimens have advantages in settings with high rates of resistance to second-line drugs where it may be difficult to find a standardized regimen that is appropriate for all patients.

A strategy using a combination of standardized and individualized treatment will often be used, as mentioned above. For example, a programme may choose to do DST of H, R, E and S only and place any patients with documented resistance on different standardized regimens based on the pattern of resistance found. Here, the programme is using individualized DST but then applying a set number of standardized regimens. This is the most frequently used strategy in settings where second-line drugs have not been widely used.

7.5 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. For more information on individual drugs, see Annexes 1, 2 and 5.

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

GROUPING	DRUGS (ABBREVIATION)
Group 1 – First-line oral antituberculosis agents	Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z)
Group 2 – Injectable antituberculosis agents	Streptomycin (S); Kanamycin (Km); Amikacin (Am); Capreomycin (Cm); Viomycin (Vi)
Group 3 Fluoroquinolones	Ciprofloxacin (Cfx); Ofloxacin (Ofx); Levofloxacin (Lfx); Moxifloxacin (Mfx); ^a Gatifloxacin (Gfx) ^a
Group 4 – Oral bacteriostatic second-line antituberculosis agents	Ethionamide (Eto); Protionamide (Pto); Cycloserine (Cs); Terizidone (Trd); <i>P</i> -aminosalicylic acid (PAS); Thioacetazone (Th) ^b
Group 5 – Antituberculosis agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)	Clofazimine (Cfz); Amoxicillin/Clavulanate (Amx/Clv); Clarithromycin (Clr); Linezolid (Lzd)

^a The long-term safety and efficacy for MDR-TB treatment have not yet been fully confirmed and therefore use is not yet recommended for treatment of MDR-TB.

^b Thioacetazone should be used only in patients documented to be HIV-negative and should usually not be chosen over other drugs listed in Group 4.

7.6 Standard code for antituberculosis regimens

There is a standard code for antituberculosis regimens, and each drug has an abbreviation (shown in the list of abbreviations, Table 7.1 and Annex 5). An MDR-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 subscript number after a letter is the number of drug doses per week. If there is no subscript number, treatment is daily (or six times a week). An alternative drug(s) appears as a letter(s) in parentheses. The drugs in the higher groups are written first followed in descending order of potency. An example is given in Box 7.1.

BOX 7.1

Example of standard drug code used to describe a regimen **6Z-Km(Cm)-Ofx-Eto-Cs/12Z-Ofx-Eto-Cs**

The initial phase consists of five drugs and lasts for at least 6 months, or 6 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 agent is kanamycin (Km), but there is an option for capreomycin (Cm). Sometimes only the initial treatment is written and the assumption is that either the regimen will be adjusted following DST or the injectable agent will be stopped according to the programme protocol. This type of notation is used without a coefficient, i.e. **Z-Km-Ofx-Eto-Cs**

7.7 Regimen design

The following basic principles are involved in any regimen design:

- Regimens should be based on the history of drugs taken by the patient.
- Drugs and regimens commonly used in the country and the 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 drug is unclear, the drug can be included in 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, if effectiveness is questionable for an agent(s) or if extensive, bilateral pulmonary disease is present.
- Drugs are administered at least six days a week. When possible, pyrazinamide, ethambutol and fluoroquinolones should be given once per day because the high serum levels 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/protonamide, cycloserine and PAS have traditionally been given in split doses during the day.

- The drug dosage should be determined by body weight. A suggested weight-based dosing scheme is given in Annex 2.
- An injectable agent (an aminoglycoside or capreomycin) is used for a minimum of 6 months (see section 7.6).
- Treatment is for a minimum duration of 18 months beyond conversion (see section 7.8).
- Each dose is given as DOT throughout the treatment. A treatment card is marked for each observed dose.
- DST, when available and from a reliable laboratory, should be used to guide therapy. It should be noted that the full assessment of DST of some first-line and most of the second-line drugs in terms of reliability and clinical value has not been determined. DST does not predict the effectiveness or ineffectiveness of a drug with complete certainty (*I*). Nonetheless, regimens should include at least four drugs that are highly likely to be susceptible, based on DST and/or the drug history of the patient.
- Pyrazinamide can be used for the entire treatment if it is judged to be effective. Many MDR-TB patients have chronically inflamed lungs, which theoretically produce the acidic environment in which pyrazinamide is active.
- Early MDR-TB detection and prompt initiation of treatment are important factors in achieving successful outcomes.

7.7.1 Drug selection for the treatment of MDR-TB

Antituberculosis drugs may be placed into five groups, as illustrated in Table 7.1. The order of the five groups is based on potency, evidence of efficacy, experience of use and drug class.

- **Group 1 – First-line oral antituberculosis drugs.** Group 1 drugs are the most potent and best tolerated antituberculosis drugs. They should be used in patients only where there is laboratory evidence or clinical history to suggest their efficacy. Patients who have strains that test resistant to low levels of isoniazid but are susceptible to higher concentrations may benefit from high doses of the drug. However, since the benefit may be small, isoniazid in this situation should not be included as one of the four core drugs. The newer rifamycins should be considered ineffective if results of DST show resistance to rifampicin.

- **Group 2 – Injectable antituberculosis agents.** A Group 2 injectable agent should be given to all patients in whom susceptibility is documented or suspected, according to a hierarchical order based on efficacy, adverse effects and cost. If the strain is susceptible, streptomycin is the usual injectable agent of choice. Kanamycin or amikacin is the logical second choice given the low cost of these drugs and good experience of their use. Amikacin and kanamycin are considered to be very similar and have close to 100% cross-resistance. If an isolate is resistant to both streptomycin and kanamycin, capreomycin should be used. Viomycin is very similar to capreomycin, and these agents also share a high level of cross-resistance.
- **Group 3 – Fluoroquinolones.** A Group 3 drug should be used if the strain is susceptible. Currently, the most potent available fluoroquinolones in descending order based on in vitro activity and animal studies are: moxifloxacin = gatifloxacin > levofloxacin > ofloxacin = ciprofloxacin (2–3). However, the long-term safety of the newer-generation fluoroquinolones has not yet been fully evaluated.
- **Group 4 – Oral bacteriostatic second-line antituberculosis drugs.** Group 4 drugs are added on the basis of estimated susceptibility, drug history, efficacy, adverse effects profile and cost. If only one of these agents is needed, ethionamide/protonamide is often added because of its proven efficacy and low cost. If cost is not a constraint, PAS may be added first because the enteric-coated formulas are relatively well tolerated. If two agents are needed, cycloserine is commonly used in conjunction with ethionamide/protonamide or PAS. Since the combination of ethionamide/protonamide and PAS has a high incidence of gastrointestinal adverse effects, these two agents are commonly used together only when all three Group 4 agents are needed. Ethionamide/protonamide should be started at a low dose (250 mg) for a few days and then gradually increased every 3–5 days until the full dose is reached. Terizidone contains two molecules of cycloserine and can be used instead of cycloserine because its efficacy is assumed to be similar, although there are no direct studies comparing the two. The use of thioacetazone is limited by the development of rashes that are more prevalent in HIV-positive individuals and can result in Stevens-Johnson syndrome and death. In addition, thioacetazone has cross-resistance with the thioamides (ethionamide and protonamide) and is considered a relatively weak antituberculosis agent.
- **Group 5.** The Group 5 drugs are not recommended by WHO for routine use in MDR-TB treatment because their contribution to the efficacy of multidrug regimens is unclear. However, they can be used in cases where adequate regimens are impossible to form with the medicines from Groups 1–4.

7.7.2 Standardized treatment regimens

A standardized empirical regimen should be designed for each group through the use of representative DRS data from specific treatment categories. Some groups, such as “relapse” and “return after default”, can often safely use the standard Category II regimens (2HRZES/1HRZE/5HRE), while other groups will need a standardized regimen of second-line drugs. The survey data in each group help to determine the rate of MDR-TB and drug resistance to other antituberculosis drugs such as ethambutol, streptomycin and pyrazinamide. Evaluating the prevalence of resistance to some second-line drugs (kanamycin, capreomycin, fluoroquinolones) in these groups is also recommended and aids design of the regimen, especially in settings with widespread use of second-line drugs.

It is strongly recommended that MDR-TB be confirmed in all patients enrolled on a standardized Category IV regimen. Otherwise, misclassification of patients will either deny isoniazid and rifampicin to patients who would benefit from these drugs, or unnecessarily expose patients to potentially toxic first- or second-line drugs that they do not need. For a standardized 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 patterns of resistance. In most cases, an injectable agent and a fluoroquinolone form the core of the regimen (see examples provided in Box 7.2).

7.7.3 Individualized treatment regimens based on DST

The design of an individualized regimen differs from that of standardized treatment regimens in that it uses the resistance pattern of the infecting strain of the individual patient as another source of data, in addition to the patient’s treatment history and the prevailing resistance patterns in the community. The method for designing the individualized regimen is described in Table 7.2.

The above design is heavily dependent on knowing the results of DST of first-line drugs. If DST results are not known for all the first-line drugs, the choice can be guided by knowledge of prevalence of resistance based on sample surveys, for which the assistance of experts in conducting drug resistance surveys is necessary.

Empirical regimens are commonly used in specific groups of patients while DST is pending. They can be standardized (i.e. all patients from a certain group receive the same regimen until DST results return) or individualized for each patient on the basis of the patient’s treatment history and contact history. Empirical regimens are strongly recommended since most DST methods have a turnaround time of several months. A patient is placed on an empirical regimen while DST results are pending to avoid 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

BOX 7.2 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 ethambutol (E) and 29% are resistant to streptomycin (S). DST 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 isoniazid (H) and rifampicin (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 a regimen that is considered adequate; many others based on the principles in this chapter would be just as adequate.)

Example 2. DST is not available locally in Country X, but survey data from a supranational TB reference laboratory in 82 consecutive patients in whom Category II regimen failed demonstrate resistance to each of the following 11 drugs: H(93%), R(90%), E(56%), Z(38%), S(69%), Km(11%), Cm(8%), Ofx(3%), Eto(18%), Cs(1%) and PAS(3%). What are some of the possible strategies that use a standardized regimen?

Answer: Given the high rates of MDR-TB in this group, it is possible that all failures of Category II regimen enter into a standardized regimen with second-line drugs without confirmation of MDR-TB. This should be done only until local laboratory capacity is available; thereafter DST can be performed at the start of the regimen with second-line drugs and adjusted if MDR-TB is not found (this will occur in approximately 10% of patients).

Appropriate standardized regimens include:

- Km-Ofx-Eto-CS-PAS would place 93% on four or more effective drugs and no patients on two or fewer drugs.
- Z-Km-Ofx-Eto-Cs would place 81% of patients on regimens with four or more effective drugs, and 2.3% on two or fewer drugs.
- Cm-Ofx-Cs-PAS would place 84% of patients on regimens with four or more effective drugs and no patients on two or fewer drugs.

Note that the percentage of effective drug numbers in this example is based on DST and calculated from the data given here (full DST patterns for each of the 82 patients were needed for the calculations).

There are other possible regimens in addition to the three that are listed here. Each regimen must be considered in the context of what the programme can support. Unless excellent patient support is in place, the combination of Eto and PAS in a standardized regimen may cause a high default rate, negating the benefit from the first option. The third option employs the three most expensive antituberculosis agents (Cm, PAS and Cs) making it a costly regimen, yet it uses the lowest quantity of drugs and may have the fewest adverse effects. The second regimen has the disadvantage of placing approximately 2% of the patients on a regimen with only two effective drugs, but would be significantly less toxic and expensive than the other two options.

TABLE 7.2 Individualized regimen design based on DST for first-line drugs

PATTERN OF DRUG RESISTANCE	SUGGESTED REGIMEN (DAILY UNLESS OTHERWISE STATED)	COMMENTS
H-R	Z-E-injectable agent-fluoroquinolone (\pm one or two Group 4 agents)	One Group 4 agent is sufficient if E and Z susceptibility has been ascertained. Two Group 4 agents should be used in extensive disease, or if the DST result is questionable (i.e. reported susceptibility to E or Z despite a history of these agents being used in a failing regimen).
H-R (\pm S) and E or Z	Z or E-injectable agent-fluoroquinolone (+ two or more Group 4 agents)	Only use the first-line agents to which the patient's strain is susceptible. Use alternative injectable agent if S resistance is present. More than two Group 4 agents should be used in extensive disease or if resistance to E and Z is present or suspected. Group 5 agents can be considered if an adequate regimen of four drugs cannot be formed based on DST.

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

time of 1 to 2 weeks. In addition, in a patient with chronic disease treated several times with second-line 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 to indicate which drugs are likely to be ineffective. The probability of acquired resistance to a drug increases with the length of time it has been administered. In particular, evidence of clinical or bacteriological treatment failure (positive smears or cultures) during a period of regular drug administration is highly suggestive of drug resistance. If a patient used a drug for longer than one month with persistent positive smears or cultures, the strain should be considered as "probably resistant" to that drug, even if by DST it is reported as susceptible. Resistance can develop in some cases in less than one month (4).

The results of DST should complement rather than invalidate other sources of data about the likely effectiveness of a specific drug. If a history of previous antituberculosis drug use suggests that a drug is likely to be ineffective as a result of resistance, this drug should not be relied upon as one of the four core drugs in the regimen even if the strain is susceptible in the laboratory. However, if the strain is resistant to a drug in the laboratory, but the patient has never taken it 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 the turnaround time necessary for DST. The patient may have already received months of a standard or empirical 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 relied on as one of the four drugs in the core regimen.

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 previously received the drug as part of DOT. Box 7.3 gives three examples of how to design initial individualized regimens.

7.8 Completion administration of the injectable agent (intensive phase)

The recommended duration of administration of the injectable agent, or the intensive phase, is guided by smear and culture conversion. The minimal recommendation is that the injectable agent should be continued for at least 6 months and at least 4 months after the patient first becomes and remains sputum smear- or culture-negative.

The use of an individualized approach that takes account of the results of cultures, smears, X-rays and the patient's clinical status may also help in deciding whether to continue an injectable agent for longer than the recommended period. This would apply particularly in the case of patients for whom the susceptibility pattern is unknown, the effectiveness of a drug(s) is uncertain, or extensive or bilateral pulmonary disease is present.

Intermittent therapy with the injectable agent (three times weekly after an initial period of 2–3 months of daily therapy) can also be considered for patients in whom the injectable agent has been used for a prolonged period and when the risk of toxicity increases.

If the patient has been on an empirical regimen containing five or six drugs, discontinuation of drugs other than the injectable agent can be considered once the DST results are available and provided that the patient continues with at least three of the most potent agents.

7.9 Duration of treatment

The recommended duration of treatment is guided by smear and culture conversion. The minimal recommendation is that treatment should last for at least 18 months after culture conversion. Extension to 24 months may be indicated in patients defined as “chronic cases” (5) with extensive pulmonary damage.

BOX 7.3**Examples of how to design initial individualized regimens**

Example 1. A patient in whom Categories I and II treatments failed. A review of DST results reveals that the patient's TB infection is resistant to H-R-S and susceptible to all other medications including E-Km-Cm-Ofx-Eto-Cs-PAS; 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, it may be the first choice in this case:

■ Km(Cm)-Ofx-Eto(Pto)-Cs

(Many clinicians will add Z or E to this regimen; others may use PAS instead of Eto or Pto.)

Example 2. A patient in whom Categories I and II treatments failed. A review of DST results reveals that the patient's infection is resistant to H-R-Z-E-S-Km and susceptible to all other medications including Cm-Ofx-Pto-Cs-PAS. The patient has not received any antituberculosis drugs since the date of the DST. What individualized regimen is recommended?

Answer: There are two options in this case:

1. Cm-Ofx-Pto-Cs

Regimen 1 may have the advantage of increased compliance since it requires the minimum amount 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 has not been fully determined) 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.

Example 3. A patient in whom a 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-Eto and susceptibility to Km-Cm-Ofx-Cs-PAS. What individualized treatment regimen is recommended?

Answer: Weak regimens are to be avoided because patients for whom regimens with second-line drugs fail are very difficult to cure. This patient may now be resistant to Ofx and Km. These drugs cannot be relied upon in the regimen but they may be included until new DST results become available. Options for a regimen are limited. The recommended regimen is Cm-Ofx-Cs-PAS. A Group 5 drug may be added until new DST confirms that the patient is susceptible to Ofx.

7.10 Extrapulmonary MDR-TB and MDR-TB treatment

The treatment strategy is the same for patients with pulmonary and extrapulmonary MDR-TB. If the patient has symptoms suggestive of central nervous system involvement and is infected with MDR-TB, the regimen should use drugs that have adequate penetration into the central nervous system (6–7). Rifampicin, isoniazid, pyrazinamide, protionamide/ethionamide and cycloserine have good penetration; kanamycin, amikacin and capreomycin penetrate effectively only in the presence of meningeal inflammation; PAS and ethambutol have poor or no penetration.

7.11 Surgery in Category IV treatment

Surgical treatment of TB was common before the advent in the 1950s of highly effective antituberculosis drug combinations. When rifampicin and pyrazinamide were combined with isoniazid in the 1960s and 1970s, short-course chemotherapy became so effective that nearly all patients could be cured without surgery and the indications for surgical intervention, especially in pulmonary TB, declined. Without safe, highly effective short-course chemotherapy, surgical intervention for specific indications may once again be necessary to maximize the likelihood of cure in selected cases.

Surgery for TB requires highly experienced surgeons as well as appropriate pre- and post-operative care, trained support personnel and specialized facilities with availability of safe blood transfusion services. Specialized facilities should also 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 manipulations.

The most common operative procedure in patients with pulmonary MDR-TB is surgical resection (taking out part or all of the lung). Surgical resection has been shown to be effective and safe under appropriate surgical conditions (8). It is considered to be an adjunct to chemotherapy and appears to be beneficial for patients when skilled thoracic surgeons and excellent postoperative care are available (9). Surgery is not indicated in patients with extensive bilateral disease.

Regardless of the specific procedure, surgery should be timed to offer the patient the best possibility 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 and when the disease is still localized to one lung or one lung lobe. Generally, at least two months of therapy should be given before surgical resection to decrease the bacterial infection in the surrounding lung tissue. The Category IV regimen should continue according to the local protocol without interruption except for the immediate one or two days during the postoperative period. Doctors and nurses of the surgical departments must be familiar with the drugs used in the Category IV regimens. Even with successful resection, an additional 12–24 months of chemotherapy should be given.

Many programmes will have limited access to surgical treatment. General indications for surgical resection for programmes with limited access to surgery include patients who remain sputum smear-positive, with resistance to a large number of drugs, and have localized pulmonary disease. In programmes with suboptimal surgical facilities and no trained thoracic surgeons, resection is contraindicated as it may lead to increased morbidity or mortality.

7.12 Adjunctive therapies in MDR-TB treatment

In addition to surgery (discussed above), a number of other measures can be used to lessen adverse effects and morbidity as well as improve MDR-TB treatment outcomes.

7.12.1 Nutritional support

In addition to causing malnutrition, MDR-TB can be exacerbated by poor nutritional status, low body mass index and severe anaemia (10–12). Without nutritional support, patients can become enmeshed in a vicious cycle of malnutrition and disease, especially those already suffering from baseline hunger. The second-line drugs may also further decrease the appetite, making adequate nutrition a greater challenge. Nutritional support can take the form of providing free staple foods, and whenever possible should include a source of protein.

Vitamin B₆ (pyridoxine) should also be given to all patients receiving cycloserine or terizidone to prevent adverse neurological effects (see Chapter 11). Vitamin (especially vitamin A) and mineral supplements can be given in areas where a high proportion of the patients have deficiencies. If minerals (zinc, iron, calcium, etc.) are given, they should be administered at a different time from the fluoroquinolones, as they can interfere with the absorption of these drugs.

7.12.2 Corticosteroids

The use of corticosteroids in MDR-TB patients can be beneficial in cases of severe respiratory insufficiency and central nervous system involvement (13–16). Prednisone is commonly used, starting the dose at approximately 1 mg/kg, with gradual decrease in the daily dose by 10 mg per week when a longer 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 tapering course 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.

7.13 Conclusion

MDR-TB treatment is a complex health intervention and no single strategy will fit all situations. Epidemiological, financial and operational factors must be taken into consideration in deciding which strategy to use. Table 7.4 provides a summary of the principles of regimen design.

TABLE 7.4 Summary of general principles for designing a regimen

BASIC PRINCIPLES	COMMENTS
1. Use at least 4 drugs certain or highly likely to be effective	<p>Effectiveness is supported by a number of factors (the more present the more likely the drug will be effective in the patient):</p> <ul style="list-style-type: none"> A. DST results show susceptibility. B. No previous history of treatment failure with the drug. C. No known close contacts with resistance to the drug. D. Drug resistance survey indicates resistance is rare in similar patients. E. The drug is not commonly used in the area. <p>If at least 4 drugs are not certain to be effective, use 5–7 drugs depending on the specific drugs and level of uncertainty.</p>
2. Do not use drugs for which resistance crosses over	<ul style="list-style-type: none"> A. All rifamycins (rifampicin, rifabutin, rifapentene, rifalazil) have high levels of cross-resistance. B. Fluoroquinolones are believed to have variable cross-resistance, with in vitro data showing that some higher-generation fluoroquinolones remain susceptible when lower-generation fluoroquinolones are resistant. In these cases, it is unknown whether the higher-generation fluoroquinolones remain clinically effective. C. Not all aminoglycosides and polypeptides cross-resist; in general, only kanamycin and amikacin fully cross-resist.
3. Eliminate drugs that are not safe in the patient	<ul style="list-style-type: none"> A. Known severe allergy or unmanageable intolerance. B. High risk of severe adverse effects including renal failure, deafness, hepatitis, depression and/or psychosis. C. Quality of the drug is unknown or questionable.
4. Include drugs from Groups 1–5 in a hierarchical order based on potency	<ul style="list-style-type: none"> A. Use any Group 1 (oral first-line) drugs that are likely to be effective (see section 1 of this table). B. Use an effective aminoglycoside or polypeptide by injection (Group 2 drugs). C. Use a fluoroquinolone (Group 3). D. Use the remaining Group 4 drugs to make a regimen of at least 4 effective drugs. For regimens with ≤ 4 effective drugs, add second-line drugs most likely to be effective, to give up to 5–7 drugs in total, on the basis that at least 4 are highly likely to be effective. The number of drugs will depend on the degree of uncertainty. E. Use Group 5 drugs as needed so that at least 4 drugs are likely to be effective.
5. Be prepared to prevent, monitor and manage adverse effects for each of the drugs selected.	<ul style="list-style-type: none"> A. Ensure laboratory services for haematology, biochemistry, serology and audiometry are available. B. Establish a clinical and laboratory baseline before starting the regimen. C. Initiate treatment gradually for a difficult-to-tolerate drug, split daily doses of Eto/Pto, Cs and PAS. D. Ensure ancillary drugs are available to manage adverse effects. E. Implement DOT for all doses.

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CHAPTER 8

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

8.1 Chapter objectives

This chapter describes the recommended treatment strategies for patients with drug-resistant 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.

8.2 General considerations

WHO does not recommend the inclusion of specific efforts to diagnose mono- and poly-resistant strains of TB in routine DOTS programmes. However, 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 short-course chemotherapy 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 short-course chemotherapy), programmes can use different regimens based on DST patterns as described below.

8.3 Consequences for reporting

Patients whose regimens require minor adjustments (with no risk of amplification that would require the use of an empirical regimen for MDR-TB) 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 standard short-course chemotherapy, 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.

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 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.

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

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 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)

periodically. The panel consists of specialized personnel who are trained in the treatment of drug-resistant TB. 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 intensive 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 the Z is resistant 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 4.

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CHAPTER 9

Treatment of drug-resistant tuberculosis in special conditions and situations

9.1 Chapter objectives

This chapter outlines the management of drug-resistant 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 drug-resistant 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 drug-resistant 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 drug-resistant TB. The risks and benefits of treatment should be carefully considered, with the primary goal of smear conversion to protect the health of the mother and child, both before and after birth. The following are some general 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 carry the same 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 drug-resistant 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 MDR-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 drug-resistant TB generally have primary resistance transmitted from an index case with drug-resistant TB. 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 drug-resistant 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 drug-resistant 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. MDR-TB is life-threatening, and no antituberculosis drugs are absolutely contraindicated in children. Children who have received treatment for drug-resistant 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 MDR-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 MDR-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
Ciprofloxacin	20–40	Twice daily	2 g
Ofloxacin	15–20	Twice daily	800 mg
Levofloxacin	7.5–10	Once daily	750 mg
Moxifloxacin	7.5–10	Once daily	400 mg
Gatifloxacin	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 drug-resistant TB. The health-care provider should be in close communication with the physician who manages the patient's diabetes. Oral hypoglycaemic agents are not contraindicated during the treatment of drug-resistant TB but may require the patient to

BOX 9.1**Example of regimen design for paediatric cases**

A mother who has been following 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 drug-resistant TB is:

Resistance to H,R,Z,E,S

Susceptible to Am-Cm-Ofx-Eto

DST to PAS and Cs not done

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 Am.

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 $\frac{1}{4}$ or $\frac{1}{2}$ 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 ($\frac{1}{4}$ tablet) in the morning and 50 mg ($\frac{1}{4}$ 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 ($\frac{1}{4}$ tablet) in the morning and 62.5 mg ($\frac{1}{4}$ 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 ($\frac{1}{4}$ capsule) in the morning and 62.5 mg ($\frac{1}{4}$ capsule) in the evening.**

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

increase the dosage. Use of ethionamide or prothionamide 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, prothionamide 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 drug-resistant TB chemotherapy regimens provided there is no clinical evidence of chronic liver disease, hepatitis virus carriage, past 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 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 drug-resistant TB during acute hepatitis, the combination of four non-hepatotoxic drugs is the safest option.

9.9 Seizure disorders

Some patients requiring treatment for drug-resistant TB will have a previous or current medical history of a seizure disorder. The first step in evaluating such patients is to determine whether the seizure disorder is under control and whether the patient is taking anti-seizure medication. If the seizures are not under control, initiation or adjustment of anti-seizure medication will be

TABLE 9.2 **Adjustment of antituberculosis medication in renal insufficiency^a**

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)
Ciprofloxacin	Yes	1000–1500 mg 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
Gatifloxacin	Yes	400 mg per dose three times per week (not daily)
Cycloserine	Yes	250 mg once daily, or 500 mg/dose three times per week ^c
Terizidone	–	Recommendations not available
Prothionamide	No change	250–500 mg per dose daily
Ethionamide	No change	250–500 mg per dose daily
<i>P</i> -aminosalicylic acid ^d	No change	4 g/dose, twice daily
Streptomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily) ^e
Capreomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily) ^e
Kanamycin	Yes	12–15 mg/kg per dose two or three times per week (not daily) ^e
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 To take advantage of the concentration-dependent bactericidal effect of many antituberculosis drugs, standard doses are given unless there is intolerance.

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

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

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

needed before the start of drug-resistant TB therapy. In addition, any other underlying conditions or causes of seizures should be corrected.

Cycloserine should be avoided in patients with active seizure disorders that are not well controlled with medication. However, in cases where cycloserine is a crucial component of the treatment regimen, it can be given and the 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 drug-resistant 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 drug-resistant TB should work closely with a mental health specialist and have an organized system for psychiatric emergencies. Psychiatric emergencies include psychosis, suicidal ideation and any situation involving the patient'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 drug-resistant TB, a full chapter (Chapter 10) is devoted to this subject.

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CHAPTER 10

HIV infection and MDR-TB

10.1 Chapter objectives

This chapter addresses the management of MDR-TB in the presence of known or suspected HIV infection and provides guidance on recent developments in the approach to TB/HIV.¹ The chapter outlines:

- recommended collaborative MDR-TB/HIV activities;
- diagnostic and clinical guidelines for management of MDR-TB in HIV-infected patients;
- potential drug interactions, toxicities and monitoring requirements in the concomitant treatment of drug-resistant TB and HIV;
- implications of HIV for infection control.

10.2 General considerations

HIV coinfection is a significant challenge for the prevention, diagnosis and treatment of drug-resistant TB, especially in the case of MDR-TB. The local epidemiological prevalence of HIV, MDR-TB and HIV-associated MDR-TB is important in guiding strategies for treatment of HIV and drug-resistant TB. All DR-TB control programmes are therefore strongly encouraged to determine the extent of the overlap between MDR-TB and HIV epidemics.

10.3 Recommended collaborative activities for TB/HIV control

WHO recommends that certain collaborative activities are carried out to decrease the joint burden of TB and HIV (see Table 10.1) (1–3).

These activities are the backbone of the WHO TB/HIV collaborative strategy. Just as the basic DOTS programme should be in place before undertaking MDR-TB treatment strategies, these TB/HIV collaborative strategies should be in place before embarking on HIV/MDR-TB activities. It is not appropriate to carry out expensive HIV/MDR-TB activities if basic TB/HIV activities are not already in place.

¹ TB/HIV is the term used for the context of the overlapping of the two epidemics of TB and HIV/AIDS. It is often used to describe collaborative activities to control TB and HIV/AIDS. Patients with HIV-associated TB should be referred to as such.

TABLE 10.1 **WHO-recommended collaborative activities for TB/HIV control^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
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 (1)*

When the activities listed in Table 10.1 are in progress, programmes may seek to add activities for HIV/MDR-TB. The activities a programme chooses to add often depend on the resources available. These guidelines recommend the highest standard of care whenever possible, which includes the following HIV/MDR-TB activities:

- **Determine the prevalence of TB drug resistance in patients with HIV.** Programmes should determine the extent of the overlap of the MDR-TB and HIV epidemics. This can be done in two ways: data from TB DRS can be linked with HIV testing of those TB patients included in TB DRS; and/or when HIV surveillance among TB patients is implemented (4), TB DST can be included for all patients or for an unbiased subset.
- **Perform routine HIV testing in all TB patients.** WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommend that all patients with TB should be routinely offered an HIV test (5), and these data can be used as the basis for surveillance of HIV among TB patients. Priority should be given to those countries and administrative areas where the adult HIV prevalence is $\geq 1\%$, or where the HIV prevalence among patients with TB is $\geq 5\%$ (1).
- **Use mycobacterial culture.** Mycobacterial culture of sputum or other fluids and tissues is increasingly recommended and used to help in the diagnosis of sputum smear-negative TB. This is especially important for HIV-infected TB patients (see below).

- **Use DST at the start of TB therapy when antituberculosis drug resistance is known to be a significant problem in the area.** Unrecognized MDR-TB in an HIV patient carries a high risk of mortality. However, the exact prevalence at which TB drug resistance becomes a significant mortality risk, necessitating DST at the start of antituberculosis treatment in all HIV-infected patients, is not well defined. Analysis of DRS data and the available resources will guide a country's decisions on whether DST is warranted at the outset of TB therapy or whether only HIV-infected patients identified with risk factors for MDR-TB (see Chapter 5) need DST. For example, in most countries in Africa where MDR-TB rates are low and technical capacity is limited, the circumstances do not warrant DST in all cases of active TB in HIV-infected individuals, but DST will be indicated in patients with risk factors for MDR-TB or in areas where high rates of MDR-TB have been identified.
- **Introduce antiretroviral therapy (ART) promptly in MDR-TB/HIV patients.** TB is an indicator disease for ART, irrespective of CD4 cell count. If CD4 cell counts are available, they can guide the decision on when to start ART (6). ART is similarly recommended for MDR-TB/HIV-infected cases, given the elevated mortality in these coinfecting patients. In general, ART should not be delayed for fear of giving the patient too many medicines. The usual protocols to prevent immune-reconstitution syndrome should be followed (6).
- **Arrange close treatment follow-up by a specialized team.** The team should be familiar with the treatment of both MDR-TB and HIV, with close monitoring of potential additive adverse effects, prophylaxis and treatment of opportunistic infections, general primary care, vaccinations and nutritional support.
- **Provide additional socioeconomic support.** Patients with MDR-TB and HIV are often at very high risk for inability to adhere to treatment. Additional socioeconomic support should be in place for such patients.
- **Ensure strict infection control.** TB infection control should be ensured in health care and congregate settings for both drug-susceptible and drug-resistant TB (1). Administrative measures include early recognition, diagnosis and treatment of TB suspects, particularly those with pulmonary TB, and separation from others, particularly those with HIV infection, until a diagnosis is excluded or the patient adequately treated. Environmental and personal protection measures should also be considered.
- **Involve the TB/HIV coordinating body.** This board should be involved in the planning and monitoring of HIV/MDR-TB activities and programmes.

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

The presentation of MDR-TB in the HIV-infected patient does not differ from that of drug-susceptible TB in the HIV-infected patient (7).

The diagnosis of TB in HIV-positive 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. This can result in misdiagnosis or delays in diagnosis and, in turn, higher morbidity and mortality. The use of X-ray and/or culture improves the ability to diagnose TB in HIV patients and is recommended where available.

In areas where MDR-TB is known to be a problem in HIV-positive patients, and where resources permit, all HIV patients with TB should be screened for MDR-TB with DST. Rapid diagnostic techniques for MDR-TB should be employed when possible since HIV-infected patients with TB on inadequate antituberculosis treatment, or no treatment, for even short periods of time are at a high risk of death.

10.5 Concomitant treatment of drug-resistant TB and HIV

The recommended treatment of TB, whether drug-susceptible or -resistant, is the same for HIV-infected and non-HIV-infected patients, except for the use of thioacetazone, which should not be used in HIV-infected patients (8). However, treatment is much more difficult and adverse events more common. Deaths during treatment, caused by TB itself or by other HIV-related diseases, are more frequent in HIV-infected patients, particularly in the advanced stages of immunodeficiency.

The use of ART in HIV-infected patients with TB improves survival and slows progression to AIDS. However, initiation of ART in HIV-infected patients with drug-susceptible or drug-resistant TB is often associated with adverse events that may lead to the interruption of both TB and/or HIV therapy. Information on when and how to design regimens for HIV treatment is available in other WHO publications (6). However, given the large amount of pills that need to be ingested and the potential of overlying toxicities, the following issues should be considered.

10.5.1 Potential drug interactions in the treatment of drug-resistant TB and HIV

There are several known interactions between drugs used to treat TB and HIV. Rifamycins (rifampicin, rifabutin), while not used in MDR-TB treatment, are needed in the treatment of many poly- and mono-resistant cases. Rifamycins may lower the levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors, contributing to the development of resistance to these drugs. In this regard, rifabutin has the least effect of all the rifamycins.

Antiretroviral drugs increase the level of rifampicin and the risk of toxicity. The interactions between rifamycins and antiretroviral drugs are described elsewhere in detail (10).

Other interactions include those between fluoroquinolones and didanosine. Nonenteric-coated didanosine contains an aluminium/magnesium-based antacid that, if given jointly with fluoroquinolones, may result in decreased fluoroquinolone absorption; it should therefore be given six hours before or two hours after fluoroquinolone administration. Clarithromycin, a drug not routinely recommended for MDR-TB by WHO but used by some programmes, has several interactions with HIV medications (11–12).

10.5.2 Potential drug toxicity in the treatment of drug-resistant TB and HIV

In general, HIV patients have a higher rate of adverse drug reactions to both TB and non-TB medications (13–14). Known adverse effects of increased severity in coinfecting patients include peripheral neuropathy (15) (stavudine, aminoglycosides, cycloserine, pyrazinamide), cutaneous and hypersensitivity reactions (thioacetazone) (16), gastrointestinal adverse effects (17), renal toxicity (injectables) and neuropsychiatric effects (cycloserine, efavirenz).

10.5.3 Monitoring of drug-resistant TB and HIV therapy in coinfecting patients

Unlike MDR-TB treatment, which can be omitted on one day of the week, HIV medicines must be given every day. While the treatment of MDR-TB is being administered, DOT of ART should be included.

The complexity of antiretroviral regimens and treatment of drug-resistant TB, each with its specific toxicity profiles – some of which may be potentiated by concomitant therapy – demands rigorous monitoring in this particular group of patients (18). Ideally, ART should be initiated and monitored in collaboration with a health-care provider knowledgeable in both drug-resistant TB and HIV. Chapter 11 describes the monitoring requirements for treatment of drug-resistant TB and also indicates where monitoring in HIV-infected individuals is required with increased frequency. Standard monitoring procedures for those on ART should be followed.

Monitoring of chest X-rays, smears and cultures in the coinfecting patient is the same as for HIV-negative MDR-TB patients. If the patient shows signs of treatment failure, the same evaluation as described in Chapter 13 is warranted. In addition, the ART regimen should be re-evaluated as described above.

Patients with HIV-associated MDR-TB will usually require special socio-economic support. The regimens together are particularly difficult to tolerate, the stigma of both diseases can result in serious discrimination and the risk of mortality is very high.

10.6 Implications of HIV for MDR-TB infection control

MDR-TB outbreaks have overwhelmingly involved HIV-positive patient populations and nosocomial transmission. Delay in recognition of MDR-TB, prolonged periods of infectiousness, crowded wards, and mixing TB and HIV patients all contribute to nosocomial transmission. These practices have contributed to MDR-TB outbreaks that affect both HIV-positive and HIV-negative patients.

Implementation of adequate infection control precautions significantly reduces nosocomial transmission. Home-based measures of separate living quarters, masks for visitors and adequate ventilation can also be effective. Infection control measures for MDR-TB are described in Chapter 15.

10.7 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. A joint plan can be made to treat patients in whom drug-resistant TB and HIV infection have been diagnosed. Alternatively, components can be introduced in their respective programmes to ensure adequate diagnosis, care, treatment and referral of patients with HIV-associated drug-resistant 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 national and district levels must be clearly defined, as well as the roles of individual team members.

10.8 Summary

Understanding the regional prevalence of HIV, MDR-TB and MDR/HIV coinfection is the first step in guiding the strategies for MDR-TB/HIV activities. In some areas, MDR-TB is an important potential problem for HIV-infected patients. Before programmes embark on MDR-TB/HIV control strategies, the activities listed in Table 10.1 should be implemented. The patient with drug-resistant TB disease and HIV will require intensive medical care to decrease the high level of mortality. Rigorous infection control measures should be part of the planning. Coordination between the team treating drug-resistant TB and the HIV control programme for training, care and treatment is an essential component. MDR-TB/HIV coinfection has the potential to increase rapidly. All drug-resistant TB and HIV control programmes should coordinate the collaborative activities described in this chapter, which are an integral element of both HIV/AIDS and TB control, aimed at avoiding epidemics of HIV-associated MDR-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 drug-resistant TB,
- monitoring actions for early detection of adverse effect detection,
- adverse effects associated with different second-line drugs,
- strategies for the treatment of adverse effects.

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, renal insufficiency, acute or chronic liver disease, thyroid disease, mental illness, drug or alcohol dependence, HIV infection, pregnancy, lactation and others). The management of MDR-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 grow-

ing 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.

Sputum conversion is slower in MDR-TB than in drug-susceptible TB. Paucibacillary culture results should not be automatically regarded as negative when treating MDR-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 MDR-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. 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.

Nephrotoxicity is a known complication of the injectable drugs, both of the

TABLE 11.1 **Monitoring during treatment of drug-resistant 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 smear and cultures	Monthly until conversion, then monthly smears and quarterly cultures. (Note: some programmes may choose to do smears and cultures monthly)
Weight	At baseline and then monthly
Drug susceptibility testing (DST)	At baseline in programmes doing individualized treatment 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
Serum potassium	Monthly while receiving an injectable agent
Thyroid stimulating hormone	Every 6 months if receiving ethionamide/protonamide and/or PAS; and monitor monthly for signs/symptoms of hypothyroidism
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
HIV screening	At baseline, and repeat if clinically indicated
Pregnancy tests	At baseline for women of childbearing age, and repeat if indicated

aminoglycosides and of capreomycin. This adverse effect is occult (not obviously noted by taking the history of the patient or by physical examination) in onset and can be fatal. The optimal timing for checking serum creatinine is unknown, but most current treatment programmes for drug-resistant TB check serum creatinine at least monthly. In addition, patients with a history of renal disease (including 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.

11.5 Management of adverse effects

Second-line drugs have many more adverse effects than the first-line anti-tuberculosis 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 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.

Prompt evaluation, diagnosis and treatment of adverse effects are extremely important, even if the adverse effect is not particularly dangerous. Patients

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

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

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.

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

Psychosocial support is an important component 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 agents and the suggested management strategies.

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 is a list of indications and commonly used medications for the management of adverse reactions. The list is an example of a formulary that programmes may want to have available and will assist programmes in planning 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 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 11.3 Adverse effects, suspected agent(s) and management strategies

ADVERSE EFFECT	SUSPECTED AGENT(S) ^a	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Seizures	Cs	1. Suspend suspected agent pending resolution of seizures.	1. Anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agent discontinued.
	H, fluoro-quinolones	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 reinstitute suspected agent at lower dose, if essential to the regimen. 5. Discontinue suspected agent if this can be done without compromising regimen.	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, H	1. Increase pyridoxine to maximum daily dose (200 mg per day).	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.
	S, Km, Am, Cm, Vi, Eto/Pto, fluoro-quinolones	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.	2. Neuropathy may be irreversible; however, some patients may experience improvement when offending agents are suspended.

TABLE 11.3 Adverse effects, suspected agent(s) and management strategies (continued)

ADVERSE EFFECT	SUSPECTED AGENT(S) ^a	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Hearing loss	S, Km, Am, Cm, Clr	<ol style="list-style-type: none"> 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. Increase 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. 	<ol style="list-style-type: none"> 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.
Psychotic symptoms	Cs, H, fluoro-quinolones, Eto/Pto	<ol style="list-style-type: none"> 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. 	<ol style="list-style-type: none"> 1. Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy. 2. Previous history of psychiatric disease is not a contra-indication 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	<ol style="list-style-type: none">1. Improve socioeconomic conditions.2. 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.	<ol style="list-style-type: none">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.
Hypo-thyroidism	PAS, Eto/Pto	<ol style="list-style-type: none">1. Initiate thyroxine therapy.	<ol style="list-style-type: none">1. Completely reversible upon discontinuation of PAS or ethionamide/protonamide.2. The combination of ethionamide/protonamide with PAS is more frequently associated with hypothyroidism than the individual use of each drug.
Nausea and vomiting	Eto/Pto, PAS, H, E, Z	<ol style="list-style-type: none">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.	<ol style="list-style-type: none">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 Adverse effects, suspected agent(s) and management strategies (*continued*)

ADVERSE EFFECT	SUSPECTED AGENT(S) ^a	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Gastritis	PAS, Eto/Pto	<ol style="list-style-type: none"> 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. 	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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. 	<ol style="list-style-type: none"> 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, Cn, Vi	<ol style="list-style-type: none"> 1. Discontinue suspected agent. 2. Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen. 3. Consider dosing 2 to 3 times a week if drug is essential to the regimen and patient can tolerate (close monitoring of creatinine). 4 Adjust all TB medications according to the creatinine clearance. 	<ol style="list-style-type: none"> 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 Cm , Km, Am, S (hypokalaemia and hypomagnesaemia)	<ol style="list-style-type: none">1. Check potassium.2. If potassium is low also check magnesium (and calcium if hypocalcaemia is suspected).3. Replace electrolytes as needed.	<ol style="list-style-type: none">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.
Optic neuritis E	<ol style="list-style-type: none">1. Stop E.2. Refer patient to an ophthalmologist.	<ol style="list-style-type: none">1. Usually reverses with cessation of E.2. Rare case reports of optic neuritis have been attributed to streptomycin.
Arthralgias Z , fluoro-quinolones	<ol style="list-style-type: none">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.	<ol style="list-style-type: none">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.

Fluoroquinolones = Crx, Ofx, Lfx, Gfx, Mfx

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

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 fluoroquinolone
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, thiorazine, risperidone (consider benztropine 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

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CHAPTER 12

Treatment delivery and adherence

12.1 Chapter objectives

This chapter outlines the strategies for treatment delivery that will improve adherence among patients receiving treatment for drug-resistant TB. It focuses on patients with MDR-TB because the treatment for MDR-TB is the most difficult. However, the same strategies can also be used for any patient with drug-resistant, or even drug-susceptible, TB.

12.2 Education of patients

All patients and their families should receive education about MDR-TB, its treatment, potential adverse drug effects and the need for adherence to therapy. Educational interventions should commence at the start of therapy and continue throughout the course of treatment. Education can be provided by physicians, nurses, lay and community health workers 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 Treatment delivery settings

There are several strategies for the delivery of MDR-TB treatment, including hospitalization, clinic-based treatment and community-based care (1–2). Regardless of the mode of delivery, the management of MDR-TB depends on a steady supply of medicines provided to patients free of charge through a reliable network of educated providers.

Although early in the history of MDR-TB treatment, strict hospitalization of patients was considered necessary, home-based care provided by trained lay and community health workers 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 community health workers or volunteers. The roles and responsibilities of each of these groups of providers will vary depending on the needs and resources available in specific settings.

Hospitals should provide acceptable living conditions, sufficient activities so that patients avoid boredom, adequate food, a proper heating system in cool areas, fans or cooling systems in hot climates and proper infection control

measures. Prisons require specific measures to improve adherence, which are described in detail in the WHO guidelines for TB control in prisons (3).

12.4 Adherence to therapy

Patients with MDR-TB are more likely to have had problems with non-adherence in the past (4). Adherence to MDR-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, MDR-TB patients are at increased risk of non-adherence to treatment. Adherence is an essential element to prevent the generation of pan-resistant strains with the potential for community-wide spread and virtually no possibility of cure for the patient (6).

MDR-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: nutritional supplementation, emotional support, education of patients, family and peers on MDR-TB treatment, and early and effective management of adverse effects.

12.5 Directly observed therapy (DOT)

Because MDR-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 MDR-TB, it is recommended that all patients receiving treatment for MDR-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.

12.5.1 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 work places. 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 MDR-TB than those that 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 MDR-TB patient, and a family observer could be subject to subtle manipulation by the patient, relatives, employers, etc.

12.5.2 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.

12.6 Socioeconomic interventions

Socioeconomic problems, including hunger, homelessness and unemployment, should be addressed to enable patients and their families to adhere to MDR-TB 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.

12.7 Social and emotional support

Having MDR-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 MDR-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).

12.8 Follow-up of the non-adherent patient

When a patient fails to attend a DOT appointment, a system should be in place that allows prompt patient follow-up. Most commonly this involves a DOT worker visiting the patient's home the same day to find out why the patient has defaulted 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.

12.9 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 MDR-TB. In most cases, management of adverse effects can be accomplished using relatively simple and low-cost interventions without compromising the integrity of the MDR-TB treatment regimen (8). Management of adverse effects is addressed in more detail in Chapter 11.

12.10 Conclusion

Treatment delivery to patients with MDR-TB can be accomplished in even the most resource-poor settings. It may be carried out using a hospital- 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 MDR-TB in the national TB control programme. Non-adherence to treatment is one of the primary factors leading to poor outcomes for patients with MDR-TB. There are many reasons why patients may not adhere to therapy, and most of these stem from socioeconomic constraints. Higher rates of adherence can be achieved if patients are offered a comprehensive package of services aimed at promoting adherence. These include DOT, social support and effective management of adverse effects. The human resources required to deliver the proper support should not be underestimated (see Chapter 3). Provision of these services should be viewed as an essential part of treatment programmes for drug-resistant TB worldwide.

BOX 12.1

Adherence promotion strategies for DR-TB control programmes

- DOT
- Social support
- Support to treatment adherence using a team approach
- Effective management of adverse effects

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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 failure

Patients who do not show signs of improvement after four months of treatment are at risk for treatment failure. In 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 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 resistance to all known antituberculosis drugs; the "super-resistant" strain 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.

Reference

Palliative care: symptom management and end-of-life care. Geneva, World Health Organization, 2004 (WHO/CDS/IMAI/2004.4).

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.

14.2 General considerations

Opportunities to halt the spread 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 no access to 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).

14.3 Management of symptomatic adult contacts of a patient 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 spread 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.

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 and culture: if the child is aged under 5 years or cannot expectorate sputum, induced sputum or gastric aspiration for smear and culture should be considered. Sputum induction may be preferable to gastric aspiration since the yield of one sample from sputum induction with chest percussion has been shown to be equivalent to three gastric aspirates, although replication of this finding is required before its widespread use can be recommended (6).
- DST, if possible.

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 short-course chemotherapy 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, work places, 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 MDR-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.

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 MDR-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 MDR-TB case, infection control needs to be a leading programmatic priority. It is equally important to protect health workers in the MDR-TB setting.

15.2 The priorities of infection control

MDR-TB is transmitted in the same manner as drug-susceptible TB. Well-documented outbreaks of highly drug-resistant TB constitute convincing evidence that MDR-TB is transmissible, especially among highly vulnerable populations and in institutional settings. Moreover, because MDR-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 MDR-TB does not significantly alter the basic TB infection control strategies. However, in view of its seriousness, every programme attempting to treat MDR-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 MDR-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 MDR-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 MDR-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 MDR-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 with known or suspected TB together with other TB or MDR-TB patients should always be avoided.

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.

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 MDR-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 out of doors 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.

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 MDR-TB require particularly strict environmental controls. These aspects are addressed in other WHO documents 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 MDR-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 MDR-TB from others. Patients who are identified by rapid tests can be properly separated or isolated immediately (in addition to starting proper empirical regimens). Chapter 6 provides further information on 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 resources 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 drug-resistant 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 national TB control programme.
- 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.

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

TRAINING/COMPETENCE	STAFFING/MOTIVATION
<ul style="list-style-type: none"> ■ Inadequate skills of existing staff: <ul style="list-style-type: none"> — 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 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 	<ul style="list-style-type: none"> ■ Imbalances in human resources for TB control: <ul style="list-style-type: none"> — 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: <ul style="list-style-type: none"> — Impact of AIDS — Low staff retention — Low staff motivation <ul style="list-style-type: none"> • 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

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 national TB control programme.
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 drug-resistant TB.
3. Assess the current human resources situation of the national TB control programme/health system and determine the number of staff of the relevant categories available at each programme level.
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 drug-resistant 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 drug-resistant 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 acancies).
 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 (I)* and other sources (2–3).

References

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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 drug-resistant 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 MDR-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.

BOX 17.1

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

Ciprofloxacin	Levofloxacin	Ofloxacin
Kanamycin	Amikacin	Capreomycin
Cycloserine	Ethionamide	<i>P</i> -aminosalicylic acid

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.

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 drug-resistant 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 national TB control programme to import drugs that are not locally registered.

To preserve quality, the drugs should be stored and transported by the supplier and the national TB control programme 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 drug-resistant TB should meet the WHO recommended standards for safety, efficacy and quality. The WHO prequali-

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).

fication project¹ aims at producing a list of second-line drugs and manufacturers that meet specific approved standards. The manufacturers selected to supply second-line antituberculosis drug should be (as a minimum) compliant with the WHO standards of “Good Manufacturing Practices”.²

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

National TB control programmes 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 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.³ 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).

¹ <http://mednet3.who.int/prequal/>

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

³ <http://www.who.int/tb/dots/dotsplus/en/>

References

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2. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003 (Technical Report Series No. 908).
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CHAPTER 18

Category IV recording and reporting system

18.1 Chapter objectives

This chapter describes the information system for patients who are entered in the Category IV Register, with the objective of recording information needed to monitor programme performance and treatment outcomes. It defines the minimum instruments and variables of the system that are necessary to implement and monitor Category IV treatment.

18.2 Aims of the information system

The aims of the information system are twofold:

1. To allow managers of national TB control programmes at different levels to monitor overall programme performance as a basis for programme and policy developments. Performance indicators include:
 - the outcome of patients with drug-resistant TB, including MDR-TB,
 - the results of Category IV treatment, and the results in subgroups.
2. To aid staff in treatment units to provide adequate management of individual patients.

18.3 Scope of the information system

The information system for treatment of drug-resistant TB is based upon, and is an extension of, the basic DOTS information system (1–4). The forms have therefore been designed to be as similar as possible to the standard forms used in DOTS programmes.

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

While this core information system will be applicable across settings, the reporting forms can be modified as necessary to suit the local context. For instance, additional variables that are considered valuable in specific situations can be included.

18.4 Main forms/registers and flow of information

This section describes the core set of forms that enable proper recording of diagnosis, monitoring and care, in addition to the reporting of outcomes of Category IV treatment. Chapter 4 defines the case registration groups and outcome definitions.

18.4.1 Category IV Treatment Card (Form 01)

This card is a key instrument for health staff who administer drugs to patients on a daily basis. A patient registered for Category IV treatment should have a Category IV Treatment Card completed by the health-care worker. 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.

When a patient moves (for example from a specialized hospital to a province or district of origin after the first months of treatment), the card, or a copy of the card, must follow the patient. A copy of this card may be used as a notification form and to record the final outcome of treatment.

The Category IV Treatment Card contains the following sections:

Page 1

- **Basic demographic and clinical information.** Name, address, sex, age, weight, etc.
- **Category IV registration number.** This is a new unique identification number for each patient who enters Category IV.
- **Date of Category IV registration.**
- **Previous district TB registration number and date of registration.**
- **Registration group according to history of previous antituberculosis treatment.** The five registration groups have been defined in Chapter 4, section 4.5. For the purpose of the recording and reporting system, patients should be further classified according to the treatment outcomes: failed, defaulted and relapse. For this reason, seven registration groups will be used. Group assignment is determined by history of previous treatment at the time of collection of the sputum sample that was later used to confirm MDR-TB.
 1. **New.** Patients who have never received antituberculosis treatment, or who have received treatment for less than one month. This includes patients who had DST at the start of a WHO Category I regimen and are then switched to a Category IV regimen because of resistance (see Chapter 4, section 4.5).
 2. **Relapse.** Patients previously treated for tuberculosis who have been declared cured or treatment completed, and then diagnosed with MDR-TB.

3. **Treatment after default.** Patients who return to treatment with confirmed MDR-TB after interruption of treatment for two months or more.
 4. **Treatment after failure of first treatment.** Patients who return after the first treatment has failed.
 5. **Treatment after failure of re-treatment.** Patients who return after the re-treatment has failed.
 6. **Transfer in.** Category IV patients who have been transferred from another register for treatment of drug-resistant TB to continue Category IV treatment. Their outcomes should be reported to the transferring unit so that it can report their outcomes in the cohort in which they originally started Category IV treatment. This group is excluded from the quarterly reports of the receiving unit on registration and treatment result.
 7. **Other.** Category IV patients who do not fit the above definition. This group includes Category IV patients who were treated outside DOTS programmes and for whom the outcome of the latest treatment is unknown.
- **Previous treatment episodes.** This section lists and describes any previous antituberculosis treatment and outcomes. Start with the most distant treatment and label it number 1. The specific drugs can be placed in the block according to the standard code for antituberculosis regimens described in Chapter 7, section 7.6 (abbreviations are also given on the front of the treatment card). The outcome of any previous treatment is also noted here (cured, completed, failed or defaulted).
 - **Used second-line drugs previously?** In this section answer “yes” if the patient received any of the second-line drugs listed on the front of the chart for the treatment of TB for more than one month. Otherwise answer “no”.
 - **HIV information.** This section records whether HIV testing was ever done, the date of the test and whether the patient is on ART and/or co-trimoxazole preventive therapy (CPT).
 - **Review panel meetings.** These guidelines promote the idea of periodic meetings with the group of caregivers involved with Category IV patients. This section provides a space to record any major changes by the panel.

Page 2

- **Monitoring of smear and culture.** Record the date, sample number and result of smear and culture. The date of the smear and culture that determined the registration of the patient in Category IV should also be recorded. Month “0” is the time of sputum sample collection at the start of the Category IV regimen. Requirements for monitoring of smear and culture are described in Chapter 11.

- **DST results.** Record the date and results of all DST performed.

Pages 3 and 4

- **Regimen.** The initial Category IV regimen is recorded on the treatment card and any change to it is recorded in the same section. One line is used for each date on which a drug (or drugs) is changed. If drug dosage is progressively increased (for example, starting 250 mg of ethionamide daily and increasing by 250 mg thrice daily until the full dose is reached), this is usually not recorded on the treatment card but should be recorded in the patient's medical record.
- **Record of daily observed administration of drugs.** One line per month makes it easy to assess adherence. One box is marked for each day the treatment is administered. Some programmes may prefer to design treatment cards with a more detailed system where a box is checked for each drug daily, since there may be some irregularity in administration of drugs.
- **Weight, laboratory and X-ray monitoring.** These items can be recorded on the treatment card in the monthly drug administration section in the last column. Recommendations regarding the interval for monitoring these indicators can be found in Chapter 11.
- **Outcome of treatment.** At the end of treatment the outcome should be recorded on the treatment card. Chapter 4 provides definitions of treatment outcomes.

18.4.2 Category IV Register (Form 02)

These guidelines recommend a system in which the national TB control programme has two registers: a District Tuberculosis Register and a Category IV Register.

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 will need to be modified in three ways:

1. If culture is being done in addition to smear examination in a substantial number of cases, space for dates of collection and results must be added to both the initial testing and the follow-up areas.
2. An area to record DST must be added – one or two columns for date of collection of DST and for 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 be noted as such. These patients are removed from the outcome analysis of Categories I, II and III (their final outcome will be noted in the Category IV Register).

Patients who have mono- or poly-resistant TB that requires minor adjustments of drugs should stay in the District Tuberculosis Register, where the adjustment of their regimen should be recorded. However, if such patients are suspected to have developed MDR-TB and are being placed on a new regimen designed to treat MDR-TB, they should be placed in the Category IV Register, which is described below.

The Category IV Register is the record of all patients who meet the diagnostic criteria for Category IV regimens (see Chapter 4, section 4.1, for a general definition of Category IV patients; individual country protocol may define in greater detail who enters Category IV treatments – see Chapter 5). This register allows quick assessment of the implementation of Category IV, facilitating quarterly reporting and analysis of case-finding and treatment outcomes.

The national TB control programme should define where the Category IV Register will be located. If the first months of Category IV treatment are centralized to one treatment unit (usually hospitalized, sometimes ambulatory), this unit should have a Category IV Register. If part or all of the Category IV treatment takes place at the provincial or district levels, and the number of cases in the province or district is considerable, there should be a provincial or district Category IV Register.

The Category IV Register is completed using information from the Category IV Treatment Card and should be updated regularly with any new information. Usually only the first eight columns are filled in at the initial registration; the rest of the registration information is completed from the treatment card over time.

The person responsible for the Category IV Register should enter the patient into the Category IV Register as soon as the patient is determined to meet the diagnostic criteria to enter Category IV, which is defined by the programme protocol (i.e. some programmes may routinely record failures of Category II regimens in the Category IV Register). This point will define the date of Category IV registration. Patients should be recorded consecutively by their date of registration. There should be a clear separation (extra line) when a new quarter is started.

Some patients registered in Category IV may later prove to have drug-susceptible disease when the DST results become available. Patients who are wrongly registered as Category IV can safely return to a Category I, II or III treatment regimen and should do so. It is recommended that they be crossed out of the Category IV Register (but with their names left legible) and a comment noted in the last column that they have drug-susceptible disease. The DST results should be completed in the Category IV Register. Patients who are entered in the Category IV Register and whose DST results subsequently show mono- or poly resistance, but not MDR-TB, can also complete their treatment in the traditional District Tuberculosis Register; the regimen is

adjusted according to the DST pattern (see Chapter 8). All patients who are switched back should be analysed in their original line in the District Tuberculosis Register. They do not need to appear in Forms 07, 08 and 09.

All patients for whom a Category IV regimen is indicated should be entered in the Category IV Register, whether or not a Category IV treatment is started.

The following information is recorded in the Category IV Register:

- **Category IV registration number.** This is a unique identification number for each patient who enters Category IV.
- **Date of registration.**
- **Name, sex, date of birth, address.**
- **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.** Pulmonary or extrapulmonary (note: a patient who has both pulmonary and extrapulmonary disease should be recorded as a pulmonary case).
- **Registration group.** Described in Chapter 4.
- **Second-line drugs already received.** State “yes” or “no” (see explanation for Form 01 above).
- **DST.** Date and results. Patients may have had more than one 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. Follow-up DSTs are not recorded in the register. If the patient has more than one DST, results are recorded on the treatment card.
- **Reason for Category IV registration.** Reasons include confirmed MDR-TB or suspected MDR-TB, which is defined by the country protocol. Although it can be determined that patients have MDR-TB from the DST columns for H and R, the register should have a separate column that differentiates documented MDR-TB patients from suspected Category IV patients.
- **Category IV regimen.** Record the initial Category IV regimen using the drug abbreviations and enter the date the regimen was started.
- **Smear and culture monitoring results.** Date and outcome. Instructions and codes for recording smear and culture outcomes are summarized on page 4 of the register (Form 02).
- **Final outcome.** See Chapter 4 for definitions.

- **HIV status.** If available.
- **Comments.** This section is reserved for any additional information.

18.4.3 Patient identity card (Form 03)

A patient in whom TB is diagnosed should have a patient identity card completed by the health-care provider at the same time that the treatment card is completed. The card should be kept by the patient. The card, which is wallet-sized, contains the name, age, sex, TB identification number, essential information about the treatment (start date, regimen, allergies and severe adverse effects to medications), and the health centre where the patient will receive treatment. It also has a place to write the date of the next appointment.

18.4.4 Request for sputum examination (Form 04)

A sputum smear examination is needed in all cases of suspected TB. When smear examination alone is requested, the regular DOTS request for sputum examination can be used. When requesting culture and/or DST, Form 04 should be used. The first part of Form 04 is exactly the same as that recommended for DOTS programmes (since culture is also carried out on specimens sent for smear); the middle portion of the form is for requesting culture and DST; the last section is used for reporting the results. The completed form is then sent promptly to the treating unit with the results.

18.4.5 Laboratory registers (Forms 05 and 06)

Laboratories will have separate registers for sputum smear microscopy and culture, while reference laboratories carrying out DST should have an additional DST register. Form 05 is based on the sputum smear microscopy laboratory register for DOTS. It should be used as the primary laboratory register recording results on smear, whether this test is done for diagnosis or for monitoring. Form 06 is the laboratory register used to record culture results. The DST register should be compared regularly with the Category IV Register to ensure that all resistant cases are entered in the Category IV Register and in the quarterly reports on case-finding.

18.4.6 Quarterly report on Category IV case registration (Form 07)

The quarterly report is completed from the Category IV Register and is designed to report the number of patients registered in diagnostic Category IV and how many were started on Category IV regimens. A considerable delay usually occurs between registration and the start of treatment, so the information gives an approximate indication of the coverage of treatment. The quarterly report also shows how many patients with MDR-TB were registered during the quarter, by type of case.

This report should be completed with a delay of one quarter, to allow time

for culture and DST results to be available. For instance, TB patients registered during the first quarter of a year (1 January to 31 March), should be reported in the quarterly report after 1 July.

18.4.7 Six-month interim outcome assessment (Form 08)

Each quarterly cohort defined by date of the start of Category IV treatment should have an interim or preliminary outcome report. This report should be prepared by the central TB unit and based on the Category IV Register. A delay of 2 to 3 years occurs before final results are known, so it is helpful for programmatic monitoring to report preliminary results for all cohorts.

These guidelines recommend reporting interim results at 9 months after the closing day of the cohort. This allows culture information at 6 months 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 “Six-Month Interim Outcome Assessment Form” filled out from 1 January of the following year.

In situations where it is important to measure the treatment coverage (the proportion of registered cases that are started on treatment), an additional form could be used to compare the number of patients with confirmed MDR-TB who are registered during the quarter with the number of these cases that were started on treatment.

18.4.8 Annual report of treatment outcome of Category IV regimens (Form 09)

This report shows the final result of treatment by year since the start of treatment, in total and stratified by smear and culture results and by patient registration category. Since treatment is of long duration, the results reflect retrospectively the management of treatment over a prolonged period. Form 09 is completed at both 24 and 36 months after the last patient starts treatment in the cohort. Most of the patients will have finished treatment by 24 months and this allows preliminary assessment of cure rates. Since a few patients may be on treatment for longer than 24 months, the form is completed again at 36 months after the last patient in the cohort starts treatment. The 36-month evaluation is considered the final *Treatment Cohort Analysis* result.

As noted above, patients who are entered into the Category IV Register but later found to have drug-susceptible forms of TB are placed back in the District Tuberculosis Register and their outcome is recorded there.

18.5 Addressing the backlog of patients defined as “chronic cases”

Many programmes may have a large group of patients defined as “chronic cases” (those who are still sputum smear-positive after supervised re-treat-

ment; proven or suspected MDR-TB) (*I*) from previous years waiting to enter a new Category IV regimen. Programmes that have not yet started Category IV treatment should keep a list of such patients. When Category IV treatment becomes available, chronic cases with evidence of active disease should be registered in the Category IV Register and treatment started.

As the Category IV treatment programme progresses, the list of patients defined as chronic cases will become smaller and eventually it will include only cases that have failed Category IV treatment.

18.6 Other programme indicators

In addition to the 6-month indicators and the final outcome of MDR-TB treatment cohorts, programmes should examine other programme indicators. Some suggested programme indicators are:

- Burden of MDR-TB defined as the absolute number of MDR cases among new cases, and re-treatment cases including failures of Category IV regimens.
- Percentage of MDR-TB among different treatment history groups: new, relapses, return after default, failures of Category I, failures of re-treatment.
- DST coverage in different treatment history groups: new, relapses, return after default, failures of Category I, failures of re-treatment.
- MDR-TB treatment coverage (number of patients placed on treatment divided by the total number of MDR-TB patients notified). This indicator can be analysed separately for each treatment history group.

18.7 Computerized systems

All the forms can be handwritten. However, an electronic version entering the data from the Category IV treatment card (Form 01) is highly desirable since it facilitates better quality of information as well as data analysis. The Category IV Register and Forms 07–09 can then be generated easily from the computerized register.

The forms discussed in this chapter are available on the WHO Stop TB web site (www.stoptb.org). In addition, alternative versions of forms for programmes doing DST in all new patients will be placed on the web site.

18.8 Training

The information system for drug-resistant TB requires basic knowledge of the DOTS information system, with additional training on the specifics of the forms. Regular supervisory visits by the central team to the units using the information system are fundamental to maintaining the quality of the information.

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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	<p>Frequent: pain at injection site, proteinuria, serum electrolyte disturbances including hypokalaemia and hypomagnesaemia.</p> <p>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.</p> <p>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.</p>
Drug interactions	<p>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.</p> <p>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.</p> <p>Penicillins: in vitro inactivation (possible). Do not mix together before administration.</p>
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	<ul style="list-style-type: none"> — 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, azotemia, 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	<ul style="list-style-type: none"> — 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	<p>Mexiletine: fluoroquinolones may inhibit cytochrome P450 1A2 resulting in increased mexiletine concentration.</p> <p>Warfarin: case reports of ciprofloxacin enhancing anticoagulation effect of warfarin.</p>
Contraindications	Pregnancy, intolerance of fluoroquinolones.
Monitoring	No specific laboratory monitoring requirements.
Alerting symptoms	<ul style="list-style-type: none"> — 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	<p>Bacteriostatic against <i>M. leprae</i>, active in vitro against <i>M. tuberculosis</i>. Clinical effectiveness against <i>M. tuberculosis</i> not well established.</p> <p>Clofazimine appears to bind preferentially to mycobacterial DNA (principally at base sequences containing guanine) and inhibit mycobacterial replication and growth.</p> <p>Excreted in faeces as unabsorbed drug and via biliary elimination. Little urinary excretion.</p>
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	<p>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.</p> <p>Renal disease: usual dose.</p> <p>Hepatic disease: dose adjustments should be considered in patients with severe hepatic insufficiency.</p>
Adverse effects	Frequent: ichthyosis, and dry skin; pink to brownish-black discoloration of skin, cornea, retina and urine; anorexia and abdominal pain.
Drug interactions	<p>May decrease absorption rate of rifampicin.</p> <p>Isoniazid increases clofazimine serum and urine concentrations and decreases skin concentrations.</p> <p>Ingestion of clofazimine with orange juice resulted in a modest reduction in clofazimine bioavailability.</p>
Contraindications	Pregnancy, severe hepatic insufficiency, hypersensitivity to Cfz.
Monitoring	No specific laboratory monitoring requirements.
Alerting symptoms	<ul style="list-style-type: none"> — 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	<ul style="list-style-type: none"> — 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	<p>Pregnancy/breastfeeding: safety class C. Animal studies have shown ethionamide to be teratogenic. Newborns who are breast-fed by mothers who are taking ethionamide should be monitored for adverse effects.</p> <p>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.</p> <p>Hepatic disease: thionamides should not be used in severe hepatic impairment.</p> <p>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.</p>
Adverse effects	<p>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.</p> <p>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.</p> <p>Rare: reports of peripheral neuritis, optic neuritis, diplopia, blurred vision, and a pellagra-like syndrome, reactions including rash, photosensitivity, thrombocytopenia and purpura.</p>

ETHIONAMIDE (Eto)
PROTIONAMIDE (Pto)
DRUG CLASS: CARBOTHIONAMIDES GROUP, DERIVATIVES OF ISONICOTINIC ACID

Drug interactions	<p>Cycloserine: potential increase incidence of neurotoxicity.</p> <p>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.</p> <p>PAS: possible increase in liver toxicity, monitor liver enzymes; hypothyroidism in case of combined administration.</p>
Contraindications	<p>Thionamides are contraindicated in patients with severe hepatic impairment and in patients who are hypersensitive to these drugs.</p>
Monitoring	<p>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.</p>
Alerting symptoms	<ul style="list-style-type: none"> — 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	<p>Mexiletine: fluoroquinolones may inhibit cytochrome P450 1A2, resulting in increased mexiletine concentration.</p> <p>Warfarin: case reports of gatifloxacin enhancing anticoagulation effect of warfarin.</p>
Contraindications	Pregnancy, intolerance of fluoroquinolones.
Monitoring	No laboratory monitoring requirements.
Alerting symptoms	<ul style="list-style-type: none"> — 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	<p>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.</p> <p>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.</p> <p>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.</p>
Adverse effects	<p>Frequent: pain at injection site, renal failure (usually reversible).</p> <p>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.</p> <p>Ototoxicity potentiated by certain diuretics (especially loop diuretics), advanced age, and prolonged use. The effect of non-depolarizing muscle relaxants may be increased.</p> <p>Penicillins: in vitro antagonism.</p>
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	<p>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.</p> <p>Nephrotoxic agents (amphotericin B, foscarnet, cidofovir): additive nephrotoxicity. Avoid co-administration; if used together, monitor renal function closely and discontinue if warranted.</p> <p>Penicillins: in vitro inactivation (possible). Do not mix together before administration.</p>
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	<ul style="list-style-type: none"> — 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	<p>Bactericidal: acts by inhibiting the A subunit of DNA gyrase (topoisomerase), which is essential in the reproduction of bacterial DNA.</p> <p>Levofloxacin is generally considered to be about twice as active as its isomer, ofloxacin.</p> <p>Minimal hepatic metabolism; 87% of dose excreted unchanged in the urine within 48 h via glomerular filtration and tubular secretion.</p>
Preparation and dose	<p>Tablets (250, 500, 750 mg).</p> <p>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.</p> <p>Usual dose: 750 mg/day.</p>
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	<p>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.</p> <p>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.</p> <p>Hepatic disease: given the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.</p>
Adverse effects	<p>Generally well tolerated.</p> <p>Occasional: gastrointestinal intolerance; CNS-headache; malaise; insomnia; restlessness; dizziness; allergic reactions; diarrhoea; photosensitivity.</p> <p>Rare: QT prolongation; tendon rupture; peripheral neuropathy.</p>
Drug interactions	<p>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).</p> <p>Sucralfate: decreased absorption of fluoroquinolones caused by the chelation by aluminium ions contained in the sucralfate.</p> <p>Antacids (magnesium, aluminium, calcium, Al-Mg buffer found in didanosine): antacid binding to fluoroquinolone antibiotics resulting in decreased absorption and loss of therapeutic efficacy.</p>

LEVOFLOXACIN (Lfx)	
DRUG CLASS: FLUOROQUINOLONE	
Drug interactions	<p>Probenecid: probenecid interferes with renal tubular secretion of fluoroquinolones, which may result in 50% increase in serum level of levofloxacin.</p> <p>Vitamins and minerals containing divalent and trivalent cations such as zinc and iron. Formation of fluoroquinolone-ion complex results in decreased absorption of fluoroquinolones.</p> <p>Mexiletine: fluoroquinolones may inhibit cytochrome P450 1A2 resulting in increased mexiletine concentration.</p>
Contraindications	Pregnancy; hypersensitivity to fluoroquinolones; prolonged QT.
Monitoring	No specific laboratory monitoring requirements.
Alerting symptoms	<ul style="list-style-type: none"> — 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	<p>Bactericidal: acts by inhibiting the A subunit of DNA gyrase (topoisomerase), which is essential in the reproduction of bacterial DNA.</p> <p>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).</p>
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	<p>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.</p> <p>Renal disease: no dosage adjustment is required in renally impaired patients, including those on either haemodialysis or continuous ambulatory peritoneal dialysis.</p> <p>Hepatic disease: no dosage adjustment is required in patients with mild or moderate hepatic insufficiency.</p>
Adverse effects	<p>Generally well tolerated.</p> <p>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.</p>
Drug interactions	<p>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).</p> <p>Sucralfate: decreased absorption of fluoroquinolones caused by the chelation by aluminium ions contained in the sucralfate.</p> <p>Antacids (magnesium, aluminium, calcium, Al-Mg buffer found in didanosine): antacid binding to fluoroquinolone antibiotics resulting in decreased absorption and loss of therapeutic efficacy.</p> <p>Vitamins and minerals containing divalent and trivalent cations such as zinc and iron: formation of fluoroquinolone-ion complex results in decreased absorption of fluoroquinolones.</p>
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	<p>Bactericidal: acts by inhibiting the A subunit of DNA gyrase (topoisomerase), which is essential in the reproduction of bacterial DNA.</p> <p>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.</p>
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	<p>Pregnancy/breastfeeding: usually compatible with breastfeeding.</p> <p>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.</p>
Adverse effects	<p>Generally well tolerated.</p> <p>Occasional: gastrointestinal intolerance; CNS-headache, malaise, insomnia, restlessness, and dizziness.</p> <p>Rare: allergic reactions; diarrhoea; photosensitivity; increased LFTs; tendon rupture; peripheral neuropathy.</p>
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	<ul style="list-style-type: none"> — 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 <i>N</i> -acetyl- <i>p</i> -aminosalicylic acid and <i>p</i> -aminosalicylic acid, which are excreted via glomerular filtration and tubular secretion.
Preparation and dose	Tablets, sugar-coated, containing sodium salt: sodium <i>p</i> -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).

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				
<i>Isoniazid (H)</i> (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
<i>Rifampicin (R)</i> (150, 300 mg)	10–20 mg/kg daily	450–600 mg	600 mg	600 mg
<i>Ethambutol (E)</i> (100, 400 mg)	25 mg/kg daily	800–1200 mg	1200– 1600 mg	1600– 2000 mg
<i>Pyrazinamide (Z)</i> (500 mg)	30–40 mg/kg daily	1000–1750 mg	1750– 2000 mg	2000– 2500 mg
GROUP 2: INJECTABLE ANTITUBERCULOSIS DRUGS				
<i>Streptomycin (S)</i> (1 g vial)	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg
<i>Kanamycin (Km)</i> (1 g vial)	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg
<i>Amikacin (Am)</i> (1 g vial)	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg
<i>Capreomycin (Cm)</i> (1 g vial)	15–20 mg/kg daily	500–750 mg	1000 mg	1000 mg

Weight-based dosing of antituberculosis drugs in the treatment of drug-resistant TB
(continued)

MEDICATION (DRUG ABBREVIATION), (COMMON PRESENTATION)	WEIGHT CLASS			
	<33 KG	33–50 KG	51–70 KG	>70 KG (ALSO MAXIMUM DOSE)
GROUP 3: FLUOROQUINOLONES				
Ciprofloxacin (Cfx) (250, 500, 750 mg)	20–30 mg/ kg daily	1500 mg	1500 mg	1500 mg
Ofloxacin (Ofx) (200, 300, 400 mg)	Usual adult dose for MDR-TB is 800 mg	800 mg	800 mg	800–1000 mg
Levofloxacin (Lfx) (250, 500 mg)	Usual adult dose for MDR-TB is 750 mg	750 mg	750 mg	750–1000 mg
Moxifloxacin (Mfx) (400 mg)	Usual adult dose for MDR-TB is 400 mg	400 mg	400 mg	400 mg
Gatifloxacin (Gfx) (400 mg)	Usual adult dose for MDR-TB is 400 mg	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 g
Sodium PAS	Dosing can vary with manufacture and preparation: check dose recommended by the manufacturer.			
Thioacetazone (Th)	Usual dose is 150 mg for adults			
GROUP 5: AGENTS WITH UNCLEAR EFFICACY (NOT RECOMMENDED BY WHO FOR ROUTINE USE IN MDR-TB PATIENTS)				
Clofazimine (Cfz), Amoxicillin/Clavulanate (Amx/Clv), Clarithromycin (Clr), Linezolid (Lzd). Efficacy and dosing in the treatment of drug-resistant TB not fully determined.				
Detailed information on each drug is given in Annex 1.				

ANNEX 3

Suggestions for further reading

Policy issues

1. *Anti-tuberculosis drug resistance in the world. Third global report. The WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance, 1999–2002.* Geneva, World Health Organization, 2004 (WHO/HTM/TB/2004.343).
2. Espinal M et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in six countries. *Journal of the American Medical Association*, 2000, 283(19), 2537–2545.
3. Program in Infectious Disease and Social Change/Open Society Institute. *Global impact of drug resistant tuberculosis.* Boston, Harvard Medical School, 1999.
4. Kim JY et al. From multidrug-resistant tuberculosis to DOTS expansion and beyond: making the most of a paradigm shift. *Tuberculosis*, 2003, 83: 59–65.

Laboratory services

1. *Laboratory services in tuberculosis control. Parts I, II and III.* Geneva, World Health Organization, 1998 (WHO/TB/98.258).
2. *Guidelines for surveillance of drug resistance in tuberculosis.* Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003/320; WHO/CDS/CSR/RMD/2003.3).
3. *Guidelines for drug susceptibility testing for second-line anti-tuberculosis drugs for DOTS-Plus.* Geneva, World Health Organization, 2001 (WHO/CDS/TB/2001.288).
4. Laszlo A et al. Quality assurance programme for drug susceptibility testing of *Mycobacterium tuberculosis* in the WHO/IUATLD Supranational Reference Laboratory Network: first round of proficiency testing. *International Journal of Tuberculosis and Lung Disease*, 1997, 1:231–238.
5. *The public health service national tuberculosis reference laboratory and the national laboratory network: minimum requirements, roles, and operation in low-income countries.* Paris, International Union Against Tuberculosis and Lung Disease, 1998.

6. Hong Kong TB Treatment Services/British Medical Research Council Investigation. A study in Hong Kong to evaluate the role of pretreatment susceptibility tests in the selection of regimens of chemotherapy for pulmonary tuberculosis. *American Review of Respiratory Disease*, 1972, 106(1): 1–22.

Diagnosis and treatment

1. *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003.313).
2. *Tuberculosis: a manual for medical students*. Geneva, World Health Organization, 2003 (WHO/CDS/TB/99.272).
3. *The PIH guide to medical management of multidrug-resistant tuberculosis*. Boston, MA, Partners In Health, Program in Infectious Disease and Social Change, Harvard Medical School, Division of Social Medicine and Health Inequalities, Brigham and Women's Hospital, 2003.
4. American Thoracic Society/Centers for Disease Control and Prevention/ Infectious Diseases Society of America. Treatment of tuberculosis. *American Journal of Respiratory and Critical Care Medicine*, 2003, 167(4):603–662.
5. Nathanson E et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. *International Journal of Tuberculosis and Lung Disease*, 2004, 8(11):1382–1384.
6. Bastian I, Portaels F, eds. *Multidrug-resistant tuberculosis*. London, Kluwer Academic Publishers, 2000.

HIV and MDR-TB

1. Centers for Disease Control and Prevention, American Thoracic Society, Infectious Disease Society of America. Treatment of tuberculosis. *Morbidity and Mortality Weekly Report*, 2003, 52(RR11):1–77.
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).
6. *Strategic framework to decrease the burden of TB/HIV*. Geneva, World Health Organization, 2002 (WHO/CDS/TB/2002.296, WHO/HIV_AIDS/2002.2).

7. *Guidelines for implementing collaborative TB and HIV programme activities*. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003.319; WHO/HIV/2003.01).
8. *Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach*. Geneva, World Health Organization, 2003.
9. *TB/HIV: a clinical manual*. Geneva, World Health Organization, 2003 (WHO/HTM/TB/2004.329).

Human resources

1. *Training for better TB control. Human resource development for TB control: a strategic approach within country support*. Geneva, World Health Organization (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.

Drug procurement

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 (WHO Technical Report Series, No. 908).
3. *Procurement manual for DOTS-Plus projects approved by the Green Light Committee*. Geneva, World Health Organization, 2003 (WHO/HTM/TB/2003.328Rev1).

Recording and reporting

1. *Management of tuberculosis: training for health facility staff* [modules a–k]. Geneva, World Health Organization, 2003 (WHO/CDS/2003.314a–314k).
2. *Management of tuberculosis: training for health facility staff. How to organize training for health facility staff on TB control*. Geneva, World Health Organization, 2004 (WHO/CDS/2004.332).
3. Laserson KF et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 2005, 9(6):640–645.

ANNEX 4

List of complementary documents available on the WHO web site

The following complementary documents are available on the WHO web site at <http://www.who.int/tb/en/>

- Electronic versions of Category IV treatment forms 01 to 09
- Alternative versions of quarterly reporting for programmes doing culture and DST in all patients
- Additional information on the GLC and how to apply
- Adverse event management protocols for DR-TB control programmes (flow diagrams):
 - Protocol 1: Management of anaphylaxis and allergic reaction
 - Protocol 2: Management of nausea and vomiting
 - Protocol 3: Management of gastritis
 - Protocol 4: Management of diarrhoea
 - Protocol 5: Evaluation and management of hepatitis
 - Protocol 6: Management of headaches
 - Protocol 7: Management of depression
 - Protocol 8: Management of hypothyroidism
 - Protocol 9: Management of psychosis
 - Protocol 10: Management of peripheral neuropathy
 - Protocol 11: Management of seizure
 - Protocol 12: Management of nephrotoxicity
 - Protocol 13: Management of hypokalaemia
- Supranational reference laboratory addresses and contact information
- Further information on DST techniques and updated information on rapid DST testing
- Additional information on data collection and analysis
- Alerts and updates

ANNEX 5

Drug groupings and abbreviations

GROUP	DESCRIPTION	DRUG	ABBREVIATION
1	First-line oral antituberculosis drugs	Isoniazid	H
		Rifampicin	R
		Ethambutol	E
		Pyrazinamide	Z
2	Injectable antituberculosis drugs	Streptomycin	S
		Kanamycin	Km
		Amikacin	Am
		Capreomycin	Cm
		Viomycin	Vm
3	Fluoroquinolones	Ciprofloxacin	Cfx
		Ofloxacin	Ofx
		Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
4	Oral bacteriostatic second-line antituberculosis drugs	Ethionamide	Eto
		Protionamide	Pto
		Cycloserine	Cs
		Terizidone	Trd
		<i>P</i> -aminosalicylic acid	PAS
		Thioacetazone	Th
5	Antituberculosis drugs with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)	Clofazimine	Cfz
		Amoxicillin/Clavulanate	Amx/Clv
		Clarithromycin	Clr
		Linezolid	Lzd

Forms

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: _____

Review panel meetings: dates and decisions

Date	Decision	Next date

	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: <input type="checkbox"/> Y <input type="checkbox"/> N <input type="checkbox"/> unknown
Date of test: ___/___/___ Results:
Started on ART: <input type="checkbox"/> Y <input type="checkbox"/> N Date: ___/___/___
Started on CPT: <input type="checkbox"/> Y <input type="checkbox"/> N Date: ___/___/___

ART = antiretroviral therapy; CPT = cotrimoxazole preventive therapy

Previous tuberculosis treatment episodes

No.	Start date (if unknown, put year)	Regimen (write regimen in drug abbreviations)	Outcome

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
Cfx = Ciprofloxacin
Ofx = Ofloxacin
Lfx = Levofloxacin
Mfx = Moxifloxacin
Gfx = Gatifloxacin
Pto = Protionamide
Eto = Ethionamide
Cs = Cycloserine
PAS = P-aminosalicylic acid

DR-TB Control Programme

Month #

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

Date*

Sputum smear microscopy

Sample No.

Result

Month #

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

Date*

Culture

Sample No.

Result

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

1-9 AFB per 100 HPF

10-99 AFB per 100 HPF

1-10 AFB per HPF

>10 AFB per HPF

0

Scanty (and report number of AFB)

+

++

+++

Notation method for recording cultures

No growth reported

Fewer than 10 colonies

10-100 colonies

More than 100 colonies

Innumerable or confluent growth

0

Report number of colonies

+

++

+++

Notation method for DST:
R = resistant
S = susceptible
C = contaminated

Drug susceptibility testing (DST) results

Date*	S	H	R	E	Z	Km	Am	Cm	Fq	Pto/Eto	PAS	Cs	Other	Other

Patient name: _____

ADMINISTRATION OF DRUGS (continued):

[illegible]

Mark in the boxes:

O = directly observed
N = not supervised
Ø = drugs not taken

	Outcome	Mark one	Date
Comments	Cured		
	Completed		
	Died		
	Failed		
	Defaulted		
	Transferred out		

Category IV Register

DR-TB Control Programme

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 or Site of disease registration (P/EP)	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	R	H	E	S	Km	Cm	Fq	Pto/Eto	Other	Other	Date the patient took first dose for DST	Second-line drugs already received
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

FORM 02

DR-TB Control Programme

Reasons for entering in Category IV Register		Category IV treatment	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)																													
			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 documented	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
		Date	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	
		Date	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	
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		Date	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	
		Date	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	
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[illegible]

Outcome Cured Completed Died Defaulted Transferred out	TB/HIV activities				
	Testing done (Y/N/unknown)	HIV testing Date of test	Result	ART Y/N Start Date	CPT Y/N Start date
Date outcome given					
/ /					
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Notation method for recording smears
(for non-centrifuged specimens)

No. AFB	Scanty (and report number of AFB)
1–9 AFB per 100 HPF	0
10–99 AFB per 100 HPF	+
1–10 AFB per HPF	++
>10 AFB per HPF	+++

Notation method for recording cultures

No growth reported	Report number of colonies
Fewer than 10 colonies	0
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
Cfx = Ciprofloxacin
Ofx = Ofloxacin
Lfx = Levofloxacin
Mfx = Moxifloxacin
Gfx = Gatifloxacin
Pto = Protionamide
Eto = Ethionamide
Cs = Cycloserine
PAS = Paminosalicylic acid

Patient Identity Card

Name: _____

Address (in full): _____

Sex: ☐ M ☐ F Age: _____ Date of birth: / /

District TB unit: _____

Health unit _____

Disease classification

Pulmonary ☐ Extrapulmonary ☐
Site

Date treatment started

Day Month Year

Type of patient

New ☐ Treatment after default ☐
Transfer in ☐ Relapse ☐
Treatment after failure ☐ Other (specify) ☐

Treatment Category

I

II

III

IV

Initial treatment:

Change in treatment:

Allergies: _____

Severe adverse reaction: _____

Appointment dates

[illegible]

REMEMBER

1. Take care of your card.
2. You can be cured if you follow your treatment regimen by taking your prescribed drugs regularly.
3. Tuberculosis can spread to other people if you do not take your medication.

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 examinationTest 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)

Date _____

Examined by (signature) _____

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	+++

Culture results

Date collected	Specimen	Laboratory specimen no.	Result (mark one)					Contaminated
			neg.	1-9	+	++	+++	
		1						
		2						

Date _____

Examined by (signature) _____

No growth reported	0
Fewer than 10 colonies	Report number of colonies
10-100 colonies	+
More than 100 colonies	++
Innumerable or confluent growth	+++

DST results

Date taken	Laboratory specimen no.	S	H	R	E	Z	Km	Am	Cm	Ofx	Pto/Eto	Other
	1											
	2											

Date _____

Examined by (signature) _____

R = resistant
 S = susceptible
 C = contaminated

The completed form (with results) should be sent promptly to the treatment unit

Laboratory Register for smear microscopy

DR-TB Control Programme

[illegible]

* Facility that referred the patient for sputum smear examination to the laboratory/health facility.

** Indicate month of treatment at which follow-up examination is performed.

FORM 06

Laboratory Register for culture

DR-TB Control Programme

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

DR-TB Control Programme

Reason for examination		Result of culture***	Result of confirmatory test for <i>M. tuberculosis</i> (positive or negative)	Culture sent for DST (Yes or No)	Name of person reporting 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	+++

Quarterly report on Category IV case registration

Name of district: _____
District No.: _____
Name of district coordinator: _____
Signature: _____

Patient registered in the Category IV Register
during _____ quarter of year _____
Date of completing this form: _____

Block 1: Patients registered in Category IV and started on Category IV treatment

Patients	Confirmed MDR-TB	Suspected MDR-TB
Registered in Category IV diagnostic group		
Started on Category IV treatment during the quarter		

Block 2: Confirmed MDR-TB cases registered during the quarter

New	Pulmonary				New extrapulmonary	Other*	Total
	Relapse	Previously treated		After failure of Category II treatment			
		After default	After failure of Category I treatment				

* Other cases include previously treated pulmonary patients without known outcome status, and all previously treated extrapulmonary TB patients.

Six-month interim outcome assessment
(to be filled out 9 months after treatment initiation)

Name of district: _____
District No.: _____
Name of district coordinator: _____
Signature: _____

Patient registered in the Category IV Register
during _____ quarter of year _____
Date of completing this form: _____

	Number started on treatment	Smear and culture results at 6 months of treatment										No longer on treatment		
		Smear negative			Smear positive			Smear unknown				Died	Defaulted	Transferred out
		Culture negative	Culture positive	Culture unknown	Culture negative	Culture positive	Culture unknown	Culture negative	Culture positive	Culture unknown				
MDR-TB documented cases														
Suspected MDR-TB cases														
TOTAL														

Annual report of treatment outcome of Category IV regimens
(to be filled in 24 and 36 months after the closing date of year of treatment)

Name of district: _____

District No.: _____

Name of district coordinator: _____

Signature: _____

Patient registered in the Category IV Register
during _____ quarter of year _____
Date of completing this form: _____

BLOCKS 1 AND 2 ARE FOR ALL PATIENTS WHO ENTER CATEGORY IV REGIMENS

Block 1: Patients by smear and culture result at initiation of Category IV treatment (all patients)

	Cured	Treatment completed	Failed	Defaulted	Died	Transferred out	Still on treatment	Total
S+ C+								
S- C+								
S+ C-								
S- C-								
Unknown								
Total								

S = smear, C = culture

Block 2: Patients by registration category (for all patients entering Category IV)

Registration group	Cured	Treatment completed	Failed	Defaulted	Died	Transferred out	Still on treatment	Total
New								
Relapse								
After default								
Failure after re-treatment								
New extrapulmonary TB								
Other								
Total								

Year of cohort treatment: _____

BLOCKS 3 AND 4 ARE FOR MDR-TB PATIENTS ONLY

Block 3: Patients by smear and culture results at initiation of Category IV treatment (for patients with documented MDR-TB)

	Cured	Treatment completed	Failed	Defaulted	Died	Transferred out	Still on treatment	Total
S+ C+								
S- C+								
S+ C-								
S- C-								
Unknown								
Total								

S = smear, C = culture

Block 4: Patients by registration category (for patients with documented MDR-TB)

Registration group	Cured	Treatment completed	Failed	Defaulted	Died	Transferred out	Still on treatment	Total
New								
Relapse								
After default								
Failure after first treatment								
Failure after re-treatment								
New extrapulmonary TB								
Other								
Total								