
Guidelines for Clinical and Operational Management of Drug-Resistant Tuberculosis

2013



International Union Against
Tuberculosis and Lung Disease

Guidelines for Clinical and Operational Management of Drug-Resistant Tuberculosis

2013

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Abbreviations

2LI	second-line injectable drug
AFB	acid-fast bacillus
Am	amikacin
Amx/Clv	amoxicillin/clavulanate
ART	antiretroviral therapy
ARV	antiretroviral (drug)
ATS	American Thoracic Society
AUC24	area under the concentration-time curve from 0 to 24 h
BTS	British Thoracic Society
CD4 cells	CD4+T lymphocytes
Cf	clofazimine
Cfx	ciprofloxacin
Cm	capreomycin
CPC	cetylpyridinium chloride
Cs	cycloserine
DALY	disability-adjusted years of life
DM	diabetes mellitus
DOT	directly observed treatment
DOTS	originally an acronym for directly observed treatment, short course, DOTS became the term used to describe the tuberculosis control strategy recommended by the WHO
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
E	ethambutol
EBA	early bactericidal activity
Eth	ethionamide
FDA	fluorescein diacetate used for vital staining
FDC	fixed-dose combination
FLD	first-line drug
FQ	fluoroquinolone
GDF	Global Drug Facility
GFATM	The Global Fund to Fight AIDS, Tuberculosis and Malaria
Gfx	gatifloxacin

GLC	Green Light Committee (WHO)
H	isoniazid
HAART	highly active antiretroviral therapy
HEPA filter	high-efficiency particulate air filter
HIV	human immunodeficiency virus
IC	infection control
ICF	intensified case finding
IPT	intermittent preventive treatment
Km	kanamycin
MDR-TB	multidrug-resistant tuberculosis; <i>Mycobacterium tuberculosis</i> strain resistant to at least isoniazid and rifampicin
NEML	National Essential Medicines List
NTM	non-tuberculous mycobacteria
NTP	national tuberculosis programme
Ofx	ofloxacin
PAS	p-aminosalicylate (p-aminosalicylic acid)
PIH	Partners in Health
PLH	person/people living with HIV
Pto	prothionamide
QALY	quality-adjusted years of life
REMA	resazurin microplate assay
R	rifampicin
rGLC	regional Green Light Committee
S	streptomycin
SLD	second-line drug
TB	tuberculosis
TB-IRIS	TB-immune reconstitution inflammatory syndrome
TBTEAM	TB <u>T</u> Echnical <u>A</u> ssistance <u>M</u> echanism
TDR-TB	totally drug-resistant TB
Tdf	tenofovir
Th	thiacetazone
The Union	International Union Against Tuberculosis and Lung Disease
TLA	thin layer agar
UVGI	ultraviolet germicidal irradiation
Vi	viomycin
VWS	ventilated workstation
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis; multidrug-resistant tuberculosis plus resistance to fluoroquinolones plus one second-line injectable drug
Z	pyrazinamide

Justification for the Guidelines

José A. Caminero

-
- Justification for the Guidelines: DR-TB can be cured
 - The challenge of a new epidemic and the lack of anti-TB medicines
 - Lack of evidence in DR-TB clinical and operational management
 - Objectives of the Guidelines
-

Decades after tuberculosis (TB) became a curable illness in nearly all cases, the appearance of Mycobacterium tuberculosis strains with resistance to the most active existing drugs has once again made it a significant menace to global public health. Once again, there is talk of incurable forms of TB, with the accompanying alarm and fear this creates. The

first important message that must be sent to everyone tasked with managing TB patients is that, with good clinical and operational case management, all forms of drug-resistant TB (DR-TB) have the potential for cure, including those cases with a very extensive pattern of resistance. Obviously, the chances for success are clearly reduced as the patient's patterns of resistance increase. Numerous publications nonetheless show that even TB cases with extensive patterns of resistance are curable with proper clinical and operational management.

The problem we are facing is a new epidemic with practically no evidence to support one management protocol over another. There are controversies regarding choice of clinical and operational management scenarios for DR-TB. While the international recommendations are quite valid and must be followed as closely as possible, there remain many questions and doubts about the daily management of these patients. Thus, it is of utmost importance to discuss the controversial aspects of TB management in depth to ensure that the best standard of care is offered. In view of the above, The Union has written these Guidelines to address and discuss each fundamental aspect of the clinical and operational management of DR-TB patients.

Justification for the Guidelines: drug-resistant tuberculosis can be cured

DR-TB is an important new challenge in our fight against *M. tuberculosis*. After decades during which scientific advances made it possible for TB to be diagnosed and treated with relative ease, this new form of the disease is reaching epidemic proportions around the world, and is again challenging the medical community and humankind. In recent years, DR-TB has become a growing threat to global public health, a threat that has generated

fear not only in the scientific and medical communities, but also among the general public. Articles published in the world's most renowned medical journals have been sounding the alarm about the possible consequences of this type of difficult-to-cure TB. The primary message which must be delivered to everyone responsible for managing TB cases is that for all forms of DR-TB, cure is possible with optimal clinical and operational case management, including for those patients with a very long-standing pattern of resistance. Obviously, the chances for success are clearly reduced as the patient's patterns of resistance increase. This is why urgent action is needed.

The first premise to keep in mind when tackling the challenge of DR-TB cases is that all patients are potentially curable with good clinical and operational management. This was demonstrated in the era prior to the discovery of rifampicin (R) and fluoroquinolones (FQs), when patients with resistance to isoniazid (H) + streptomycin (S) + p-aminosalicylic acid (PAS) were very similar to current extensively drug-resistant TB (XDR-TB) patients. Indeed, a number of publications from the pre-rifampicin era showed that the specific three-drug combination (to which the patient's organism was sensitive) could achieve bacteriological conversion and cure rates of over 80%. There are also recent publications demonstrating that a significant percentage of multidrug-resistant TB (MDR-TB) patients, as well as XDR-TB cases, can be cured with appropriate treatment and management. Problems arise in trying to define the best standard of approach for treating these patients, because evidence is so scarce on this recent epidemic that there is unfortunately more controversy than evidence regarding the management of DR-TB. The Union undertook the creation of these Guidelines to address such controversial aspects of clinical and operational management and discuss them in depth, and to reasonably present the best management standards from the operational viewpoint of national tuberculosis control programmes (NTPs) and from the individualised and clinical viewpoint.

The challenge of a new epidemic and the lack of anti-tuberculosis medicines

Humankind's fight against TB took a radical turn between 1950 and 1970 with the onslaught of anti-TB drug research on drugs that rendered most cases curable. Simultaneously, studies were conducted to determine why *M. tuberculosis* may become resistant to these different drugs. The widely held belief at that time was that to prevent such resistance, it was necessary to combine a minimum of three different drugs. Nearly all of the following drugs were discovered in that era: S, PAS, H, thiacetazone (Th), pyrazinamide (Z), kanamycin (Km), amikacin (Am), viomycin (Vi), capreomycin (Cm), ethionamide (Eth), cycloserine (Cs), clofazimine (Cf), R and ethambutol (E).

However, initial optimism has gradually given way to pessimism due to the appearance of more resistant forms of TB and the near absence of new drug discoveries in the last 45 years. In an era of the great antibiotic revolution for the treatment of all infectious diseases, only FQs have been incorporated into the arsenal against TB. The present armamentarium has proved insufficient in the face of the progressively virulent resistance of the bacillus, which has taken advantage of inadequate therapeutic practice. *M. tuberculosis* has continued to develop mono-resistance, poly-resistance, multidrug resistance (MDR-TB is defined as resistance to at least H+R), extensive drug resistance (XDR-TB is defined as MDR-TB plus resistance to FQs and at least to a second-line injectable) and the newly named, but not universally accepted, concept of totally drug-resistant TB (TDR-TB), that is resistant to all the anti-TB drugs tested in the laboratory.

Unfortunately, when a pharmacological combination therapy was developed over 40 years ago that led to TB cure in just 6 months, countries with economic resources ceased research for new drugs. The result has been there are scarcely a dozen drugs with the ability to fight a disease that needs at least three to four drugs administered in combination to conquer it. The most effective drug to fight *M. tuberculosis* is R, probably the only one capable of killing the aggressor microorganism under all metabolic growth conditions. R-resistant TB is especially hard to cure and has resulted in poorer prognoses in many regions of the world without access to the limited armamentum of anti-TB drugs. Perhaps the second-best drug is H, with its unequalled ability to kill the bacilli in their continuous division phase, making it a crucial weapon in the early weeks of treatment.

R and H are the two best drugs to fight *M. tuberculosis* because they are the most effective, the best tolerated and the most inexpensive. Treatment of R+H-resistant *M. tuberculosis* is therefore less effective, much more prolonged and more poorly tolerated. This challenge has led to the coining of a specific term, MDR-TB, to define this hard-to-manage TB. In MDR-TB cases, two other classes of drugs should be part of all treatment regimens, because they are the most active against *M. tuberculosis* in the face of R+H resistance. They are the FQs and the injectables (aminoglycosides and polypeptides), although among the latter, the most active, S, should not be considered an option due to the elevated rate of H resistance associated with this drug in most of the world. As noted above, XDR-TB involves resistance to the best-known drugs for fighting TB.

These newer forms of DR-TB were an isolated and relatively unimportant problem until about 20 years ago. In the past 10 years or so, they have reached epidemic proportions in large areas around the globe. TB resistance was thought eradicated in the 1950s and R resistance, first described in the 1970s, did not become a concern until well into the 1990s. Massive and

often indiscriminate use of R between the 1970s and 1990s gave rise to a truly worrisome situation. The problem is that because they were globally quite rare up until 2000, DR-TB cases were treated at leading centres in resource-rich countries, often according to rather disparate criteria and always with highly individualised clinical management. This individualised clinical management is by any reckoning insufficient to tackle the DR-TB problem. We are facing a new epidemic about which much is unknown, and learning to manage it one day at a time. Opportunities for success in treatment depend on the proper clinical and operational management of these patients.

Lack of evidence in drug-resistant tuberculosis clinical and operational management

At this point in time, there is virtually no quality evidence to show that one diagnostic and/or therapeutic approach (i.e., based on randomised clinical studies) is better than another. Controversies thus outweigh solid evidence for the clinical and operational management of these patients. Debates abound regarding the best approach for dealing with a patient's resistance pattern, identification of the best drug combination, the duration of the intensive treatment period and the role of surgery in such complex cases. Therefore, current international recommendations are based on the opinions of the experts who write them, relying on the weak evidence available. Although such recommendations must be considered valid and should be followed, numerous questions and doubts arise in day-to-day clinical and operational management. It is thus necessary to analyse the more controversial aspects to work out the best treatment and management approaches for these patients, with the goal of offering the greatest chance for cure and quelling the threat of new presentations of incurable TB.

Objectives of the Guidelines

The objectives of these Guidelines are as follows:

- 1 Describe the current global epidemiologic situation of DR-TB
- 2 Describe the biological characteristics and conditions of *M. tuberculosis* growth and the nature of resistance to anti-TB drugs
- 3 Review the approaches to case finding for DR-TB and the prioritisation of these approaches in various settings
- 4 List the strengths and weaknesses of various diagnostic approaches to MDR- and XDR-TB, including the value and limitations of drug susceptibility testing for various first- and second-line anti-TB drugs

- 5 Explain the principles of MDR- and XDR-TB treatment, including numbers of drugs, duration of treatment and individualised versus standardised treatment approaches
- 6 Describe the mechanism of action of the main drugs available for MDR-TB treatment
- 7 List common adverse reactions to second-line anti-TB drugs and detail appropriate management
- 8 Review the management of MDR-TB in special situations such as HIV co-infection and pregnancy
- 9 Analyse the drug resistance problem in a given setting to determine the best treatment approach for specific national tuberculosis programmes (NTPs)
- 10 Discuss common challenges and potential solutions for managing DR-TB from a programmatic perspective.

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Historical background and global epidemiology of *Mycobacterium tuberculosis* resistance

Donald A. Enarson, Anthony D. Harries

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- Historical background of anti-TB drug resistance
 - Surveillance of anti-TB drug resistance
 - Distribution and determinants of anti-TB drug resistance
-

Resistance to anti-tuberculosis (anti-TB) drugs is an important challenge in global TB control. Mutations in wild-type Mycobacterium tuberculosis that cause it to occur naturally become clinically significant under selection pressure from the misuse of anti-TB drugs. Subsequently, by transmission of resistant microorganisms, such mutations become enmeshed in the TB epidemic and are passed from one individual to another. Establishment of monitoring of the size and trend of anti-TB drug resistance through the World Health Organization/International Union Against Tuberculosis and Lung Disease (WHO/IUATLD) Global Drug Resistance Survey has resulted in reporting of four rounds of tests performed in various countries. These results demonstrate the appearance throughout the world of drug-resistant tuberculosis (DR-TB) and its more advanced forms—multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB) and, more recently, TB that is resistant to all drugs tested—creating huge treatment challenges. Poor case management is consistently associated with drug resistance. Subsequent transmission of drug-resistant organisms is facilitated by all the factors associated with infection with M. tuberculosis including prevalence, overcrowding, delayed diagnosis, inadequate treatment and poor institutional infection control practices. Sadly, to date, there have been no clinical trials to guide treatment of MDR-TB and XDR-TB. This chapter looks at the historical background of anti-TB drug resistance and includes the surveillance of anti-TB drug resistance and its determinants and distribution.

Historical background of anti-tuberculosis drug resistance

Resistance to antimicrobial agents is an innate characteristic of *M. tuberculosis*. It is related to genetic mutations that occur naturally in large populations of microorganisms. These mutations are thought to be associated with loss of fitness so that, in the wild state, where specific antimicrobial agents

have never been used, this resistance has no clinical significance. Clinically significant drug resistance consistently has its origins in the incorrect use of antimicrobial agents and is in this sense a 'man-made' phenomenon.

Many specific mutations associated with resistance to antimicrobial agents have been identified. Resistance to some antimicrobials is primarily linked to a limited number of bacterial chromosomal mutations, while others have a variety of associated mutations. These mutations are the target of diagnostic tests used to screen patients presenting with symptoms suggestive of TB and to detect resistance more rapidly. Every large population of microorganisms (as might be found in patients with sputum smear-positive and cavitary pulmonary TB) contains some mutations that are naturally resistant to antimicrobial agents due to genetic mutations. If such patients are treated with only one antimicrobial (or only one to which the microorganisms are susceptible), the susceptible microorganisms are rapidly killed, leaving the resistant microorganisms to multiply and form an entire population of drug-resistant microbes. Resistance to more than one antimicrobial agent usually develops when consecutive antimicrobial agents are used incorrectly, selecting successive populations of increasingly drug-resistant microorganisms.

This is illustrated by comparing the distribution of isoniazid (H) mono-resistance in various countries, as reported by Professor Kleeberg of South Africa in the 1970s, with the distribution of multidrug-resistant microorganisms in the 1990s, obtained from consecutive reports of the Global Drug Resistance Survey. The prevalence of MDR-TB in the latter period among patients retreated for TB is closely related to the prevalence of H resistance 20 years before, thereby illustrating the step-wise development of resistance to a series of antimicrobial agents. This concept of drug resistance development is also suggested by a simple comparison of drug resistance prevalence among patients never previously treated for TB with those coming for retreatment after previous treatment (here again based on the reports of the Global Survey). The prevalence of resistance in previously treated patients is approximately ten times higher than in patients never previously treated, again illustrating the step-wise process by which increasing drug resistance is produced.

Using these assumptions, it is possible to reconstruct the process by which drug resistance is promoted. H was first widely introduced for treatment of TB in the late 1950s. Widespread prevalence of resistance to H was measurable in a variety of locations by the early 1970s, around 15 years later. This relatively prolonged period of emergence of clinically significant drug resistance follows the natural history of TB. The drugs must be available and widely used (or misused) for some years (approximately 5) before a substantial number of patients presents with drug-resistant organisms as a cause of TB. It then takes another 5 years or so to accumulate sufficient

numbers of these patients who in turn infect a substantial number of other individuals, and then 5 more years for a sufficient number of them to go on to develop disease and be measurable in a survey—a period of about 15 years in total, as noted above. This process can be illustrated once again with the emergence of MDR-TB. Rifampicin (R) was widely introduced into TB treatment in the mid 1970s; by 1990, we were seeing alarming reports about the development and spread of MDR-TB, initially associated with large outbreaks and nosocomial transmission in New York City.

This step-wise development of drug resistance is not a particularly new phenomenon. It was seen following the introduction of widespread antimicrobial use in the late 1940s and early 1950s, and served as a basis for the development of multidrug therapy for TB by Crofton and his colleagues in Edinburgh. When investigators introduced new drugs for treatment of TB as they were developed, they found that the bacterial populations selected by the treatment were resistant to the medications that had previously been used.

Whereas the initial appearance of drug resistance is a ‘man-made’ phenomenon (poor quality case management), its establishment and spread in a community rapidly passes into the mainstream pattern of TB transmission. Drug-resistant TB is clearly infectious and can be transmitted from one individual to another. It is likely that the prolonged duration of drug-resistant cases associated with delays in diagnosis and lower efficacy of treatment overcomes any ‘protective effect’ of the loss of biological fitness associated with the mutation(s), and results in more extensive transmission of the microorganism due to the longer period of infectiousness, as compared with drug-susceptible cases in which infectiousness can be rapidly curtailed by prompt diagnosis and effective treatment.

Since the first use of antimicrobials for TB treatment, the emergence of clinically significant drug resistance has been progressive, extending to each new antimicrobial agent as it becomes widely used in a community. We have thus moved from drug mono-resistance to multidrug resistance and extensive drug resistance. Progress in the management of a given stage of the drug resistance cascade is complicated by the fact that resistance advances to the next stage with resultant challenges for case management. Unfortunately, our record of strategy development to proactively address this challenge is not good, and we do not seem to have prepared ahead of time for a process that is biologically inevitable.

Surveillance of anti-tuberculosis drug resistance

Surveillance is defined as ‘the systematic and continuous collection, analysis and interpretation of data’. In public health, this usually refers to the

monitoring of populations and may involve various approaches. The first is the monitoring of routinely collected information such as is done for TB to evaluate case finding and treatment outcome. It is occasionally used in anti-TB drug resistance surveillance when individual patients are tested for anti-TB drug resistance and the results are regularly reported as part of case notification. This is the norm, for example, in North America and Australia. A second approach to surveillance is the periodic measurement of certain selected groups based on their risk, termed sentinel surveillance, and most notably carried out to determine trends in prevalence of infection with human immunodeficiency virus (HIV). The third approach, and the one used for global surveillance of anti-TB drug resistance, is the periodic survey of a representative sample of the group to be studied. Four reports have been published by WHO/IUATLD, the most recent in 2008. The fourth report provides an analysis of drug resistance surveys and surveillance data from 93 different countries and geographical settings between 2002 and 2007 by the WHO/IUATLD Global Drug Resistance Surveillance Project.

The challenge of determining prevalence and trends in anti-TB drug resistance includes the inherent challenges of prevalence surveys for TB. First, the disease is in fact rare, meaning that obtaining precise estimates for both the level and trend of disease is extremely complex. An additional challenge is that this method is based on 'clinical' material from a source that is not comprehensive. Only patients diagnosed within specific institutions are included in the surveys. Consequently, patients receiving care in other institutions (for example, in the private sector) are not included. Lastly, participation in the global assessment of anti-TB drug resistance is voluntary and dependent on grant support, meaning that only a small number of countries have reported data and, in many large countries where the problem is greatest, only specific sites have reported results (meaning there are no representative national samples). As the assessments are based on laboratory tests, the reliability of the test results is crucial if comparisons are to be made. Therefore, the WHO/IUATLD Global Drug Resistance Surveillance Project has established a system of quality assurance based on a supra-national network of laboratories.

Distribution and determinants of anti-tuberculosis drug resistance

Today, MDR-TB is widespread and has been reported wherever drug resistance surveys have been undertaken. Although concentrated in some 'hot spots' (notably in the former Soviet Union, China and India), it travels 'with people' who move from one location to another, and who now account for the majority of TB patients in most countries in which the disease has declined to low levels. Although MDR-TB is a natural phenomenon, occurring

in all wild-type populations of *M. tuberculosis*, its clinical significance originates in clinical mismanagement. It is associated with the disruption of routine services (such as during the economic and social crises associated with the collapse of the Soviet Union), with a lack of standardisation of management for new TB cases (as in China prior to the end of the 'Cultural Revolution'), and with an active private sector that does not systematically apply standard case management (as in India).

While there is no evidence of an association of drug resistance with HIV infection per se, the HIV epidemic 'speeds up' the emergence of drug resistance in communities by shortening the natural history of TB, resulting in a higher proportion of individuals who develop TB disease at a more rapid pace. Consequently, when both HIV infection and drug resistance are present in a community, the spread of drug resistance and subsequent catastrophic clinical outcomes are typically seen (as in South Africa, where nosocomial transmission of drug-resistant TB among people living with HIV was associated with a high case fatality rate). A description of the epidemiology of DR-TB should include a summary of epidemiological evaluation of efficacious treatment. Sadly, this is as yet impossible as there have been no clinical trials for such evaluation.

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Basic concepts and definitions of drug resistance in tuberculosis

Chen-Yuan Chiang

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Mycobacterium tuberculosis is aerobic and its growth rate is highly affected by oxygen concentrations. In cavitory lesions of lung parenchyma where oxygen concentration is high, *M. tuberculosis* replicates rapidly. Resistance to anti-tuberculosis (anti-TB) drugs is caused by spontaneous chromosomal mutation. The proportion of wild-type resistant mutants in an untreated *M. tuberculosis* population is usually very small. Treatment with anti-TB drugs imposes selection pressure on a population of *M. tuberculosis*, resulting in a decline of drug-susceptible bacilli, advantageous reproduction of drug-resistant mutants and emergence of drug resistance: this is acquired resistance, implying that resistance emerges during anti-TB treatment. Primary resistance in TB refers to patients infected with *M. tuberculosis* that is resistant to anti-TB drugs from the outset, prior to anti-TB treatment. Drug resistance among new TB patients who have never been treated with anti-TB drugs before is due to transmission. Drug resistance among previously treated TB patients can come from three potential sources, namely primary infection with resistant bacilli, acquisition of resistance during treatment and reinfection with resistant bacilli. To date, there is no single chromosomal mutation that has been found to cause resistance to two or more anti-TB drugs (except for cross-resistance between some drugs). Resistance to two or more drugs is caused by sequential mutations in different genes.

When patients receive isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z), the first drug to which *M. tuberculosis* becomes resistant is usually H. Inappropriate regimens, use of lower-than-recommended dosage, poor drug quality and poor adherence to treatment are commonly associated with emergence of drug resistance in TB patients.

Biological characteristics of *Mycobacterium tuberculosis*

M. tuberculosis complex includes several species, namely *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, *M. caneti* and *M. pinnipedi*, all belonging to the *Mycobacterium* genus and the *Mycobacteriaceae* family. Mycobacteria are acid-fast. When stained with carbol fuchsin (Ziehl-Neelsen method), mycobacteria resist decolourisation with acid and alcohol, due to the unique cell wall composed of peptidoglycans, arabinogalactan and mycolic acids. This cell wall is thick with high lipid content and is highly impermeable to hydrophilic molecules. Due to their high lipid content, mycobacteria are resistant to chemical decontamination (with, for instance, sodium hydroxide and detergents). *M. tuberculosis* is resistant to cold (remaining viable for weeks at 4°C) but susceptible to heat, sunlight, UV light and X-rays. Slow-growing, with generation times ranging from 13 to 20 hours, *M. tuberculosis* is preferential aerobic, and its growth rate is highly affected by oxygen concentrations. *M. tuberculosis* replicates rapidly in cavitory lesions of lung parenchyma where oxygen concentration is high. In caseous foci where oxygen concentration is low, *M. tuberculosis* multiplies slowly or intermittently (Figure 3.1).

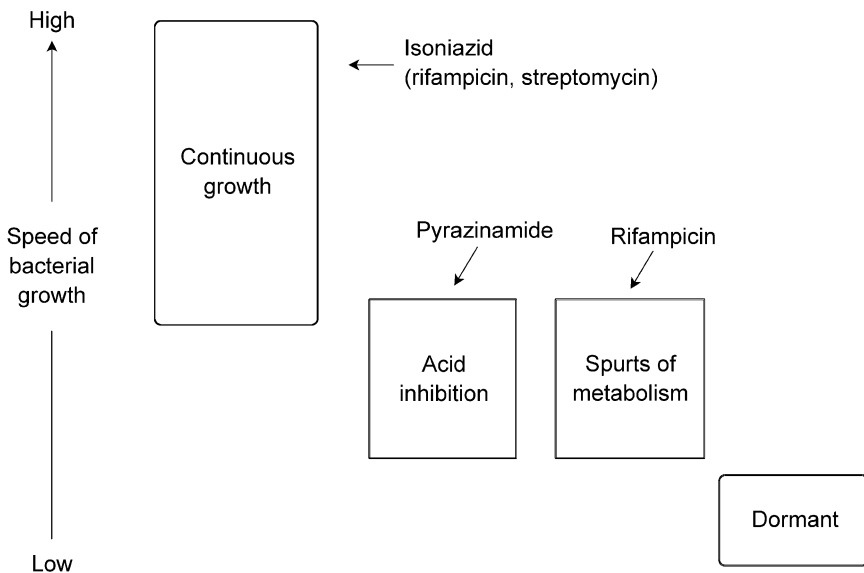


Figure 3.1 Hypothesis: Specific populations of the bacterial population in certain lesions are killed by different drugs. (Adapted from Mitchison, Treatment of tuberculosis, page 93.)

Basic concepts of resistance

What is resistance?

Antimicrobial agents are drugs that are used to kill or suppress the replication of microorganisms that infect human hosts. Antibiotics that are efficacious on one organism may not be efficacious on another, or may have reduced efficacy due to various factors. Similarly, there are different types of TB resistance including natural resistance, primary resistance, acquired resistance, combined resistance, resistance among new patients, resistance among previously treated patients, mono-resistance, poly-resistance, multi-drug resistance and extensive drug resistance.

What is natural resistance in tuberculosis?

M. tuberculosis has a highly hydrophobic cell wall and several potential resistance determinants, which make it naturally resistant to many antibiotics including penicillin and sulfonamides. These antibiotics cannot be used to treat TB. Although Z is an efficacious anti-TB drug, it has no effect on *M. bovis*, which is naturally resistant to it.

What are wild-type mutants in tuberculosis?

Whereas several bacterial species acquire resistance through mobile genetic elements (such as plasmids and transposons), resistance to anti-TB drugs is caused by spontaneous chromosomal mutation. In an untreated population, there are wild-type mutants that have spontaneous chromosomal mutations. David reported that the average mutation rate per bacterium per generation is 2.56×10^{-8} for H, 2.95×10^{-8} for streptomycin (S), 2.2×10^{-7} for E and 2.25×10^{-10} for R. Alangaden and colleagues reported that fluoroquinolone (FQ)-resistant mutants appeared at frequencies of 2×10^{-6} to 1×10^{-8} . Spontaneous chromosomal mutations that confer resistance to each drug are independent; it was therefore assumed that the risk of a wild-type mutant that is resistant to two drugs is the product of the risk related to each of the two drugs (10^{-18} to both H and R per bacterium per generation).

The prevalence of mutants is related to mutation rates and the size of the bacterial population. In larger bacterial populations, the probability that resistant mutants are present is higher. The size of the population of *M. tuberculosis* is estimated to be of the order of 10^7 – 10^9 in a cavity and 10^2 – 10^4 in caseous foci. In general, the bacillary population in smear-positive pulmonary TB is larger than in smear-negative pulmonary TB and extra-pulmonary TB. Typically, the prevalence of wild-type resistant mutants in an untreated *M. tuberculosis* population is very small. David estimated the prevalence of mutants at 3.5×10^{-6} for H (0.2 ug/ml), 3.8×10^{-6} for S (2.0 ug/ml), 3.1×10^{-8} for R (1.0 ug/ml) and 0.5×10^{-4} for E (2.0 ug/ml).

What is acquired resistance in tuberculosis?

The emergence of acquired resistance involves a process of selection in an environment of drugs that favours replication of drug-resistant mutants. An anti-TB drug kills or suppresses replication of susceptible bacilli but allows drug-resistant mutants to replicate. Selection pressure imposed by an anti-TB drug on a population of *M. tuberculosis* results in a decline of drug-susceptible bacilli and advantageous reproduction of drug-resistant mutants, which is known as the 'fall and rise phenomenon'. Consequently, drug-resistant mutants may outnumber drug-susceptible bacilli and become the dominant bacilli. This is acquired resistance. As the size of the bacillary population is larger and the prevalence of mutants higher in cavitory lesions than caseous foci, the risk of selective multiplication of resistant mutants is higher in cavitory lesions; likewise, it is higher among smear-positive pulmonary TB patients than smear-negative pulmonary and extra-pulmonary TB patients.

Acquired resistance can be demonstrated if the drug susceptibility pattern of TB bacilli is determined before anti-TB treatment and repeated at a later point in treatment, and if genotyping of TB strains is available. *M. tuberculosis* that is susceptible to one drug prior to treatment but becomes resistant to that drug after treatment represents acquired resistance in most cases. However, reinfection with a resistant strain may result in the observation of different susceptibility patterns between pre-treatment and post-treatment strains. Acquired resistance can therefore be ascertained only if reinfection is excluded by genotyping of *M. tuberculosis* with results showing that post-treatment strains and pre-treatment strains are the same.

What is primary resistance in tuberculosis?

Primary resistance in TB refers to patients infected with *M. tuberculosis* that is resistant to anti-TB drugs from the outset, prior to anti-TB treatment. Patients in whom *M. tuberculosis* acquires drug resistance during anti-TB treatment may spread the drug-resistant tuberculosis in the community. Primary resistance is caused by the transmission of drug-resistant bacilli followed by the development of drug-resistant TB among those who are primarily infected with drug-resistant strains.

Definitions of drug resistance in tuberculosis

What is drug resistance among new tuberculosis patients?

Primary resistance and acquired resistance are theoretical constructs that may not be discernible if additional information is not available. In surveillance of drug-resistant TB, patients are categorised into new patients and

previously treated patients. New TB patients are those who have never been treated with anti-TB drugs or who were treated briefly (for a period of less than 1 month). Patients who have been treated with a standardised anti-TB regimen for less than 1 month are at low risk for development of acquired resistance. Therefore, it is likely that drug resistance among new patients represents primary resistance due to transmission. The proportion of new patients with drug-resistant TB in a population-based survey or surveillance is used as a measure of transmission of drug-resistant TB in a community. However, patients may not remember whether they have been previously treated with anti-TB drugs, or may not know that they were treated for TB (for instance, R and FQs can be used to treat other infectious diseases). Further, health-care workers may not take appropriate care when obtaining histories from previous TB patients. This may lead to a misclassification of previously treated TB cases as new TB patients. As the prevalence of drug resistance among previously treated cases is commonly higher than that among new TB patients, misclassification of previously treated cases as new cases may distort drug-resistant TB surveillance results by overestimating drug resistance among new patients.

What is drug resistance among previously treated tuberculosis patients?

Drug resistance among previously treated TB patients refers to the presence of drug-resistant *M. tuberculosis* in patients who have been treated with anti-TB drugs for 1 month or more. Drug resistance among previously treated TB patients has three potential sources, namely primary infection with resistant bacilli, acquisition of resistance during treatment and reinfection with resistant bacilli. As susceptibility testing is not routinely performed for new TB patients, patients who are primarily infected with resistant strains may not be identified at the initiation of TB treatment but found to be infected with drug-resistant strains in retreatment. As a previous history of TB does not guarantee full protection against reinfection, TB patients may be reinfected with resistant strains during or after treatment. Therefore, drug resistance among previously treated TB patients does not necessarily indicate acquired resistance. Though sources of resistance among previously treated cases vary, in most settings, previously treated cases have a higher prevalence of drug-resistant TB than new TB cases and are the target for case finding of multidrug-resistant TB (MDR-TB). As the prevalence of drug resistance among previously treated cases is commonly higher than that of new TB patients, misclassification of new cases as previously treated may underestimate the proportion of drug-resistant TB among previously treated patients. This type of misclassification is less likely to occur than misclassification of previously treated cases as new cases.

What is combined resistance?

Combined resistance refers to the proportion of drug resistance among all TB cases regardless of history of anti-TB treatment. The combined proportion of drug resistance among all cases enrolled in a survey does not take previous treatment into account. In several settings where history of TB treatment cannot be reliably obtained, combined resistance is reported. Combined resistance may roughly represent the overall burden of drug resistance among all TB cases in a community.

What is transient resistance?

Transient resistance is a phenomenon observed in patients who have multiple sputum samples collected at several time points during treatment. Drug-resistant bacilli may be seen in sputum from patients who have adequate response to treatment in a positive culture that consists of a small number of colonies (usually less than 5–10), which usually appears shortly before sputum conversion, especially when drug action is bacteriostatic. For example, in patients treated with a regimen consisting of H and p-aminosalicylic acid (PAS), H-susceptible strains are killed by H and H-resistant mutants by PAS. As H has high bactericidal activities, an H-susceptible strain will be rapidly killed. Because PAS is bacteriostatic, H-resistant mutants will die slowly and may slightly outnumber H-susceptible strains at certain points in time during treatment before sputum conversion. These resistant bacilli are transient and may not arise predominantly during treatment. Patients will eventually achieve sputum conversion without a change of the treatment regimen.

What are monodrug, polydrug, multidrug and extensive drug resistance?

Monodrug resistance is defined as resistance to one anti-TB drug, while polydrug resistance refers to resistance to two or more drugs. Multidrug resistance is a specific form of polydrug resistance defined as resistance to at least H and R. MDR-TB is difficult to manage; its treatment involves second-line anti-TB drugs (SLDs) that are more expensive and toxic than first-line drugs (FLDs). Extensively drug-resistant TB (XDR-TB) is a special form of MDR-TB defined as resistance to at least H and R with further resistance to an FQ and a second-line injectable agent (2LI—amikacin, kanamycin or capreomycin). In general, outcomes of XDR-TB are less favourable than for MDR-TB cases. Recently, the term ‘totally drug-resistant’ TB (TDR-TB) has been used by researchers to describe strains that are resistant to all TB drugs tested. As drug susceptibility testing (DST) may not be sufficiently accurate for several of the reserved drugs, and new drugs currently undergoing

clinical trials may prove effective against TDR strains, TDR-TB remains a theoretical concept of an unwanted outcome eventually arising out of inadequate management of drug-resistant TB.

Emerging drug resistance in *Mycobacterium tuberculosis*

How multidrug resistance emerges

To date, there has been no single chromosomal mutation found to cause resistance to two or more anti-TB drugs. Polydrug-resistant TB (including MDR-TB) is caused by sequential mutations in different genes. Susceptible TB bacilli develop resistance first to one drug (acquired resistance) and subsequently to another drug (amplification of resistance). This evolution involves multiple cycles of 'fall' (susceptible strains) and 'rise' (resistant strains) in tubercle bacilli. The first cycle includes a decline in susceptible bacilli and predominant multiplication of a strain resistant to one drug, and results in monodrug resistance. The second cycle occurs in the background of monodrug resistance and results in acquisition of resistance to another drug (amplification of resistance), while the third cycle in the background of resistance to two drugs leads to acquisition of resistance to the third drug. Therefore, resistance to multiple drugs takes time to develop and is the cumulative result of human errors. It is worth noting that Colijin and colleagues recently reported that the rate of spontaneous occurrence of MDR-TB may be much higher than previously expected. Because *M. tuberculosis* bacilli in an immunocompetent host are killed by immune response, a bacillary population observed in vivo likely has experienced more replication events than the same size of bacillary population in vitro without death. They estimated that the probability of the emergence of resistance to both H and R before anti-TB therapy ranges from 10^{-5} to 10^{-4} .

Emergence of resistance to a first drug

The size of the bacillary population is the largest and the probability of chromosomal mutations the highest in the subset of bacilli that multiply the fastest. In the current standard regimen of H, R, Z and E, H has the highest early bactericidal activity of the drugs and kills the majority of the subpopulation of rapidly replicating bacilli. Selection pressure imposed by H on a population of susceptible *M. tuberculosis* usually exceeds other first-line anti-TB drugs (Figure 3.1). When patients are administered a regimen of H, R, Z and E, the first drug to which *M. tuberculosis* becomes resistant is usually H. H has the highest ability to prevent resistance to companion drugs, followed by R. It is essential to pay attention to H-resistant TB because it is the precursor of MDR-TB. In the background of H resistance, resistance to R may

emerge, resulting in MDR-TB. Certain conditions may promote the emergence of R resistance prior to H resistance, resulting in R mono-resistance; examples include monotherapy with R, infection with HIV, use of rifampentine and inadequate dosage or poor quality of H.

Common mechanisms associated with the emergence of drug resistance in individuals

An inappropriate drug regimen, use of a lower-than-recommended dosage, inferior drug quality and poor adherence to treatment are commonly associated with the emergence of drug resistance in individual patients. Inappropriate regimens include exposure to (functional) monotherapy, continued administration of a failing regimen and inadequate modification of a failing regimen. Examples of monotherapy include the use of an FQ in the treatment of TB patients who are misdiagnosed with pneumonia and the administration of H preventive therapy in individuals with undiagnosed TB. Examples of functional monotherapy include the use of H and R in the treatment of patients with H-resistant TB. Continued administration of a failing regimen for a prolonged period may result in the emergence of resistance to one drug followed by amplification of resistance to another drug. For example, in a patient who has poor response to a regimen consisting of H, R and E, H resistance may emerge; if the patient continues H, R and E after the emergence of H resistance without proper modification of the regimen, resistance to R may develop. Inadequate modification of a failing regimen, such as adding a single drug to a failing regimen, may result in amplification of resistance to the newly added drug. Use of a lower-than-recommended dosage may result in inadequate serum concentration of drugs, and use of poor quality drugs may have the same effect as using a

Table 3.1 Grading of drugs for preventing the emergence of acquired resistance

<i>Activity</i>	<i>First-line drugs</i>	<i>Second-line drugs</i>
High	Isoniazid	Fluoroquinolones*
	Rifampicin	
	Streptomycin	Ethionamide
	Ethambutol	p-aminosalicylic acid
	Thiacetazone	Cycloserine
Low	Pyrazinamide	Capreomycin

Source: Adapted from Mitchison, Treatment of tuberculosis, page 92.

*Levofloxacin, moxifloxacin, gatifloxacin.

lower-than-recommended dosage. Poor adherence to treatment includes 1) selective intake of drugs of a treatment regimen and 2) irregular intake of a treatment regimen. Selective intake of one drug or another may result in functional monotherapy. With irregular intake of a treatment regimen, even if non-selective (such as in a fixed-dose combination formulation), drug resistance may still emerge.

Why irregular intake of fixed-dose combinations may result in drug resistance

In the article 'How drug resistance emerges as a result of poor compliance during short course chemotherapy for tuberculosis,' Mitchison proposed four theoretical mechanisms that may result in selective multiplication of drug-resistant mutants due to irregular intake of anti-TB drugs: 1) differences in bactericidal activity during initial killing, 2) monotherapy resulting in sterilisation of specific populations, 3) sub-inhibitory drug concentrations during regrowth, and 4) differences in post-antibiotic effects during regrowth. These mechanisms may change the ratio of the population size of susceptible and resistant bacilli in each cycle of irregular intake of drugs.

Genetic markers of resistance to anti-tuberculosis drugs

Genetic markers of resistance to isoniazid

H is a prodrug that requires the activation of the catalase-peroxidase enzyme (*katG*) of *M. tuberculosis* to generate reactive radicals (including reactive oxygen species such as superoxide, hydrogen peroxide and hydroxyl radical, nitric oxide and reactive organic species such as isonicotinic-acyl radical or anion) that attack multiple targets in *M. tuberculosis*. The primary target of H-reactive radicals is the *inhA* enzyme, which is involved in the elongation of fatty acids in mycolic acid synthesis. *M. tuberculosis* bacilli with *katG* mutation have reduced ability to activate the prodrug H, which then results in H resistance. Mutation in *katG* is the main mechanism of H resistance: *M. tuberculosis* bacilli with high-level resistance to H commonly lose the catalase and peroxidase enzyme encoded by *katG*, but low-level resistant strains may still possess catalase activity. The *katG* S315T mutation is the most common mutation among H-resistant strains. Resistance to H also occurs with mutations in *inhA*, which are less frequent than the *katG* mutation. Mutations in *inhA* usually result in low-level resistance to H, and also cross-resistance to ethionamide (Eth). The frequency of *katG* mutation in H-resistant strains ranges from 50% to 90%, and of *inhA* mutation from 4% to 83%. Therefore, molecular methods detecting *katG* mutation or *inhA* mutation may not be sufficiently sensitive for identification of H resistance.

Genetic markers of resistance to rifampicin

R is a broad-spectrum antibiotic that interferes with RNA synthesis by binding to the β subunit of RNA polymerase, thereby blocking elongation of the RNA chain. Most bacteria develop resistance to R via a mutation in a defined region of the RNA polymerase subunit β (*rpoB*). Mutations in the *rpoB* gene are associated with R resistance in *M. tuberculosis*, and are detected in a very high proportion of R-resistant strains in certain communities (95%). The most frequent mutation sites of the *rpoB* gene in R-resistant strains are in codons 531, 526 and 516. Mutations in *rpoB* generally result in high-level resistance to R and cross-resistance to all rifamycins. However, a small proportion of specific mutations (codons 511, 516, 518 and 522) are associated with low-level resistance to R and rifapentine but not rifabutin. Molecular methods for detecting *rpoB* mutation to identify resistance to R are commonly more sensitive than methods used for detecting *katG* mutation or *inhA* mutation to identify H resistance.

Genetic markers of resistance to pyrazinamide

Z is active against *M. tuberculosis* only in an acidic environment; its activity is enhanced under low-oxygen or anaerobic conditions. It is a prodrug that requires conversion by the pyrazinamidase/nicotinamidase enzyme (encoded by the *pncA* gene) of *M. tuberculosis* to its active form, pyrazinoic acid. The target of Z is related to membrane energy metabolism. Mutations in *pncA* are associated with Z resistance. Z-resistant *M. tuberculosis* strains lose pyrazinamidase/nicotinamidase activity and have reduced ability to activate Z. Mutations in *pncA* are found in most but not all Z-resistant *M. tuberculosis* strains (72%–97%). Z is active against *M. tuberculosis* but not *M. bovis*. Natural resistance to Z in *M. bovis* is due to a single point mutation of the *pncA* gene.

Genetic markers of resistance to ethambutol

E inhibits the biosynthesis of the cell wall in *M. tuberculosis* by inhibiting cell-wall polymerisation of arabinan, arabinogalactan and lipoarabinomannan. The target of E in *M. tuberculosis* is an enzyme involved in the synthesis of arabinogalactan, namely arabinosyltransferase, which is encoded by *embB*. Mutations in *embB* are associated with E resistance. The frequency of *embB* mutation in E-resistant strains ranges from 47% to 65%. A substantial proportion (35%) of *M. tuberculosis* with resistance to E does not have mutations in *embB*, suggesting as-yet-unidentified mechanisms related to E resistance.

Genetic markers of resistance to streptomycin

S inhibits protein synthesis in *M. tuberculosis* by binding to the 30S ribosomal subunit, resulting in misreading of the mRNA message during translation.

The site of action of S is the 30S subunit of the ribosome at the ribosomal protein S12 and the 16S rRNA. Mutations in the S12 protein encoded by the *rpsL* gene and 16S rRNA encoded by the *rrs* gene are associated with S resistance. Mutations in *rpsL* account for about 50% of S resistance and *rrs* mutations for 20%.

Genetic markers of resistance to kanamycin/amikacin/capreomycin

Kanamycin (Km) and amikacin (Am) are aminoglycosides that inhibit protein synthesis, and the site of action for both is 16S rRNA. Capreomycin (Cm) is a cyclic polypeptide that inhibits protein synthesis through 16S rRNA and 23S rRNA. Mutations at 16S rRNA (*rrs*) are associated with resistance to Km, Am and Cm, while mutation at the *tlyA* gene is associated with resistance to Cm. There are variable frequencies of cross-resistance between Km, Am and Cm depending on mutation sites. Strains that are resistant to S are usually still susceptible to Km, Am and Cm.

Genetic markers of resistance to fluoroquinolones

In *M. tuberculosis*, FQs act on DNA gyrase to inhibit reproduction of DNA. *M. tuberculosis* bacilli have *gyrA* and *gyrB* that encode A and B subunits, respectively. Mutation of *gyrA* is associated with FQ resistance. Mutation of *gyrB* is reported to be associated with FQ resistance but is relatively uncommon compared with *gyrA* mutation. The frequency of gyrase mutation in FQ-resistant strains ranges from 43% to 94%.

Transmissibility and reproductive fitness of resistant *Mycobacterium tuberculosis*

Transmissibility, or infectiousness, refers to the ability of an infectious pathogen to spread in the community. It is related to the concept of reproductive fitness, indicating the ability of infectious pathogens to survive, reproduce and generate secondary cases. It has been demonstrated that drug-resistant bacilli may have reduced virulence and transmissibility because mutations may affect gene function. Drug-resistant mutants have a survival advantage in the drug environment but reduced reproductive fitness in a drug-free environment compared with susceptible strains. The reduction in fitness of drug-resistant strains, termed the 'fitness cost', represents the cost that resistant mutants pay (not necessarily significant, as low-cost and no-cost mutations have been reported). Further, loss in reproductive fitness may be regained through a compensatory mutation. It has been shown that a common *katG* mutation (S315T) is associated with H resistance, but the virulence of the H-resistant bacilli is maintained. Likewise, R-resistant strains with *rpoB* S531L mutation may have no fitness defect. These resistant strains with no

fitness defect are commonly isolated from patients with DR-TB. A modelling exercise shows that even when the average relative fitness of an MDR strain is low, a small subpopulation of MDR strains with less reduction in reproductive fitness may eventually become the dominant bacilli and spread in the community. Reduction in reproductive fitness of resistant strains may not limit the spread of MDR-TB. Programmatic management of DR-TB must therefore aim for early diagnosis and a high cure rate.

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Building a tuberculosis programme that addresses drug resistance

Raimond Armengol

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- Minimum requirements for the diagnosis of DR-TB
 - At the health services
 - Outlying and intermediate laboratories
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-

The Stop TB Strategy includes operational care of drug-resistant tuberculosis (DR-TB) and is the reason that DR-TB surveillance, prevention, diagnosis and treatment are a basic part of the TB programme. As national tuberculosis programmes (NTPs) assume operational management of DR-TB, they face an enormous financial, organisational and inter-related network challenge, and above all the challenge of establishing sufficient credibility to make the NTP the leading entity for fighting TB. A national regulatory and oversight entity, the NTP delegates the execution of TB control activities and tasks to the various levels of the health system. If the health system is weak, anti-TB interventions will be un-

successful. In such situations, vertical and centralised interventions have been proposed to overcome operating system deficiencies. NTPs have seen scant commitment and participation under these circumstances. The first step for an NTP in confronting the DR-TB problem is to design a national advisory group to develop the necessary documentation and promote advocacy. Step two will be to prepare a national DR-TB operational care plan that includes recommendations for surveillance, prevention, diagnosis and treatment of DR-TB, beginning with a situational and structural analysis of the programme as well as an assessment of available human and financial resources, with accompanying budgets. Laboratory and laboratory network recommendations should be included in the plan. This plan will represent the programme's best available tools for advocacy and resource mobilisation. The third step will involve preparation of national DR-TB care guidelines, inclusive of a national records and information system. Step four will entail the design of the necessary operational research plans, and the fifth step will be to develop the annual or biannual operating plan in detail, including cost calculations. With an operating plan thus prepared and operating costs (whether developed through a rapid or detailed method, as explained below) that have been compared to the available budget, we will have the tools for mobilising national funds or funds from donors

such as the Global Fund. An essential aspect is obtaining sufficient trained human resources for DR-TB operational management implementation and expansion. To meet this challenge, it is essential to standardise operating procedures for DR-TB surveillance, prevention, diagnosis and treatment, including standardisation of recording and reporting systems. Training will need to be cascaded to lower levels of the health system in order to provide sufficient coverage in the shortest time possible. An important complement to proper training is supervision, with supervisors' primary job being to identify and solve technical or operating problems on the ground. Minimum infrastructure must be available. For instance, DR-TB diagnosis requires that some points of the laboratory network have the capacity to conduct necessary tests using internationally validated methods, including a national quality-assurance system for outlying laboratories performed by a national reference laboratory. Effective treatment requires trained staff and the capacity to ensure adherence and make home visits. Cost-free access to diagnosis and treatment services is fundamental to patient adherence.

Minimum requirements for the diagnosis of drug-resistant tuberculosis

A series of steps must be followed for the diagnosis of DR-TB. These steps are described in detail below.

At the health services

The first task is to identify patients who are suspected or at risk of DR-TB. The NTP should define a list of situations or conditions a patient must have or have had that point to the risk for DR-TB. Once a patient is identified as having one or more risk factors or belonging to a risk group, a decision must be made about the actions to be taken. Ordinarily, sputum samples are collected for microscopy, culture, typing and drug susceptibility testing (DST). Chest X-rays are an important consideration.

Obtaining good sputum samples requires instructing patients, ensuring their cooperation and having a suitable private space where they can collect the sample. If a sample is taken at the patient's home, the patient must also be properly informed about infection control. Containers or vials are required for collection of the sputum along with laboratory service requisition forms. Once sputum sample containers pre-labelled with the patient's information are collected, they must be delivered to the laboratory or appropriately packed and posted to the designated lab. When this is completed, a decision must be made on the actions to be taken while awaiting results, as described below. Interventions will be administered based on DST results. If needed, the patient will be referred to another level of the health system. The health service must be prepared to seek out the patient if he/she does

not return to learn the results; this is a common situation, particularly if there is a significant delay between the collection of the sample and receipt of the results. It is therefore essential to construct a proper laboratory network with excellent coordination to health services and to set up expeditious administrative procedures to shorten the time between when samples are obtained and results are received. These central and intermediate levels of health services play a very important role in this organisational structure.

Outlying and intermediate laboratories

It is crucial that outlying and intermediate laboratories have appropriate facilities with the ability to follow suitable bio-safety measures, an organised quality-assurance system (overseen by the national reference laboratory) and trained staff to perform assigned diagnostics at the corresponding level. This includes infrastructure to perform smear or cultures and, in some cases, first-line DST (at least for isoniazid [H] and rifampicin [R]) or at least access to a rapid diagnosis method like Xpert MTB/RIF.

National reference laboratory

This laboratory will be responsible for training personnel and supervising and providing technical assistance and quality control to intermediate labs. In turn, it will receive technical assistance and quality control from the corresponding supranational laboratory. In addition to performing microscopy and cultures, this laboratory is to conduct first-line (especially for H and R) and ideally second-line (fluoroquinolones [FQs] and injectables) DST, as well as *Mycobacterium tuberculosis* identification tests. The manipulation of cultures, i.e., identification and DST testing, entails a high risk of generating infectious aerosols, so infection control measures (bio-safety) must be closely monitored. All laboratories must observe the minimum bio-safety measures recommended for the types of tests they are conducting. It is generally believed that direct microscopy carries the lowest risk, sampling procedures for culture inoculation a moderate risk and manipulation of cultures a high risk.

The minimum requirements and facilities needed include:

- Receipt of samples: laboratory bench, running water, wash basin and electrical outlet.
- Microscopy section: because this activity has limited risk for generation of infectious aerosols, the preparation of the smear may be performed at a laboratory bench. Other needs include running water, a wash basin and a properly ventilated environment (6 to 12 air exchanges per hour recommended with unidirectional air flow, whether the ventilation is mechanical or natural). Facilities must have equipment for proper disposal of infectious materials.

Processing of sputum samples for the inoculation of cultures or molecular testing entails moderate risk of generating infectious aerosols during sample centrifugation and manipulation. Certain key recommendations must be considered. Below is a suggested checklist:

- ✓ Access to the area must be restricted
 - ✓ Surfaces must be impermeable and easy to clean
 - ✓ Air must not re-circulate towards other areas and there must be unidirectional airflow via either passive or mechanical ventilation
 - ✓ Windows must be kept closed
 - ✓ All work must be done inside a certified biological safety cabinet
 - ✓ There must be methods and equipment for proper disposal of infectious materials.
- Cultures section: laboratory bench, running water, wash basin, certified biological safety cabinet, centrifuge, electrical outlet and ideally an MGIT 960 unit (mycobacterial detection system). The environment will preferably have negative pressure, with air flowing unidirectionally away from the laboratory.
 - Sterilisation facilities: laboratory bench, running water, double sink, autoclave, electrical outlet.
 - Culture media processing section: laboratory bench, running water, sink, coagulator, certified biological safety cabinet, electrical outlet.
 - Refrigerator or cold room (+4°C): electrical outlets, refrigerators or cold room with temperature indicator and shelving.
 - Incubator or incubation room (+37°C): temperature control, temperature recorder connected to a printer, shelving.
 - Warehouse with shelving.

Good organisation and coordination between the health service and laboratories is indispensable for efficient and timely transport of samples and delivery of results for diagnosis and patient follow-up.

Minimum requirements for the treatment of patients with drug-resistant tuberculosis

The treatment of DR-TB patients can be organised into different modalities or combinations thereof. Outpatient treatment with daily supervised administration of medications is usually adequate and may be conducted through a health service or by a promoter or trained volunteer in the patient's home. This treatment modality requires proper training and supervision of local staff, promoters and/or volunteers.

Inpatient treatment is obviously the most costly modality. Hospitalisation is usually not required over the entire drug administration period, but treatment is initially performed on hospitalised patients and then continued on an outpatient basis. Hospitalisation is also indicated when there is a complication, a very advanced illness or socioeconomic problems that do not allow for initial treatment on an outpatient basis. The duration will depend on the solution adopted for the problem that caused the hospitalisation.

Requirements for outpatient treatment include:

- Staff trained in the care of DR-TB patients at different levels of the health-care system.
- A suitable environment (i.e., lighting, space, equipment and adequate on-site infection control) for supervised patient treatment and evaluation. The TB patient waiting area should be away from the general waiting room and have infection control measures in place.
- Availability of masks for patients and respirators for staff.
- Equipment needed for evaluation including scale with the ability to measure height, X-ray viewer, two tables (one for the patient taking medicines and the other for staff use), three chairs, filing cabinet, cabinet to securely store medications, other supplies and materials in daily use, stretcher, sharps container, waste receptacle, wash basin with paper and soap dispensers.
- Stock of first- and second-line anti-TB medications, depending on the treatment regimens used and number of patients to be treated.
- Medications to treat the most common adverse effects, including those specific to particular patients.
- Access to radiology services for chest X-rays.
- Bacteriology lab with microscopy and follow-up culture capabilities or an organised system for transporting samples from the health service to the lab.
- Clinical laboratory for pre-treatment assessment exams and periodic checkups, or an accessible health facility that provides these services.
- Access to medical specialists who can perform specific clinical evaluations on patients before and periodically during treatment including a chest physician (pulmonologist), psychiatrist, ENT specialist (ear, nose and throat), ophthalmologist, endocrinologist or internist and infectious disease specialist.
- Access to a family planning office, which can be a great help for the prevention of unwanted pregnancies in women of child-bearing age under treatment with second-line drugs (SLDs).

Cost of services and how to budget for them

The directly observed treatment, short-course (DOTS) strategy framework has been expanded in response to the complexity of managing DR-TB through the use of DOTS principles and components. The expanded DOTS-Plus framework includes: sustained policy commitment; a detection strategy for DR-TB cases including precise and timely diagnosis through culturing and DST with quality assurance; proper treatment strategies using SLDs under appropriate case management conditions; uninterrupted supply of quality-assured first-line drugs (FLDs) and SLDs; and a standardised recording and reporting system for DR-TB control. Each of the components listed involves more complex and costly interventions than those used for the control of drug-sensitive TB. It should be stressed, however, that the overall TB programme is strengthened when DR-TB treatment is also addressed.

Key terminology and economic concepts are important in the analysis of costs and cost-effectiveness. Cost analysis is based on estimated costs for a particular service, programme or intervention. It is useful to assess a programme's financial feasibility in the development of budgetary plans. The estimated costs of an intervention should be compared with the available budget. 'Cost reduction' analysis is used when comparing two or more strategies or interventions that are equally effective but are presumed to have different costs. In 'cost-effectiveness', we compare the application of alternative strategies associated with varied costs and efficacy. With cost-benefit analysis, we simultaneously refer to costs and the results associated with a health programme, service or intervention in monetary terms. It is indicative of the benefits of monetary investments related to improvements in health. QALY (quality-adjusted years of life) and DALY (disability-adjusted years of life) are generic measures of health outcomes that reflect the impact of health interventions or programmes on mortality and morbidity. As generic measures that combine both mortality and morbidity, they enable a comparison of the cost-effectiveness of health interventions directed at very different types of health problems.

It has been shown that treating DR-TB patients using the DOTS-Plus strategy and individualised drug systems may be feasible, relatively efficient and cost-effective in low- and middle-income countries (Philippines study, Tupasi et al.) despite the high necessary investment. For example, in the Philippines (2006), the average cost per treated patient was US\$3355, with US\$1557 going to the purchase of drugs. From the patients' perspective, the expense was US\$837. The mean cost for DALY gained by the DOTS-Plus project was US\$242 (range of US\$85 to US\$426).

Cost structure is influenced by the care model of the indicated treatment plan based on the prevalence of resistance to FLDs and SLDs. Increased

hospitalisation rates obviously make treatment more expensive. The WHO has developed a tool to help countries prepare plans and budgets for TB control at national and sub-national levels within the framework of the Global Plan and the Stop TB Strategy. These plans may be used to guide resource mobilisation. Based on an Excel spreadsheet, the tool contains all the principal components of the Stop TB Strategy, including those for DR-TB. Several links on the Excel sheet help users understand and use the tool effectively. This tool can be found at http://www.who.int/tb/dots/planning_budgeting_tool/en/index.html. For MDR-TB planning and care cost calculations, two exclusive methods may be selected. In the first, called 'detailed' analysis, users enter detailed data on all activities to be performed. The second, or 'fast' method, is based on four previous MDR-TB cost and cost-effectiveness study pilot projects in four countries: Russia (Tomsk), Estonia, the Philippines and Peru. These costs are shown in Table 4.1.

In the table, we see the cost differences for each of the countries, including those where medications and hospitalisation play an important role. Upon completion of planning and cost calculations, whether through the fast or detailed method, a comparison of the results to available budgets yields the information necessary for the mobilisation of funds at the national level or through donors, i.e., the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM).

Table 4.1 Estimated cost for treatment of one patient with MDR-TB in four countries

	<i>Unit cost in US\$ per MDR-TB patient treated</i>			
	<i>Peru</i>	<i>Philippines</i>	<i>Russia</i>	<i>Estonia</i>
SLDs	2898	2898	4 573	4 573
Hospitalisation	0	135	4 109	5 523
Treatment supervision visits (DOT)	666	146	950	1 096
Smears, cultures, DST, X-rays	135	266	342	386
MDR-TB training	77	324	371	158
Data and programme management	352	896	990	756
Food packages	512	0	160	0
Adverse reactions	24	216	0	15
Other	<u>280</u>	<u>279</u>	<u>1 195</u>	<u>375</u>
Total cost to treat one MDR-TB patient	4944	5160	12 690	12 882

Source: World Health Organization, Planning and Budgeting Tool for TB Control (2010).

Training and supervision in drug-resistant tuberculosis patient management

Training

As MDR-TB operational management expands, the challenges grow for human resource development. These challenges must be addressed and resolved in order to successfully continue programmatic expansion. Some examples include ensuring:

- The availability and retention of staff. It may be necessary to hire additional staff with appropriate expertise to manage programme activities at the central and other levels. Central management must estimate staff requirements for implementation and expansion of MDR-TB operational management using realistic projections based on a task analysis, review of job descriptions and estimation of the workload for staff involved in specific activities.
- That staff has the required knowledge, skills, attitudes and motivation.
- That the necessary task performance support is available.

If these challenges are to be met, it is essential that operating procedures for MDR-TB surveillance, prevention, diagnosis and treatment be standardised, including recording and reporting systems, and that staff then be trained in these standardised procedures. Depending on their level in the health structure and assignments, staff will thus learn to detect and treat DR-TB cases, manage FLD and SLD treatments, teach patients about DR-TB, monitor treatment progress and results, supervise promoters/volunteers and collect follow-up data on detection and case treatment activities for the health units. To prepare human resources development plans for implementation and expansion of DR-TB operational management, certain steps should be followed:

- Assignment of a point person in charge of DR-TB in the NTP or coordination with the respective administrative office at the ministry of health.
- Creation of a national group of trainers.
- Organisation of regional and/or district teams for DR-TB management and training.
- Assessment of staff training needs.
 - Define responsibilities and tasks to be performed at each system level and develop training materials.
 - Assign the specified tasks to each category of personnel and estimate the time required for task completion.

- Estimate the necessary number of staff per category.
- Assess the human resources currently available by level and identify any gaps and resulting training needs.
- Preparation of the training plan, considering two possibilities:
 - Clinical training and in-service staff management, which may or may not be performed in coordination with other programmes, institutions or departments that conduct in-service training.
 - New hire orientation.
- Development of training programmes that consider job descriptions and task analysis with accompanying course objectives based on the task analyses and job descriptions.
- Training of health unit staff.
- Training of hospital staff involved in DR-TB care.
- In development of training programmes, consider evaluations during and at the end of courses and other follow-up assessments.

Supervision

Direct supervision is a reciprocal, permanent, regular and planned educational process accomplished through direct contact with the health staff. Its purpose is to increase efficiency and accuracy. The supervisory process is an extension of training and is meant to increase knowledge, perfect skills, improve attitudes and strengthen staff motivation. Monitoring or follow-up, also known as indirect supervision, is a complement to direct supervision aimed at tracking programme development to verify that all scheduled activities are carried out with the quality expected. This can be accomplished through direct contact with health workers or through the evaluation of periodic reports.

The supervisor's primary job is to identify and resolve technical or operating problems on the ground. Supervision is organised and carried out at specified levels. For example, the local level is supervised by the district level, the district level by the intermediate level and the intermediate level by the central level. Supervision requires the following:

- A platform of technical norms and standard operating procedures and scheduling that quantitatively and qualitatively determine the activities to be performed at each level.
- Trained supervisors with sound technical and operating knowledge.
- Financing.
- Availability of transportation.
- A realistic timeline.

Framework for effective drug-resistant tuberculosis control: the Green Light Committee and other international alliances

In 2000, the WHO organised an initiative called the Green Light Committee (GLC; <http://www.who.int/tb/challenges/mdr/greenlightcommittee/en/>) to facilitate proper treatment with quality-assured medications at affordable prices for DR-TB patients. It subsequently launched the Stop TB Strategy (<http://www.who.int/tb/strategy/en/>) in 2006 with the aim of achieving the Millennium Development Goals for TB. The six components of the strategy are: 1) proceed with quality DOTS expansion; 2) confront TB-HIV co-infection, MDR-TB and other challenges; 3) strengthen the health system; 4) involve all health providers in TB care; 5) empower those affected and the community; and 6) promote operational research. The second major component of the Stop TB Strategy includes comprehensive DR-TB schedule management by NTPs.

In 2007, faced with the emergence of extensively drug-resistant TB (XDR-TB), the WHO launched the Global MDR-TB and XDR-TB Response Plan 2007–2008, which redefined objectives and priority countries for MDR/XDR-TB control. Ministers from the 27 priority MDR-TB countries met in April 2009 in Beijing, China (http://www.who.int/tb_beijingmeeting/en/index.html) and endorsed a 'Call for Action'. During the 62nd World Health Assembly in May 2009, health ministers signed Resolution WHA62.15, aimed at MDR/XDR-TB prevention and control and urging WHO member states to provide universal access to diagnosis and treatment of MDR- and XDR-TB including: free care; strengthening of information systems; strengthening of laboratory network systems; improvement of DOTS quality and coverage; and other improvements. In response to the need for programmes and international agencies to improve MDR-TB care management and follow up on the resolution mandate, the Stop TB Partnership proposed a new global support framework to improve access to second-line, guaranteed-quality drugs and improved and increased technical assistance. The primary features of the new framework include:

- Focus on developing countries' ability to effectively manage the expansion of DR-TB operational management through NTPs.
- Provision of comprehensive, effective and efficient technical assistance regarding DR-TB.
- Direct access to the Global Drug Facility (GDF).
- Efforts to ensure that countries can meet their commitments to achieve universal access to DR-TB operational management efficiently and within the deadline.
- Establishment of the global Green Light Committee (gGLC), sponsored by the WHO in Geneva, to advise the WHO and other partners and propose global strategic guidelines.

- Establishment of regional Green Light Committees (rGLC), sponsored by and headquartered in the regional offices of the WHO or other Stop TB Partnership members, with the purpose of supervising the provision of regional technical assistance and reviewing national expansion plans for MDR-TB operational management.

Created in 2002, the GFATM, also known as the Global Fund, is a public-private partnership and international financing institution dedicated to collecting and disbursing additional resources to prevent and treat HIV/AIDS, TB and malaria. This association between governments, civil society, the private sector and affected communities represents an innovative focus for international health financing. It works in close collaboration with other bilateral and multilateral organisations. The GFATM has committed itself to reversing the MDR-TB epidemic. Global Fund subsidies support a series of activities that underpin action plans including social support for patients, community participation and strengthening of the monitoring system. For DR-TB, the Global Fund operates closely with regional and national WHO, GDF, GLC and TB Technical Assistance Mechanism (TBTEAM) offices.

TBTEAM, which is managed by the WHO Stop TB Department and whose secretariat is also hosted by it, was created in 2007 by the Stop TB Partnership. Through it, the Stop TB Partnership member network, including national programmes, national and international non-governmental organisations, financial members and national, regional and global WHO offices, works towards a coordinated and efficient approach to technical assistance for all forms of TB including DR-TB.

The International Union Against Tuberculosis and Lung Disease (The Union) works in over 70 countries, providing technical assistance for clinical and operational research, the organisation of international conferences and national and international TB and DR-TB courses and publications in scientific journals and of technical guidelines. The Union also monitors DR-TB projects and provides technical assistance for all aspects of DR-TB clinical and operational management in Africa, Asia, Latin America and the Middle East.

Doctors Without Borders (Médecins Sans Frontière, MSF) operates TB and DR-TB clinical-operational care projects in over 15 countries and in a wide variety of urban and rural communities and marginal areas, as well as in prisons and for refugees.

Partners in Health (PIH) provides health services to underprivileged populations in over 12 countries, including those affected by DR-TB.

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How drug resistance affects tuberculosis treatment outcome and monitoring parameters

Armand Van Deun, José A. Caminero

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- Effect of drug resistance on treatment outcome
 - FLDs and regimens
 - SLDs and regimens
 - Effect on treatment monitoring parameters
 - Smear, culture and other laboratory markers
 - Clinical and X-ray manifestations
-

The effect(s) of drug resistance on the outcome of TB treatment using standard regimens depend(s) on the type and number of drugs to which the strain is resistant versus the power of the treatment regimen. The predominant bactericidal and sterilising drug is rifampicin (R) for first-line treatment and the fluoroquinolones (FQs) for current second-line treatment; therefore, only resistance to these drugs will have a clear impact on conversion and out-

comes in terms of cure versus bacteriological failure or relapse. Isoniazid (H) and second-line injectable drugs (2LIs) can also be considered for first- and second-line treatment, respectively, but the impact of resistance to these drugs when used in an effective regimen is far less clear. This chapter addresses the impact of various types of drug resistance on treatment outcomes as well as the effect on sputum smear conversion. The limitations of other types of treatment monitoring parameters are also described.

Effect of drug resistance on treatment outcome

First-line drugs and regimens

Modern first-line short-course treatment regimens for TB use R for the full 6-month duration. R resistance leads to increased rates of failure or relapse, depending on sensitivity to other drugs in the regimen (H, ethambutol (E) and pyrazinamide (Z) and sometimes also streptomycin (S)). R mono-resistance will lead to apparent cure but with frequent relapse. The same happens regularly in patients with low-level R resistance combined with resistance to other drugs (multidrug-resistant TB, MDR-TB). Additional or higher-level resistance is eventually acquired with repeated first-line treatment, leading to failure. Higher levels of R resistance, combined with H resistance, lead to 'immediate' treatment failure regardless of the other drugs

in the regimen. Overall, using only first-line drugs (FLDs), MDR-TB has less than a 50% chance of relapse-free cure, which is barely better than the natural course of untreated TB. Of note, H resistance on its own has little impact on the outcome of R-throughout regimens, increasing the frequency of adverse bacteriological outcome by only a few percent. The influence of mono-resistance to E is not known. This type of resistance is very rare and drug susceptibility testing (DST) less accurate, hence strains considered to be mono-resistant may often represent DST error. Also the influence of Z susceptibility status is unclear. Its activity in the successive phases of treatment is poorly understood, and data at the population level are very thin. Considering the activity of Z and E, initial Z resistance would be expected to lead to increased relapse, but E mono-resistance might have no impact on adverse outcome.

Resistance to H combined with E or S increases the risk of failure and relapse to about 10% using R-throughout regimens. However, with 8-month regimens without R in continuation phase, these rates increase to approximately 40%. This is also the case for the H+S combination, even for regimens not relying on S, while the level of H resistance is higher. The on-average lower level of H mono-resistance may thus explain why this leads to only 10%–15% of failure/relapse in clinical trials and under programme conditions, even using the weakest of the short-course regimens, such as the 8-month regimen with thiacetazone (Th) and H in continuation phase. The H+E+S triple combination leads to failure of any first-line regimen in one third to one half of cases, due to acquisition of R resistance with the strain developing into true MDR-TB.

Table 5.1 illustrates the impact of initial FLD resistance on outcome of treatment, using either the weakest (8-month Th) or strongest (retreatment with intermittent third phase) of the standard first-line regimens in a population free from HIV but with on-average advanced disease at diagnosis.

Except for MDR-TB and combined resistance to H, E and S, the large majority of patients with initial drug resistance will thus still be cured using the standard first-line regimens. The risk of amplification of resistance with development of MDR-TB in failure cases is real but small, at least with the 8-month or daily R-throughout regimens. Moreover, because of poor growth of some MDR-TB strains, concomitant R resistance may be missed by conventional DST. This could explain why a multi-country report published by Espinal and colleagues found significantly more failures among retreatment patients with initially H-resistant, R-susceptible disease compared with new cases with the same initial resistance, but treated with the less powerful 6-month R-throughout regimens. It is therefore reasonable to assume that some patients who carry strains resistant to H or R, but not both, will fail or relapse with an unmodified first-line regimen. The first-line retreatment

Table 5.1 Impact of initial first-line drug resistance on outcome of treatment

<i>Regimen, initial resistance group</i>	<i>n</i>	<i>Failure %</i>	<i>Relapse %</i>	<i>Success without relapse %</i>
First-line regimen 2EHRZ/6HT				
Pan-susceptible	1328	1	1	87
H mono-resistant	68	6	4	72
H combinations except MDR	36	22	17	56
MDR	13	54	15	15
Retreatment regimen 2SEHRZ/1EHRZ/5(EHR)₃				
Pan-susceptible	656	1	2	80
H mono-resistant	237	3	2	84
H combinations except MDR	169	7	3	79
MDR	154	47	7	20

Source: Data courtesy of Damien Foundation Bangladesh.

regimen should be used, with (repeat) rapid R DST in case of delayed conversion or even a switch to the MDR regimen at any time in first-line treatment, when clinical conditions seem to justify this. The alternative recommended in some other guidelines, i.e., replacing H by an FQ, would create pre-XDR (extensively drug-resistant) strains out of MDR strains that are difficult to grow and were misclassified as H+E-, H+S- or H+E+S-resistant. On the population level, this is far worse than allowing some failures and relapses, even if some of those will fail with acquired MDR-TB. The MDR-TB regimen recommended in these Guidelines will give excellent results at reasonable cost and risk for proven MDR and pre-MDR (i.e., R mono-resistance, H+E+S resistance) alike. With other resistance profiles, the standard first-line regimens without addition or switch to second-line drugs (SLDs) should be used first. The rare unfortunate cases who fail due to acquired R resistance will then still be fully curable with the recommended MDR regimen.

Second-line drugs and regimens

Even fewer data exist regarding the impact of initial second-line resistance on standard MDR-TB treatment regimens. With regimens including the later-generation FQs (gatifloxacin or moxifloxacin), FQ resistance seems to be most important. Even so, only about 10% of those with initial FQ resistance have failed or relapsed from the short regimen for 'new' MDR-TB patients

proposed in these Guidelines, using the most powerful FQs (at high dose to overcome low-level resistance). The initial level of FQ resistance was higher in these failure/relapse cases or, very rarely, high-level FQ resistance developed from initial low-level resistance due to insufficient protection by the other drugs in the regimen. 2LIs appear to be the most important of the SLDs that protect the FQ with a high risk of adverse outcome in XDR. Concomitant resistance to the first-line drug Z increases the risk of adverse outcome by about 20%.

Resistance to thioamides (ethionamide and prothionamide) in strains from patients who have never used these drugs will often be caused by cross-resistance with H, due to the *inhA* mutation. In strains that have not also acquired further H resistance due to a *katG* mutation, the level of resistance to H remains low. Resistance to thioamides does not matter in these cases if the recommended regimen, which always includes H at a moderately high dose, is used. Overall, thioamide resistance has a minimal impact on the outcome of the regimen. The remaining SLDs (p-aminosalicylate and cycloserine) have little activity and are valuable as companion drugs only. Resistance to these drugs will only matter when there is already some resistance to the FQs or other companion drugs, and possibly with weaker regimens.

Effect on treatment monitoring parameters

Smear, culture and other laboratory markers

In national tuberculosis programmes (NTPs), treatment progress is monitored by periodic sputum acid-fast bacillus (AFB) smears obtained at the end of the intensive phase, mid- and end-treatment. From the fifth month onwards, a positive smear is considered sufficient evidence of treatment failure. The limitations of using a simple AFB smear to define failure are discussed in Chapter 7.

There is confusion regarding the meaning of positive smears at the end of the intensive phase. Sputum smear conversion depends mainly on the extent of disease (cavities) and bacillary load at start of treatment, and much less so on regularity of drug intake (or quality of directly observed treatment, DOT) and drug resistance. Minor irregularity, poor DOT and resistance to drugs other than the main drugs will not be clearly visible as delayed conversion in the individual patient. It is also important to remember that programme conversion rates depend on the quality of microscopy services. The influence of initial drug resistance on smear conversion is shown in Table 5.2. Only MDR-TB clearly delays smear conversion during standard first-line treatment, even with the most powerful intensive phase Category 2 treatment. These data come from a setting with excellent microscopy services and generally advanced disease at start of treatment, often with

Table 5.2 Influence of initial drug resistance on smear conversion

	<i>n</i>	<i>AFB-negative, % of total examined at 2 months</i>
Initial resistance group at start of 2EHRZ/6HT regimen		
Pan-susceptible	1201	82
H combinations except MDR	95	81
MDR	11	27
Initial resistance group at start of 2SEHRZ/1EHRZ/5(EHR) ₃ regimen		
Pan-susceptible	460	90
H combinations except MDR	300	89
MDR	147	39

Source: Data courtesy of Damien Foundation Bangladesh.

prolonged excretion of dead bacilli. It is conceivable that there would be a difference between pan-susceptible and H-resistant non-MDR with less extensive disease or when monitoring by culture.

On the other hand, the predictive value of delayed smear conversion for MDR-TB is poor, particularly early on in first-line treatment and when prevalence among new cases is low. Smear grading and its evolution could be taken into account to improve this, but even so, confusion with dead bacilli and non-adherence would make further tests indispensable, as described in Chapter 7. The smear's predictive value improves with increasing quantification, duration of previous treatment and particularly with increasing prevalence of MDR-TB. Figure 5.1 shows the predictive value of quantified sputum smears at 3 months of first-line retreatment. Over 85% of the failures represent MDR-TB.

In principle, culture is a better parameter for treatment monitoring, but its requirements are too demanding for generalised use by NTPs. Moreover, with referred sputum samples, the results of these often paucibacillary specimens become less reliable and delays would reduce their usefulness.

With solid media and drug-susceptible but extensive disease, culture conversion often precedes smear conversion, as shown in Figure 5.2. Delayed culture conversion occurs with drug resistance but also with extensive disease at start, in which case it is predictive of drug-susceptible relapse. With serious drug resistance, the culture may never convert, contrary to the smear, or may revert to positive sooner than a smear. However, taking into account the delay in obtaining the results, this advantage may not weigh heavily under field conditions.

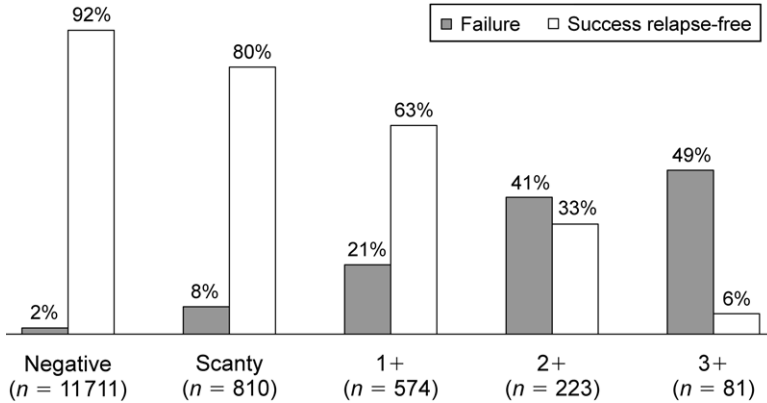


Figure 5.1 Outcome of standard first-line retreatment regimen based on quantified AFB smear at 3 months. (Data from Damien Foundation Bangladesh cohort, 1994–2007.)

Better laboratory markers for treatment monitoring have not yet been identified. Molecular techniques are currently not recommended for this purpose, because these tests may continue to yield positive results for many months with favourable evolution, amplifying the genetic material from dead TB bacilli. Further developments are expected in this field. Also, vital staining techniques seem to offer good prospects for treatment follow-up, though they can only differentiate live from dead bacilli, without indicating drug resistance.

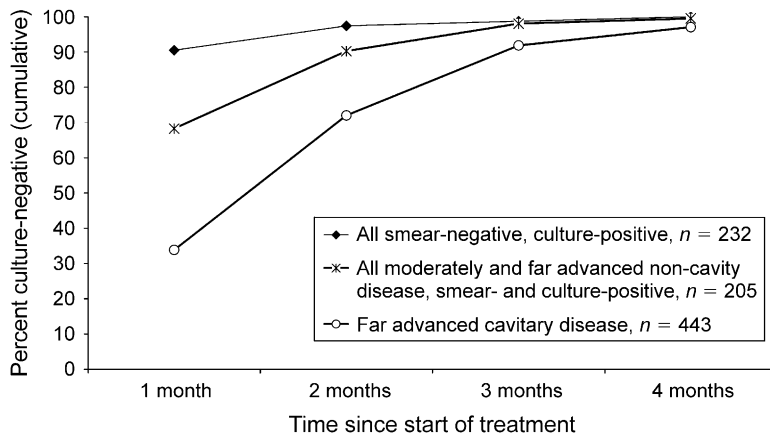


Figure 5.2 Culture conversion in initially culture-positive pulmonary tuberculosis, by type and severity of disease. (Data from Damien Foundation Bangladesh cohort, 1994–2007.)

Clinical and X-ray manifestations

Relying on clinical and X-ray manifestations has many limitations for the diagnosis of patients suspected of drug-resistant TB (DR-TB) because there are no symptoms or radiological findings differentiating susceptible from resistant TB. Also, prognosis and response to treatment cannot be decisively assessed through radiographic examination, because lesion regression may require 3 to 9 months. Although clinical manifestations and X-ray findings are very sensitive for screening TB suspects, they are nonspecific, particularly when it comes to the suspicion of DR-TB. For follow-up of patients with TB, there are no specific symptoms or radiological findings suggesting failure due to drug resistance, only lack of improvement compared with previous clinical and X-ray film manifestations. Other complications frequently associated with TB (bronchiectasis, respiratory infections, etc.) could also be responsible for this lack of improvement. As such, lack of improvement must be seen merely as arousing suspicion of DR-TB and supporting a request for DST. A diagnosis of DR-TB based only on clinical and radiological criteria should never be accepted, even if there is no improvement after several months of treatment.

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High-risk groups for drug-resistant tuberculosis

Arnaud Trébuçq

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- Case finding and prioritisation of interventions
 - Classification of MDR-TB risk by type of patient
 - Other risk factors
 - Risk factors for XDR-TB
 - Failures, bacteriological relapses, defaulters and the dangers of poor adherence
-

For practical purposes, drug resistance in TB microorganisms can be divided into resistance in patients who have never previously been treated for TB for as much as 1 month (new patients) and resistance in patients who have previously been treated for TB for at least 1 month (previously treated patients). In new patients, resistance occurs when a patient develops TB after being infected by another patient who has resistant microorganisms. In previously

treated patients, resistance may have developed during the previous course of treatment due to incorrect treatment. The highest risk groups for multidrug-resistant tuberculosis (MDR-TB) are previously treated patients, and in hierarchical order, 'retreatment with first-line drug failures' and 'initial treatment failures', followed by 'relapse cases' and 'treatment after default cases'. The level of risk in each category of patients varies widely from one setting to another, highlighting the importance of a good surveillance system for measurement of risk in subpopulations. TB patients who are in close contact with an already known MDR case constitute another important high-risk group.

The mechanisms of resistance in TB were reviewed in Chapter 3. Large populations of TB microorganisms always contain some microorganisms that have spontaneously mutated to become resistant to a drug. Consequently, treatment with a single drug in a patient with a large population of microorganisms kills the microorganisms that are susceptible to the drug, but allows those that are spontaneously resistant to the drug to multiply. When the microorganisms in a patient are resistant to all but one of the drugs received, the treatment has the same effect as when a single drug is given alone. Resistance to drugs becomes clinically important when the patient has disease caused by a whole population of microorganisms that are resistant to the drugs essential for treatment.

Case finding and prioritisation of interventions

Resistance always begins as a man-made problem, as it is the result of inadequate treatment somewhere along the chain of transmission: prescription

error, shortages of specific anti-TB drugs at the health centre level or incomplete and/or irregular intake of the drugs by the patient. In new patients, resistance occurs when a patient develops TB after being infected by another patient with resistant microorganisms. In previously treated patients, resistance may have developed during the previous course of treatment, for example, treatment with a single drug in patients with smear-positive pulmonary TB (sometimes referred to as monotherapy), or administration of powerful drugs to a patient harbouring TB microorganisms that are resistant to all but one of the drugs administered. For some patients, initial resistance is present from the start, but as systematic drug susceptibility testing (DST) is neither recommended nor possible in the majority of settings, the initial susceptibility of the patient strain is usually unknown: resistance is discovered when a patient fails treatment or returns for retreatment. This classification is interesting as it easily identifies high-risk groups. Because the regimen for MDR-TB patients must be different from those for non-MDR-TB patients, it is important that they be identified as soon as possible and offered the treatment most likely to rapidly sterilise their sputum (to avoid dissemination) and ensure definitive cure. Identification of high-risk populations for drug-resistant tuberculosis, especially MDR-TB, is a key issue for guiding investigations in resource-constrained environments (Table 6.1).

Classification of multidrug-resistant tuberculosis risk by type of patient

Studies in all countries have shown that previously treated patients have a much higher risk of harbouring MDR bacilli (or any resistance) than new patients. Based on aggregated data from several surveys around the world, the prevalence of MDR-TB is <3% among new patients and >15% for previously treated patients. National tuberculosis programmes (NTPs) must concentrate their efforts on these previously treated patients to detect MDR cases.

Previously treated patients

Whenever possible, every TB patient identified as previously treated should undergo DST against rifampicin (R) and isoniazid (H) as soon as the TB

Table 6.1 Hierarchical order of high-risk populations for multidrug-resistant tuberculosis

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- 1 Failure of FLD retreatment TB cases
 - 2 New TB patients living in contact with already known MDR-TB cases
 - 3 Failure of FLD treatment for new TB cases
 - 4 Relapse and return after default cases
-

diagnosis is made. Patients who have been treated previously for TB according to the criteria outlined above can be divided into four subcategories:

- 1 *Initial treatment failure* refers to a patient who, while on treatment for the first time with an R-containing regimen (Category 1), is smear-positive at 5 months or later during the course of treatment.
- 2 *Retreatment failure* refers to a patient who, while on the retreatment regimen with first-line drugs (FLDs, Category 2), is still smear-positive at the end of the retreatment regimen.
- 3 *A relapse case* is one where a previously treated patient who was declared cured or completed treatment becomes sputum smear-positive again.
- 4 *Treatment after default* refers to a case where a patient who had been on treatment for 1 month or longer returns to the health service sputum smear-positive after having interrupted treatment for 2 or more months.

The highest risk group for MDR is *retreatment failures*, with MDR rates frequently exceeding 85%. When the regularity of patient drug intake is monitored during the retreatment regimen, MDR treatment can sometimes be initiated before DST results are available. The second highest risk group is usually *initial treatment failures*. However, rates vary widely from one country to the next, ranging from 0% in Malawi to 22% in Benin, and as high as 88% in Peru. These variations are related to many factors: quality of directly observed treatment, short-course (DOTS), initial MDR-TB rates, initial H resistance rates, whether the regimen is intermittent or daily, extent of the disease, etc. Typically, when the initial MDR-TB rate is higher, there is a higher rate of MDR-TB after failure. Nevertheless, there are frequently circumstances in the field that result in operational failure (smear-positive at 5 months or later) in fully susceptible patients.

The prevalence of MDR among *relapse* and *treatment after default* cases also varies greatly according to setting and rates are usually fairly similar, but not always: 32% for the two categories of patients from aggregate data from 10 countries, with respective rates of 13% and 19% in Taiwan and 4% and 12% in Benin. Because the risk in each category of patients varies widely from one setting to another, it is important to have a good surveillance system capable of measuring the level of risk in each subpopulation.

New patients

Except in Russia, the former Soviet Union republics and some parts of China, the MDR rate among new cases is low, usually less than 2%–3%. However, the household contacts of MDR-TB cases deserve particular attention. Active

TB cases among contacts are not so common, but these individuals are at high risk of having MDR bacilli themselves, with risk rates often exceeding 80%. For a new TB patient, failure is declared after 5 months of treatment. In some countries, however, doctors are more comfortable looking for resistance before the fifth month. The problem is the cost-effectiveness of such strategies, because among patients who are still smear-positive at 2–3 months, much more sputum must be analysed than at month 5 to identify one MDR case.

Other risk factors

Human immunodeficiency virus

Limited information is available about the link between human immunodeficiency virus (HIV) and drug-resistant TB at the population level. In the United States and Europe, an association between HIV and MDR-TB has been reported in several studies, often related to nosocomial transmission. In sub-Saharan Africa, where HIV prevalence is very high, this association has not been documented. On the other hand, dramatic nosocomial micro-epidemics can sometimes occur in health institutions, and rigorous infection control is key to preventing such epidemics. Resistance to R alone (and not to H) is very uncommon; nevertheless, it seems that in high HIV settings, mono-resistance to R occurs more frequently.

Intermittent regimens

While there is no clear proof, intermittent treatment (twice or thrice weekly) is suspected in the development of both R resistance and MDR bacilli, probably related to irregular intake of drugs in regimens where each dose is important. This is likely to occur when an intermittent regimen is prescribed for the duration of treatment, even in the intensive phase.

Country of origin

In low-TB prevalence countries, country of birth is regularly collected as an indicator for TB surveillance. In countries with low TB prevalence, TB rates are much higher for non-native individuals than natives. The same holds true for MDR-TB in low-TB prevalence countries in that rates are much higher among foreign-born patients than the native-born, as seen, for example, in Western Europe and the United States.

Others

Some publications report an increased risk of MDR-TB in other circumstances, such as in patients treated in the private sector, patients from countries with a history of drug stock-outs or poor-quality drugs, patients

with other co-morbidities facilitating malabsorption, etc. If resources are available, culture and DST against FLDs should be performed.

Risk factors for extensively drug-resistant tuberculosis

Very few studies have been published on the risk factors for extensively drug-resistant TB (XDR-TB) because the number of cases is so limited to date. Insufficient case management of MDR-TB clearly plays a major role in XDR-TB development, and the cumulative duration of previous treatment with second-line drugs (SLDs) is identified as the main risk factor. XDR-TB occurs more frequently in settings where SLDs are widely available, especially fluoroquinolones and second-line injectables. Mortality rates are quite high in HIV-infected patients with concomitant nosocomial TB infection.

Failures, bacteriological relapses, defaulters and the dangers of poor adherence

Failures

Importantly, NTPs are considering designating treatment failure for all patients who undergo an R-containing regimen (Category 1) and are smear-positive at 5 months or later during the treatment. Note that this is an operational definition and does not always mean that a patient's organism is resistant to all the drugs administered. Specifically, there are two conditions, relatively frequent in the field, that are highly susceptible to failure: 1) conditions of very late conversion of sputum, usually because of extensive cavitary lesions that need more than 5 months for conversion (these will be smear-positive and culture-positive and the *Mycobacterium tuberculosis* will be completely susceptible); and 2) the frequently occurring situation of dead bacilli (these will be smear-positive and considered failures according to most NTPs, but they will be culture-negative). In many settings, these two circumstances may account for more than 50% of failures, especially when initial MDR-TB rates are low. Failures can also occur with bacilli that are totally susceptible to all anti-TB drugs when patients stop treatment too early or do not have good adherence to it. There exist cases, too, in which failure is assessed in patients infected by a mycobacterium other than *M. tuberculosis*, most of which are very resistant to FLDs and will thus be smear-positive at 5 months.

It is of utmost importance to consider the various circumstances described when citing treatment failure, especially for patients receiving an R-containing regimen (Category 1) for the first time. For this reason, these failures should undergo rapid molecular DST. Such situations occur much less frequently in retreatment failures who received FLDs because most have received two regimens with R, thereby increasing the probability of MDR-TB.

Relapses

Relapses may be true relapses or reinfection with a new bacillus, which is why we sometimes speak of 'recurrent' as opposed to relapse cases. A true relapse means that the same bacillus is the cause of both previous and new episodes of TB. This is due to the persistence of bacilli with very low rates of bacterial growth or no growth at all (dormant bacilli): if the bacilli have no biological activity, the anti-TB drugs cannot attack them. For some unknown reason, these bacilli can suddenly become active again and multiply. In this case, the susceptibility profile of the bacilli should be the same as the original occurrence if the correct treatment was prescribed and taken. In the case of reinfection, the susceptibility profile of the bacillus can be different from that of the first episode. To distinguish between relapse and reinfection, the genotype of the bacilli of each episode must be compared, which is usually not possible. Also, the distinction between failure and relapse is somewhat arbitrary. For instance, cases are deemed failures if bacilli are found in sputum the day before completion of treatment but classified as relapses (or 'recurrent' cases) if they are found the day after. Resistance rates among early relapse cases are probably closer to those of failure cases than cases of later relapse.

Defaulters and the dangers of poor adherence

DOT is key to preventing the selection of drug-resistant bacilli. Even when anti-TB drugs are combined in a fixed-dose combination tablet, irregularity in intake of these tablets or in the number of tablets taken can lead to the development of resistance: each drug has a different length of action during the bacterial inhibition or killing period, and during regrowth of the bacilli population. Therefore, ensuring treatment adherence is key to avoiding the selection of resistant bacilli.

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Laboratory diagnosis and treatment monitoring of drug-resistant tuberculosis

Armand Van Deun

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- Diagnosis
 - MDR-TB suspect screening
 - Referrals and transport of samples
 - Identification of organisms
 - Drug susceptibility testing
 - Treatment monitoring
-

This chapter begins by describing the diagnosis of drug resistance with an emphasis on strategies appropriate for low- and middle-income countries. It is not feasible to perform drug susceptibility testing (DST) for each new TB case; furthermore, among re-treatment cases, priorities may have to be set for reasons of cost-effectiveness as well as quality and reliability. Systematic DST of failure cases and relapses after first-line retreatment is the most cost-efficient, but screening by vital staining may be necessary to improve efficiency for failures, particularly for late converters from first treatment. Rifampicin (R), the fluoroquinolones (FQs) and sometimes also isoniazid (H) and second-line injectables (2LIs) are the main drugs to be tested. DST for other drugs is less reliable, does not clearly impact standardised treatment outcome and should be undertaken only for patients in need of an individualised regimen, i.e., those suspected of having extensively drug-resistant TB (XDR-TB). Sputum analysis is discussed in terms of the type of DST performed. This is easiest and safest when molecular methods are used, which are preferable for effective patient management. Because environmental mycobacteria regularly cause confusion with multidrug-resistant TB (MDR-TB), they always need to be distinguished from TB, and this is best accomplished using rapid molecular techniques. Although slow, conventional DST using Löwenstein-Jensen medium may be most accurate, the management of MDR-TB and XDR-TB relies on rapid DST for the main drugs with subsequent confirmation and possibly complete resistance profile determination using slow DST. The strengths and weaknesses of various rapid DST techniques are briefly described along with the parameters determining their selection. The second part of this chapter describes treatment monitoring in more detail. Other guidelines for drug-resistant TB (DR-TB) stress the importance of culture and DST for treatment monitoring. We describe the limitations of this approach, and suggest alternatives such as vital staining or molecular techniques. Lastly, various treatment response patterns and their interpretation are described.

Diagnosis

DR-TB can occur in new as well as retreatment cases, with any type of TB (pulmonary or extra-pulmonary, smear-positive or smear-negative). However, it is rarely feasible to perform DST for each and every patient. Nor would this be advisable, given the poor predictive value of resistance test results when resistance is rare (or the tests not highly specific), as is the case for second-line drugs (SLDs) in most of the world.

It should be noted that not all drug resistance is equally important. In regions with fewer resources, only the most serious types of resistance should be investigated, i.e., those carrying a poor prognosis using standard first- or second-line drug therapy. As discussed in Chapter 4, these are resistance to R (MDR-TB) and the FQs (XDR-TB). In some settings or for some patients, DST for H and 2LIs is useful, although on their own these drugs do not have a very clear impact on treatment outcome using powerful regimens. The first step will be screening and diagnosis for MDR-TB, because XDR-TB screening is most often indicated only among MDR-TB cases.

Multidrug-resistant tuberculosis suspect screening

As discussed in Chapter 6, proper suspect definitions and testing algorithms are needed for efficient and accurate detection of MDR- and XDR-TB. Only bacteriologically positive cases can be confirmed in the laboratory, and national tuberculosis programme (NTP) suspect definitions will usually have a positive acid-fast bacillus (AFB) smear as the starting point. If resources permit, all retreatment cases might have DST. Improved efficiency is often possible, not only leading to savings but also avoiding overload for the laboratories, thus improving quality and reliability. Based on experience and published results, not all types of smear-positive retreatment cases are equally rewarding to test:

- In good directly observed treatment, short-course (DOTS) programmes, failures after first-line retreatment regimen (Category 2) are 85%–90% MDR-TB.
- Relapses after the same retreatment regimen may represent MDR-TB in about 50% of cases, with drug-susceptible reinfection disease in the others. Depending on the area, there may also be many infections by other mycobacteria among these cases. With excellent DST, R mono-resistance or low-level R-resistant MDR is also less rare in this group (Damien Foundation Bangladesh, unpublished data).
- MDR-TB prevalence among failures after first treatment (Category 1) varies considerably, depending not only on TB control programme quality but also on the power of the regimen, the prevalence of MDR-TB versus extensive but drug-susceptible TB among new cases, micro-

scopy/culture quality and exact failure definition. In the average setting, the yield is estimated at around 50%, with lows of 10% and highs of 90% possible.

- Relapses after Category 1 include relatively few MDR-TB cases (around 10% in settings with low primary MDR-TB), and there will still be fewer in the group of returning defaulters of primo-treatment. With more prevalent primary MDR, or sufficient testing capacity, Category 1 relapses may nevertheless yield a good number of cases because they constitute the bulk of retreatment cases.
- Testing late converters by smear is often disappointing. Even more than with Category 1 failures, these positive smears may be due to prolonged excretion of dead or, less often, viable drug-susceptible bacilli, particularly with extensive disease; bacilli numbers may be small, with few surviving after transport and sputum decontamination. With dead bacilli, molecular methods also often fail due to fragmented genetic material. Except when MDR-TB prevalence is higher (and always for retreatment cases), testing all late Category 1 converters should be attempted only once the other groups are well covered and if sufficient capacity (lab, treatment) remains.
- Contacts of MDR-TB will usually also have MDR-TB when this condition is already prevalent and transmission has been ongoing for some time. When MDR-TB first starts to appear, almost all detected cases are secondary and only a few contacts will have MDR-TB because they will have been infected before the strain developed MDR.

Efficient detection of drug resistance will thus depend first and foremost on good AFB microscopy. In some settings, this creates problems for MDR-TB detection if smears for treatment monitoring are not sincerely examined or reported due to inappropriate insistence on conversion and cure targets. Even without drug resistance and in good DOTS programmes, about 10% of follow-up smears from initially smear-positive cases can be expected to show AFB. This proportion may even reach 25% at 2 months of treatment in some settings. Hot Ziehl-Neelsen or LED fluorescence microscopy are preferred as the most sensitive microscopy techniques, although they are also prone to detect dead AFB more often. This may explain why cultures (and molecular techniques) usually fail with samples from late converters or Category 1 failures, but not after Category 2. Measures may then be needed to limit unnecessary referrals and wasted resources at reference laboratories:

- Referrals at 3 months of treatment will be far more efficient, while only a minor fraction of those AFB-positive at 2 months will also be positive at 3 months, regardless of intensive phase extension; clinical deterioration with positive smears during treatment with

good adherence are always an exception, justifying referral at any time.

- The smear cut-off for definition of failure or MDR-TB suspects on Category 1 may be raised ten-fold from that used for diagnosis of new or relapse cases. Scanty results, for instance, would have to be confirmed by a clear-cut positive result on another sputum sample 1 month later. However, this practice may easily lead to confusion, or encourage a tendency to hide failures, and efficiency is lower because clearly positive, non-scanty results may also be due to dead bacilli.
- Screening with vital staining using fluorescein diacetate (FDA) has yielded good results in the Damien Foundation Bangladesh MDR-TB project. This simple, low-risk technique requires little in the way of equipment and materials and can be decentralised to intermediate-level laboratories. In settings with low-level primary MDR-TB and sensitive microscopy, its negative predictive value (i.e., excluding a positive culture, and especially excluding MDR-TB) routinely reaches 95%, with over 85% positive predictive value. Most useless cultures could thus be avoided. The few MDR-TB missed and in good condition can still be detected during Category 2 treatment.

Referrals and transport of samples

Referral of smear-positive suspects rather than sputum may be justified for higher risk groups if necessary for treatment start (patient preparation, intensive phase in hospital, etc.) or with decentralised screening (e.g., FDA vital staining). For laboratories, this guarantees the best possible specimens without dependence on fast or cold chain transport, and for patients it may considerably reduce delays in treatment initiation often caused by transport of specimens/transmission of results. Fast transport may be a problem when an entire population has to be reached for an indefinite time period. Possible solutions include:

- A transport preservative/mild decontaminant such as cetylpyridinium chloride (CPC 1%), on the condition that egg media are used for primary culture. Culture yield will remain satisfactory after delays up to 1 week at ambient temperature or even 1 month, provided that short NaOH decontamination is applied before inoculation.
- Molecular detection of resistance, as samples do not have to be viable for testing. For safety reasons, it is preferable to kill the bacilli before transport. This can be accomplished by boiling the specimen or using mycobactericidal disinfectants, which may be easier and leave bacillary DNA intact. Adding approximately 0.5 ml (or 10 drops) of liquefied sputum to 1.5 ml of 95% ethanol in a 2-ml cryovial has also produced good results.

- Decentralised primary culture, using simple methods (e.g., modified Kudoh) with referral of grown culture slopes or strains. This method requires considerable infrastructure and equipment, and may be feasible only in middle-income countries with a network of culture laboratories but more centralised DST. However, DST results from referred strains or culture slopes will often be delayed compared to referral of sputum because the DST laboratory will have to set up a subculture first to test the strains under the right conditions (growth phase, free of contamination).

Transport of sputum for culture requires sturdy, hermetically sealed and disposable containers. The most practical are the 50-ml sterile plastic conical tubes with screw caps (Falcon type) used for specimen decontamination and centrifugation. A small stock, possibly containing 5 ml of CPC solution, is made available by the reference laboratory to all intermediary level laboratories or supervisors responsible for referrals from specific areas. Single-use packing material is preferred over more sophisticated containers that need to be returned or pose disposal problems. National transport safety regulations should be followed, and they generally do not require special packing of sputum for domestic ground transport. Individual tubes are wrapped in a thick layer of absorbing paper and placed together in a strong plastic bag, sealed by heat or otherwise, then packed inside absorbing material in a strong outer cardboard box. Transport of grown cultures on Löwenstein-Jensen requires removal of culture water, failing which slopes may arrive completely spoiled.

Inactivated sputum for molecular testing does not require safety precautions for transport. Air transport regulations for TB cultures demand special safety packing, clear hazard labels and proper shipping documents, all of which can be very expensive. If growth from cultures is sent, a strong, hermetically sealed small vial should be used (e.g., cryovial). Experience has shown that the growth sent to reference laboratories is often partially contaminated. If a liquid culture medium is used for shipment, the TB strain will be overgrown and impossible to recover. Instead, growth should be sent in one or two drops of sterile water or in 0.5% CPC solution, or both.

Sputum for culture should preferably be collected before any treatment is started or after no more than 1 or 2 days of interruption for patients on treatment, failing which the drugs may inhibit the growth of 'not completely' resistant bacilli. A specimen found microscopically positive on the same day can still be referred.

Identification of organisms

AFB in sputum are not always *Mycobacterium tuberculosis*, but in high TB prevalence countries this is nearly always the case for new patients. Among

MDR suspects, confusion occurs because of the presence of other mycobacteria. This is because several species that tend to colonise old TB lesions and become opportunistic pathogens are also resistant to most first- and second-line anti-TB drugs. If not identified correctly, these patients will thus often be treated as MDR-TB, and may even be considered XDR-TB when they also fail this treatment. *M. tuberculosis* (complex) should thus be shown before DST is performed or results transmitted. This is easier to do today using the simple immune-chromatographic MPT64 antigen test from liquid or solid cultures or with the TB detection result provided simultaneously with commercial molecular rifampicin DST tests (Genotype LPA as well as Xpert MTB/RIF). Microcolony morphology (serpentine cording) has been proposed as sufficiently characteristic of *M. tuberculosis* complex, but experience shows that errors are frequent with a higher prevalence of non-TB mycobacteriosis. Another complication arises from the fact that these other mycobacteria often grow poorly on typical, solid media but much better in liquid media, particularly the MGIT (Mycobacteria Growth Indicator Tube) system.

The other mycobacteria in question come from the environment and may be found in 10%–20% of MDR suspects in areas with stagnant, polluted water but may be absent in dry desert areas. It is important that these suspects not be treated as MDR-TB, although they may show temporary improvement on such treatment, and it should be recalled that DST set up for TB may yield unreliable results with non-tuberculous mycobacteria (NTM). It is wise, in general, not to attempt any treatment, because of the usually unclear significance of their isolate, the meagre chances of success for expensive and toxic treatment, the lack of public health priority and the high risk of reinfection from the environment. NTPs should not consider such management to be their responsibility, particularly as long as MDR-TB is not under control. Appropriate management of NTM disease requires expert knowledge and additional resources, so referring these patients to specialist clinicians is in the former's best interest. The TB reference laboratory can provide assistance, for instance with exact species identification using a line probe or other molecular assay specific to this purpose.

Drug susceptibility testing

Methods and drugs to test, reliability of tests

DST methods can be divided into slow vs. rapid, conventional (or growth-based) vs. molecular (detection of resistance mutations) and direct (starting from the specimen) vs. indirect (starting from a pure subculture). All molecular techniques are rapid but indirect DST never is, and speed may be the most important criterion in classifying methods for MDR-TB management. Slow conventional methods are more reliable and perfect for drug resistance monitoring. The proportion method may be used most often, but

other recognised techniques (i.e., absolute concentration and resistance ratio methods) yield equivalent results. For the most difficult strains, the strong inoculum and minimal inhibitory concentration technique of the absolute concentration method may provide the clearest results. With these methods, agar media such as Middlebrook 7H10 or 7H11 are easier to prepare with high consistency of drug concentration (no heating required), but they are more costly and require additives with short shelf life, and growth of difficult strains is decreased, even when used with CO₂ enrichment as recommended. Löwenstein-Jensen egg-based medium is cheaper, ingredients are stable and easily procured, and it supports growth of all but exceptionally resistant strains. However, inspissations by heating must be very well controlled and evenly applied to all tubes. Rapid DST techniques are needed for efficient diagnosis and management of MDR-TB, but overall they are still less accurate than slow conventional methods.

Only molecular techniques are truly rapid, yielding results in a few hours or days. When a highly efficient, not very toxic and less expensive standard regimen is used, only diagnosis of R resistance is initially needed. If the patient is hospitalised for the initial phase of treatment, it is highly desirable to exclude XDR-TB as early as possible, but this is more difficult. In most settings where XDR-TB is still very rare, rapid tests to exclude XDR are mainly needed for patients who have previously received FQs and/or 2LIs for TB treatment. Systematic confirmation by slow conventional DST is generally recommended after the patient is already on MDR treatment.

It is true that in many settings, MDR-TB treatment can be started without proof of R resistance for Category 2 failures (and possibly also late Category 2 converters that are FDA-positive), a very high prevalence group. Importantly, this is not universally true, probably due to sloppy treatment observation: up to 50% of these cases have been reported to have non-MDR-TB in some settings. Infection or disease with other mycobacteria is another concern, as discussed above. On the other hand, knowledge of previous treatment regimens can give some indications regarding drugs that are likely still to work because they were never used on the patient. Resistant strains may circulate in the community, while cross-resistance with other drugs occurs as well. Constituting a regimen based on drugs previously administered will thus require good information regarding levels of primary drug resistance. There is a risk that valuable drugs will not be included because failure or relapse can occur due to resistance to the predominantly used drugs or due to non-adherence. This is even more true for Category 1 failures, which the WHO recently added to the clinical and smear indications justifying initiation of MDR-TB treatment in the absence of DST results.

Full DST covering all possible drugs may be required for treatment of XDR-TB, those previously treated with SLDs and settings with high levels

of resistance to the main SLDs. In most settings, however, the results will hardly change the management of a patient on first-time SLD treatment, and DST requirements should certainly not delay patient management. Among first-line drugs (FLDs), only R resistance determines the choice between FLD and SLD treatment. H resistance does not matter, as resistance levels are regularly low enough to be overcome by the drug typical doses in the short standard SLD regimen recommended in these Guidelines. On the other hand, the outcome of R-resistant/H-susceptible TB following treatment with FLDs is not good, peppered with relapses and, in the long term, development of MDR or death. DST for streptomycin (S) is not useful because it is never used in the recommended regimen and there is virtually no cross-resistance with 2LIs. Pyrazinamide (Z) and ethambutol (E) DST are difficult to perform correctly as there is not good agreement between different methods and resistance occurs less frequently with early detection. Due to its superb sterilising activity, Z is best included in any MDR regimen without the need to perform DST.

Reliability of DST for p-aminosalicylic acid (PAS), ethionamide, cycloserine (Cs) and thiacetazone is low and should only be performed to guide treatment of the most difficult cases because results may confuse more than help. DST for SLDs (or clofazimine, Cf) is of limited use in settings where resistance to these drugs is rare. This is always the case when they are not used to treat TB on a larger scale, i.e., in most low-income countries. In such circumstances, a resistant result will most often be wrong. Moreover, the short standard SLD regimen recommended here uses only the most valuable SLDs and, even with correct DST results, a switch to the remaining weak and toxic drugs may not improve outcomes. The exception is confirmed XDR-TB or failure of the recommended MDR regimen, because this requires individualised treatment with a limited number of still active drugs.

In such difficult cases, the range of tests performed should cover both amikacin and capreomycin, though not necessarily the weaker kanamycin, because of varying patterns of cross-resistance. It is also useful to perform DST for the FQs and possibly H using an absolute concentration method (minimum inhibitory concentration (MIC) determination). Considerably different levels of resistance exist, and MIC up to 8 µg/ml ofloxacin or 1 µg/ml of a fourth-generation FQ (moxifloxacin or gatifloxacin) will still be overcome using these powerful drugs with higher dosing. This is more important than testing weak companion drugs such as PAS or Cs.

DST for R is generally highly reliable, more so than for other drugs, but some resistant strains are very difficult to diagnose using DST based on growth. Most mutations in the *rpoB* gene conferring this resistance come at a fitness cost, though it is negligible for the most common and easily tested mutations. A more important loss of fitness causing growth problems is seen

with a wide range of other mutations that are each rare but may together make up 10%–20% of all mutated strains, particularly after first TB treatment. Routine rapid DST will regularly ‘miss’ this resistance, and call these strains R- or even pan-susceptible whereas careful testing may show that they are resistant to all FLDs (or even drugs used in XDR-TB). Doubts have been raised regarding the clinical importance of some of these mutations (e.g., 511Pro, 516Tyr and 533Pro) because their resistance level seems very low. However, using a strong inoculum with the strain in the exponential growth phase, their MIC may prove to be several times higher than the critical concentration defining resistance. Clinically, they also cause failure of treatment and, more frequently, repeated relapse after apparent cure with final poor prognosis secondary to increasing resistance. Further, despite reduced virulence, strains with these mutations were at the origin of the MDR- and XDR-TB outbreak in KwaZulu-Natal in 2006. Especially with such strains, molecular detection of R (and probably also FQ and 2LI) resistance is more reliable than conventional DST.

Rapid drug susceptibility testing methods

Molecular techniques

The reference molecular technique (DNA sequencing) can detect DNA mutations that result in resistance for any drug. However, the molecular mechanisms of resistance are well known only for only a few drugs. Furthermore, DNA sequencing is only an option for large referral laboratories or in industrialised countries. In practice, for low- and middle-income countries, currently available methods can only reliably detect R resistance. These are line probe assays (LPA) and Xpert MTB/RIF (Xpert). Both can be applied to growth from cultures and usually work for smear-positive sputum tests as well. The most widely used LPA kit (but not Xpert) also allows detection of H resistance and results report the gene involved, but its sensitivity is too low for use in early cases. The Xpert system simplifies molecular testing by fully integrating and automating the three processes (sample preparation, amplification and detection) required for real-time PCR-based molecular testing. Xpert fails less often than LPA with smear-negative sputa. Comparing the latest generation of both tests for detection of R resistance, Xpert may be more sensitive and no longer yield more false R-resistant results. Both tests contain a positive signal confirming the presence of *M. tuberculosis* DNA, but the differentiation between a partial test failure and presence of NTM is not reliable.

Molecular techniques are the best choice for diagnosis of MDR-TB with R resistance as its proxy. As described above regarding poorly growing strains, the gold standard technique, DNA sequencing of the *rpoB* gene, may be more accurate than phenotypic R DST in the average laboratory because

it misses less than 5% of resistance. Due to non-covered mutations or resistance based on mechanisms other than *rpoB*-gene point mutations, missed resistance may be a few percent higher with commercial tests such as LPA and Xpert. With the current versions of these commercial tests, false resistance is rare and is due to cross-contamination or silent mutations.

Molecular DST has other, even more important advantages. Commercial formulations demand far less infrastructure and equipment than most growth-based DST methods, mainly because techniques are safe and do not require a biohazard containment laboratory or difficult-to-certify safety cabinets. To enhance safety, samples can be 'killed' in the outlying regions prior to shipment, as described earlier, meaning that rapid or cold chain transport is not needed. The Xpert technique, in particular, is so simple that it can easily be set up and even decentralised. LPA has considerably higher requirements in terms of infrastructure, equipment and skilled staff, but its implementation has not posed major problems for start-up even in low-income countries. The main objections to molecular techniques are the relatively high (but falling) cost and the temperature-sensitivity of some equipment and supplies, although so far these have not proved to be major obstacles when there is a good selection of patients and drugs to be tested and in the absence of decentralisation beyond the intermediary service level.

LPA patterns characterised by the absence of wild-type bands should be interpreted as resistance, even without the appearance of a mutation band, provided the various control bands are sufficiently developed. Presence of NTM can be suspected on the MTBDR*plus* LPA strips, but confirmation and species identification requires running a different LPA. Another LPA, the MTBDR*sl*, is designed to detect resistance to FQs, 2LIs and E. Reported agreement with phenotypic DST has been poor for E and not quite satisfactory for the other drugs (70%–80% sensitivity at most). On the other hand, there is uncertainty regarding the clinical relevance of part of the phenotypic DST resistance results for these drugs. Until this is resolved, these techniques can at least be used to rapidly confirm (but not exclude) FQ and 2LI resistance.

Rapid methods dependent on growth or metabolism

Table 7.1 reviews the main parameters characterising the most applied and usually WHO-endorsed rapid DST techniques. Of note, a few of these are not recommended for direct DST and can thus not be considered truly rapid. This is the case for techniques depending on colourimetric detection because of the risk of error due to sometimes difficult-to-exclude contamination (nitrate reductase, resazurin microplate assay (REMA)). With direct methods, differences in sensitivity, specificity and speed are minor. However, they may be clear for the most difficult strains with *rpoB* mutations

Table 7.1 Main parameters characterising rapid DST techniques most often used (in recent past) and in most cases WHO-endorsed

<i>Method</i>	<i>Accuracy</i>	<i>Robustness</i>	<i>Ease</i>	<i>Risk</i>	<i>Requirements</i>	<i>Sampling</i>	<i>Cost</i>
MGIT automated	Moderate	Good	Easy	Moderate	High	Not easy	Very high
Nitrate reductase	Fair	Good	Easy	Moderate	Moderate	Easy	Low
REMA colourimetric	Fair	Moderate	Easy	High	High	Not easy	Low
Thin layer agar	Good	Moderate	Moderate	Moderate	Moderate	Not easy	Low
MODS	Good	Moderate	Moderate	Moderate	Moderate	Not easy	Low
Slide DST	Good	Moderate	Not easy	Low	Low	Not easy	Low
LPA	Fair	Moderate	Moderate	Low	Moderate	Very easy	High
Xpert MTB/RIF	High	Excellent	Very easy	Low	Moderate	Very easy	High

discussed above, which are more reliably detected by Xpert and methods with microscopic detection. Other parameters should be given more weight when determining the most appropriate technique for a given setting. These include:

- *Safety.* The REMA technique involves the manipulation of incubated plates with liquid medium outside of a safety cabinet, and therefore requires high-level containment laboratory practices. Direct methods only require a properly certified safety cabinet except for slide DST. This technique uses smears on microscopy slides that are manipulated only after heat and Ziehl-Neelsen stain phenol-killing of grown cultures, and may thus only require a ventilated workstation (VWS) with air extraction but no HEPA filtration. VWSs also offer sufficient protection for Xpert.
- *Applicability.* Slide DST works only from smear-positive sputum and will fail sometimes if there are scanty AFB amounts. Most rapid tests have problems with poorly growing R-resistant strains; automated MGIT utilisation will more often indicate test failure or false sensitivity.
- *Qualifications and training.* Good training and experience are indispensable for all techniques based on microscopic growth detection (thin layer agar, microscopic-observation drug susceptibility (MODS) and slide DST). Slide DST is based on a combination of interpretation criteria, making it even more difficult for new users. Conversely, with MGIT (and Xpert), the machine does the interpretation so little expertise is required, but it offers no flexibility for difficult strain analyses.

- *Sampling.* Poses problems with the direct methods, particularly those using a liquid medium. Fast or cold chain transport is necessary to limit contamination. Decentralised DST is possible but only with reduced safety requirements.
- *Standardisation.* Inoculum standardisation is more difficult to achieve (for all methods) directly from sputum, such that repeat assays are often needed. Automated MGIT analysis rejects inoculum that is too heavy; the use of control strains is difficult with tests relying on microscopic detection.

Treatment monitoring

Bacteriological tests for treatment monitoring include microscopy and culture. To date, molecular tests have not been used for this purpose because of prolonged excretion of genetic material from dead bacilli. Techniques are being developed that will allow amplification of DNA from only viable bacilli. The WHO recommends frequent cultures (preferably monthly) for treatment monitoring of MDR-TB. Despite successful treatment, dead bacilli and fragments thereof remain detectable for months via careful microscopy. Problems of interpretation arise particularly with more careful techniques, more powerful treatment regimens and more advanced disease at the start of treatment. Note that this problem does not occur in most settings because of limited microscopy sensitivity in follow-up smears characterised by low numbers of bacilli that are damaged by treatment and difficult to stain.

Culture for treatment management is not ideal because of the delay in obtaining a (negative) result and the heavy demands on infrastructure and logistics for reliable follow-up cultures in decentralised control programmes. Problems of contaminated and false-negative cultures may offset the expected gain in sensitivity. Cf is secreted in sputum and other body fluids and will inhibit growth in culture except when using egg-based media to bind the drug. Cross-contamination can easily occur with cultures, leading to false-positives and confusion regarding true failure and relapse. MGIT cultures are known to be most sensitive and may remain positive for extended periods of time during treatment. Because the number of colonies is impossible to know, interpretation of late MGIT-positives is more difficult, but time to positivity in MGIT has been used as a proxy for the number of viable bacteria remaining. Solid culture colony counts yield the same information.

Increasing resistance may be observed due to a few remaining bacilli but may not be representative of the original strain, which will eventually disappear (transient resistance, Chapter 4); however, acquired amplified

resistance may be observed. In such cases, clinical evolution and trends of culture colony counts should be taken into consideration for interpretation. In addition, false susceptible results will be seen regularly during effective treatment (i.e., strain becoming more difficult to grow, showing its resistance). Molecular tests help in these cases, as long as the DNA is not overly damaged.

FDA vital staining has been used for MDR-TB treatment monitoring as well. As shown in Figure 7.1, conversion on FDA smear and culture ran closely parallel in the Damien Foundation Bangladesh cohorts, with close to 90% of patients showing negative results after 2 months.

In contrast, conversion on regular AFB smears (usually auramine fluorescent) is considerably delayed, with only about 30% conversion seen at the second month and 90% by the fifth month. For individual patients, conversion on FDA versus culture regularly differs by 1 or 2 months and is to be expected given the limitations of both techniques with paucibacillary samples.

Non-conversion on culture and vital staining is very rare. Indeed, with the short MDR-TB regimen recommended in these Guidelines, only XDR or non-compliant cases would be expected to show high-level FQ resistance. Almost all failures appear as reversion after conversion, and with monthly to quarterly monitoring, failure smear positivity occurs almost simultaneously with culture positivity. Positive smear results at reversion will thus regularly precede the culture result, and vital staining in combination with clinical assessment can guide rapid DST needs and patient management. Failure should be declared only after finding viable bacilli (culture- and/or FDA-positive) in successive specimens with accompanying clinical deterioration.

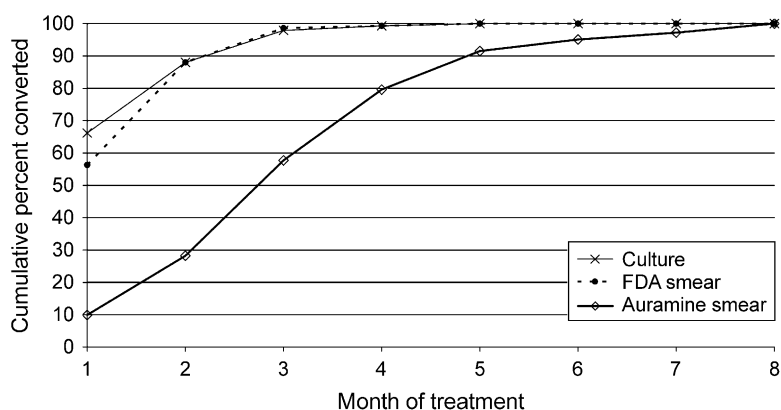


Figure 7.1 Conversion on FDA smear and culture during MDR-TB treatment, Damien Foundation Bangladesh cohort, January 2010 to June 2011.

In some settings, confusion may arise because of non-TB mycobacteriosis, i.e., in patients with a clinical MDR-TB diagnosis from whom bacilli were never isolated, or due to a laboratory error in species identification. Persistent or intermittently (scanty) positive smears (from auramine, but also vital staining), possibly with an occasional positive culture, are often found during treatment of such patients.

With the WHO-recommended long SLD regimens, smear conversion has generally been more rapid than culture conversion, and conversion is usually seen later than in the example of the short Bangladesh regimen. This may be an indication of the lower sterilising power of the WHO regimen, similarly to what has been seen in the past with the use of long-term FLD regimens not including R and Z in the intensive phase.

In HIV-negative patients, relapse is rare after the short MDR-TB regimen described in these Guidelines, but reinfection may be just as frequent in a high TB prevalence setting. Timing may be an indicator (true relapse is most likely during the first year after cure, but thereafter reinfection should be considered first). DST fingerprinting can be used when available, but DST is mainly needed to indicate whether the new TB episode is from an MDR or even XDR strain.

A positive smear or culture without clinical deterioration sandwiched between several negative tests is not especially rare during or after treatment. These isolated positives may be due to mis-identification or other laboratory errors. With cultures, cross-contamination may occur more frequently than thought. Cross-contamination and mis-identification can in principle be excluded by showing non-identity of DNA fingerprints compared to the pre-treatment strain. In practice, this is difficult and would delay results; late, isolated excretion of the original bacilli is also possible. It is preferable to repeat bacteriology studies on subsequent sputum specimens.

In summary, the following are possible scenarios with bacteriological monitoring:

- Conversion on both smear and culture within a few months. Favourable evolution is still likely with AFB smears that remain positive for a longer time, but with decreasing quantification and good clinical condition. FDA vital staining will be negative early.
- Late conversion on culture (and smear) occurs with initial FQ resistance.
- Non-conversion on smear and culture is rare, indicating XDR-TB: exclude infection by other mycobacteria.
- Reversion to persistent positivity during treatment after some months of negative smears and cultures. Depending on frequency of monitoring and quality of tests, culture and/or smear may become positive.

The clinical condition and FDA staining may be used as early indicators of reversal of active disease. Initial or acquired resistance to the main drugs (FQs), but also hidden default, may be the cause.

- Reversion to persistent positivity after treatment, usually on smear and culture simultaneously and with clinical recurrence. This is due to relapse or reinfection, which can be distinguished by comparing fingerprints of pre- and post-treatment strains. The resistance profile is also likely to be different with reinfection.
- Isolated positive smear or, frequently, an isolated positive culture during or after treatment. This can be due to incorrect identification (at the time of sampling or mislabelling of slides or tubes in the lab), cross-contaminated culture (not smear), or in rare cases isolated excretion of viable bacilli from a residual lesion. Fingerprinting and clinical condition may be decisive in these cases.

For treatment monitoring, the most sensitive technique applied to a specimen is not necessarily the most important. Both microscopy and culture (possibly with FDA vital staining as a proxy) on successive samples will usually be needed to arrive at a correct interpretation of outcome and clinical evolution. These Guidelines recommend that bacteriological monitoring by AFB smear and culture should be monthly during the intensive phase and bimonthly to quarterly in the continuation phase. At a minimum, ordinary AFB smears should be performed throughout treatment with confirmation of conversion on culture documenting the end of the intensive and continuation phases or in case of reversion to positive smear.

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Principles of treatment for susceptible and drug-resistant tuberculosis

José A. Caminero

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- Introduction: brief historical review of anti-TB chemotherapy
 - Bacteriological bases for the treatment of TB, including DR-TB
 - Prevention of resistance: the need for drug combinations
 - The need for prolonged treatments: analysis of bacillary populations of *M. tuberculosis*
 - Core versus companion drugs in the intensive and continuation phases
 - Rationale for an ideal initial treatment regimen
 - Justifications for adding a fourth drug in the initial phase of treatment
 - Length of the intensive phase and continuation phase in initial TB treatment
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 - Rationale for an ideal DR-TB treatment regimen
 - Approach to the diagnosis of a patient suspected of DR-TB; reliability of DST
 - Number of drugs necessary to treat a patient with DR-TB
 - Most rational use of effective drugs against TB in a patient with drug resistance
 - Suitable length of injectable drug administration during the initial and continuation phases of treatment
 - The role of surgery in the treatment of patients with DR-TB
 - Approach to the optimal regimen for DR-TB: standardised versus individualised regimens
 - Treatment of mono- or poly-resistant non-MDR-TB
 - Conclusions
-

The treatment of TB must be based on two important bacteriological considerations: the combination of drugs needed to avoid the selection of resistances and the need for prolonged treatment to ensure that all bacteria in their various phases of metabolic growth are effectively killed. In order to work towards cure in the large majority of patients affected with tuberculosis, a minimum of four drugs not previously utilised on the patient or with possible susceptibility should be used. Length of treatment will depend on the drugs used. If rifampicin (R) can be included, treatment may be reduced to 9 or even 6 months if pyrazinamide (Z) is also utilised. If it is not possible to use R, a minimum of 18 months of treatment is recommended, and even longer in cases where isoniazid (H) cannot be used. Recent work with multidrug-resistant TB (MDR-TB) patients has resulted in excellent cure rates with a treatment programme lasting 9 months, most likely because high doses of new fluoroquinolones (FQs) have efficacy approaching that of R. All treatment regimens must have as a core at least two very active drugs responsible for killing and sterilising Mycobacterium tuberculosis, and two or more other accompanying drugs that kill little but protect the core drugs so that the bacillus does not acquire resistance. Length of treatment and chances for success are dependent on these core drugs. The best anti-TB drugs currently are R and H, and these should always be the core of initial treatment plans. If it is not possible to

use R or H or both, whether due to resistance (MDR-TB) or adverse side effects, case management becomes exceedingly complicated. In this case it is necessary to rely

on not only more prolonged treatments but also other core drugs, among which only the FQs and second-line injectables (2LIs) are relatively reliable. However, there is always a good chance for cure when the recommended treatment bases are followed and available drugs are introduced rationally, even if the pattern of resistance is rather broad. This chapter reviews the bacteriological bases for TB treatment in all its forms and discusses the best decisions to make in the field when evidence is scarce, especially for patients who are carriers of some degree of drug-resistant TB (DR-TB).

Introduction: brief historical review of anti-tuberculosis chemotherapy

The long history of the battle between the human species and *M. tuberculosis* began to change radically when streptomycin (S) was introduced by Waksman and Schatz in 1943 and used against human TB in 1944. This antibiotic secured clinical and radiological improvement along with conversion of the sputum smear microscopy to negative. Its only problem was toxicity (the administered drug was not very purified at that time), and the fact that after 2–3 months of treatment, a significant proportion of patients suffered relapse with TB having become resistant to S. Development of drug resistance was soon a recognisable problem. Thus, the main issue for S was the appearance of resistant strains in patients who had already received S therapy for some time, usually between 2 and 3 months.

Also in 1944, therapeutic testing began with p-aminosalicylic acid (PAS). It produced effects similar to S, although with the same toxicity and resistance problems. Then, in 1949, it was discovered that when combined with S, PAS delayed or prevented the appearance of resistance to S. Still, a treatment offering efficacy, low cost, easy administration and no side effects remained elusive. Such an optimal solution was largely achieved with the introduction of isoniazid (also known as isonicotinic acid hydrazide), a substance first synthesised in 1912 but not experimentally tested in TB until 1951. In view of its advantages, H was referred to as the ‘miracle drug’ against TB, and even today, more than half a century later, no single drug has been able to surpass it in efficacy results. It nonetheless soon became evident that H alone could not solve the TB problem, and strains resistant to the drug rapidly appeared. Treatment was then reoriented towards the combined dosage of H with S and PAS in 1955. This long-duration combined chemotherapeutic regimen became the only treatment capable of completely curing TB without the accompanying fear of acquired drug resistance. The related historical data still guides all TB treatment, especially drug association, for which the fundamental purpose is to prevent natural resistant mutants that exist in all bacillus-naïve populations from selecting

for each of these drugs. A large number of randomised clinical trials have validated this important bacteriological basis. Randomised clinical trials provide the best evidence for research of treatment for any disease. Building on these important discoveries, other anti-TB drugs were introduced in the 1960s. One was R, which, with its ability to kill *M. tuberculosis* in all its growth phases under different metabolic conditions, reduced long-term TB treatment to 9 months.

Though a few other drugs have been incorporated into TB treatment since (notably FQs), the most active anti-TB drugs are still H and R, and their method of use has not changed in the last 50 years. Of the small number of drugs available against TB, only H and R are highly effective, and therefore curing tuberculosis in patients with resistance to both antibiotics becomes much more difficult. The term MDR-TB applies exclusively to patients with resistance to at least H and R, and reflects the global importance of and challenges raised by this condition. It should nonetheless be recalled that MDR-TB only came to be seen as a global epidemiological problem fairly recently (see Chapter 2).

When MDR-TB developed into a global epidemiological priority, experts agreed that treatment should be standardised as much as possible. Unfortunately, differences between MDR-TB cases are substantial. As such, efforts to randomise patients for clinical trials or group them into homogeneous sets to apply and compare different strategies have been virtually fruitless. There have thus been no controlled trials comparing the various treatment regimens or drugs; rather, anecdotal reporting has been the basis for case management. Expert opinion, though not as rigorous as a randomised clinical trial or formal observational study, is quite rich and certainly should be seriously considered when discussing these issues, bearing in mind that personal experience obviously introduces bias even in the best of situations.

Fortunately, drug-sensitive TB treatment has been widely standardised and is based on randomised clinical trials and studies with strong evidence. The bases that guide drug-sensitive TB treatment must be the same as for DR-TB. It is thus necessary to first review the bases that should guide all TB treatment before analysing the changes in treatment required by different degrees of drug resistance.

Bacteriological bases for the treatment of tuberculosis, including drug-resistant tuberculosis

At present, it is widely accepted that TB pharmacotherapy should be based on two important bacteriological considerations: the association of drugs administered concomitantly to avoid the development of resistance and the need for prolonged chemotherapy to prevent disease relapse.

Prevention of resistance: the need for drug combinations

If treatment is started in a patient with cavitary TB using only one drug, the patient experiences a first phase in which most bacilli are eliminated and symptoms improve. However, this initial phase is followed by a second period where treatment selects the resistant bacteria, which in a short time become the dominant microbial population (this is the 'fall and rise' phenomenon explained in Chapter 3). In addition, the drug in question will have become useless for that patient for the rest of his/her life because TB resistance is chromosomal, definitive and irreversible. In fact, although all the bacilli present in a colony originate from a single cell, bacteria do not show homogeneous behaviour against the various anti-TB drugs. Beyond a certain number of microorganisms, spontaneous natural mutants arise during successive bacillary divisions that possess an intrinsic resistance to some of the drugs used. Such mutations occur as random events, independent of the environment but closely associated with the number of bacilli, the type of medication administered and drug concentrations. The approximate number of bacilli needed for the appearance of a natural mutant resistant to each of the drugs is shown in Table 8.1, while Table 8.2 expresses the bacillary load calculated for each of the different types of TB lesion. Thus, in a culture of wild-type *M. tuberculosis*, spontaneous natural mutation gives rise to one H-resistant strain for every 10^5 – 10^6 bacilli. This mutation is independent for each drug used because different genetic targets are involved. The probability that resistance to two drugs will develop is consequently equal to the product of their respective mutation rates.

All monotherapeutic regimens (real or masked by combination with drugs to which resistance has previously been established or which prove ineffective) thus inevitably lead to treatment failure and the development of resistance. When administering two or more drugs, the risk of resistance is practically zero, as the weight and volume needed to sustain this bacillary

Table 8.1 Number of bacilli required for the appearance of a mutant resistant to different drugs

Isoniazid	1×10^5 – 10^6 bacilli
Rifampicin	1×10^7 – 10^8 bacilli
Streptomycin	1×10^5 – 10^6 bacilli
Ethambutol	1×10^5 – 10^6 bacilli
Pyrazinamide	1×10^2 – 10^4 bacilli
Fluoroquinolone	1×10^5 – 10^6 bacilli
Other drugs	1×10^3 – 10^6 bacilli

Table 8.2 Estimated bacterial populations in the different tuberculosis lesions

Smear-positive tuberculosis	10^7 – 10^9 bacilli
Cavitary tuberculosis	10^7 – 10^9 bacilli
Infiltrating	10^4 – 10^7 bacilli
Nodules	10^4 – 10^6 bacilli
Adenopathies	10^4 – 10^6 bacilli
Renal tuberculosis	10^7 – 10^9 bacilli
Extra-pulmonary tuberculosis	10^4 – 10^6 bacilli

load would be too large for the human body (10^{13} for H+R and 10^{19} for H+R+ethambutol (E)). Therefore, if *M. tuberculosis* is fully susceptible to all the anti-TB drugs, just two very active drugs (H+R) could be enough to cure practically all TB cases. Unfortunately, there are already a considerable number of *M. tuberculosis* strains with H resistance in the community. This percentage may exceed 10% globally, so if all those who are sick with TB in the world were given just H+R, only R could be acting on 10% of cases, indicating significant risk for expanding resistance to that drug. The addition of E to all initial plans is thus systematically advised because it is a weak drug with little ability to kill but an extraordinary ability to protect R if there is initial resistance to H. In this case, plans include a minimum of three active drugs, to which Z can be added in order to shorten treatment to 6 months (because Z can work in an acidic environment). Accordingly, to cover the risk of transmission of H- or R-resistant strains of *M. tuberculosis* in the community, including in new TB cases, recommendations now call for at least four drugs in the intensive treatment phase. The first important premise for any TB treatment is that of associating at least four drugs not used previously on the patient or that have a higher likelihood of being susceptible. Selection of the ideal drugs for each patient, based on mechanism of action and possible resistance, is discussed below.

The need for prolonged treatments: analysis of bacillary populations of *Mycobacterium tuberculosis*

M. tuberculosis is preferential aerobic and its growth and metabolic activity are proportional to the surrounding oxygen partial pressure and pH. In this sense, the ideal conditions for the bacteria are a pH of 7.40 and an oxygen pressure of 110–140 mmHg. Based on various environmental characteristics, four bacterial growth modalities have been established that condition the bases for currently used drug associations and treatment durations. These bacillary populations can be described as follows.

Metabolically active and demonstrating continuous growth

This population is also referred to as emergent flora and represents most bacilli, with a population density of 10^7 – 10^9 . These bacteria are easily detected in sputum of infected individuals, and are located within the cavitory walls, where oxygen pressure and pH conditions are ideal for growth. Located extracellularly, these bacteria are responsible for the failure of pharmacological treatment and development of resistance if not homogeneously eliminated. This population is rapidly exterminated by the bactericidal activity of H, and less rapidly by S and R. Bactericidal activity can be assessed by the percentage of negative conversion of cultures at the end of the second month of treatment. Early bactericidal activity (EBA) refers to the capacity of the drug

to kill bacteria in the first 2 days of therapy. EBA is quite important because drugs that kill many bacilli in the first days of treatment reduce the chances of patient death and transmission in the community. The best EBA is seen with the use of H, which of course is problematic because over 10% of TB patients worldwide cannot benefit from the actions of H due to resistance.

Some authors consider that negative conversion of the cultures after 2 months is an indication of the bactericidal capacity of the drug (see below). Hence, the bactericidal activity levels of drugs used in TB treatment is of utmost importance when the aim is to kill as many bacilli as possible in the first days and weeks of treatment, thus reducing the chances of patient death and infectiousness. The degree of bactericidal activity of all anti-TB drugs with recognised capacity is shown in Table 8.3, along with other parameters. The greatest possible number of drugs with bactericidal activity should always be sought in the pharmacological combination designed for individual treatment. H and R have the best overall bactericidal activity, followed by S among the first-line drugs (FLDs). Z has little bactericidal capacity in an acidic environment on rapidly dividing cells in cavitory walls, and E has practically none. Among second-line drugs (SLDs), only the FQs (especially new-generation versions) and injectables have good bactericidal activity, followed by the thioamides. Other SLDs have practically no bactericidal activity, and only linezolid (Lzd) and possibly the carbapenems may have some among the Group 5 drugs (Table 8.4). In any event, the bactericidal

Table 8.3 Chemotherapy in tuberculosis: activity of the different anti-tuberculosis drugs

<i>Activity</i>	<i>Prevention of resistance</i>	<i>Bactericidal activity</i>	<i>Sterilising activity</i>	<i>Toxicity</i>
High	Rifampicin	Isoniazid	Rifampicin	PAS
	Isoniazid	Rifampicin	Pyrazinamide	Ethionamid
	Ethambutol		New FQs?	Cycloserine Linezolid
Moderate	Injectables	Injectables	FQs	Injectables
	FQs	FQs	Injectables	Pyrazinamide
	Ethionamide	Linezolid?	Isonizide	
	Cycloserine		Linezolid?	
	PAS Linezolid?			
Low	Pyrazinamide	Ethionamide Pyrazinamide	Isoniazid	Ethambutol Rifampicin Isoniazid FQs

Table 8.4 Rational and sequential categorisation of drugs used in the treatment of tuberculosis

	<i>Daily dose</i>
1 First-line oral anti-tuberculosis drugs (use all possible drugs)	
Isoniazid	5 mg/kg
Rifampicin	10 mg/kg
Ethambutol	15 mg/kg
Pyrazinamide	25–30 mg/kg
2 Fluoroquinolones (use only one, because they share genetic targets)	
Ofloxacin	15 mg/kg
Levofloxacin	15 mg/kg (750–1000 mg)
Moxifloxacin	7.5–10 mg/kg (400 mg)
3 Injectable anti-TB drugs (use only one, because they have very similar genetic targets)	
Streptomycin	15 mg/kg
Kanamycin	15 mg/kg
Amikacin	15 mg/kg
Capreomycin	15 mg/kg
4 Other less effective second-line anti-tuberculosis drugs (use all possible drugs if necessary)	
Ethionamide/prothionamide	15 mg/kg
Cycloserine/terizidone	15 mg/kg
p-aminosalicylic acid	150 mg/kg
5 Other less effective drugs or drugs with limited clinical experience (use all possible drugs if necessary)	
Clofazimine	100 mg
Amoxicillin/clavulanate	875/125 mg/12 hours
Linezolid	600 mg
Imipenem	500–1000 mg/6 hours
Clarithromycin	500 mg/12 hours
High-dose isoniazid	10–15 mg/kg
Thiacetazone	150 mg

Source: Data from Caminero et al.

activity of these other drugs is inferior to H, the best drug of all in this regard, and also inferior to R.

Bacilli in acid inhibition phase

These are a smaller population of about 10^3 – 10^5 bacilli. Their growth is inhibited by the acidic media contained within the phagolysosomes of the macrophages located intracellularly, or by the acid pH present in the inflammatory zones of the cavitary wall. Deficient oxygenation of the surroundings also inhibits growth. Because these bacilli lack metabolic activity, they are unlikely to be eliminated by the administered drug. This bacillary population in sporadic multiplication phase therefore constitutes ‘persistent bacterial flora’, the main source of bacteriological TB relapse. The most active drug against this particular bacterial population is Z. The action of H and R decreases by practically 50% when the pH of the environment changes from 6.6 to 5.4, whereas the activity of Z increases with acidification of the surroundings. The capacity of drugs to eliminate this bacillary population and its sporadic multiplication is referred to as sterilising activity, and can be quantified by the number of relapses that follow treatment. The sterilising capacity of anti-TB drugs is also shown in Table 8.3. The sterilising capacity of Z over these bacilli populations has reduced treatment duration to 6 months. In the absence of Z, treatment must be prolonged to at least 9 months for R to be able to kill these bacilli. It is possible that the new FQs will also have a sterilising capacity on these bacilli.

Bacilli in sporadic multiplication phase

This population comprises approximately 10^3 – 10^5 bacilli, usually located in solid caseum where the pH is neutral. The bacilli undergo long dormant periods with occasional, brief metabolic activity lasting only hours. As a result, the administered medication only destroys the bacteria during these brief metabolic periods, which may not occur at all during therapy. On the other hand, the scant and occasional activity of these bacteria prevents them from developing resistance. The drug of choice for eliminating this population is R, mainly due to the rapid onset of its sterilising action (15–20 minutes versus 24 hours for H). This population, together with bacilli in acid inhibition phase, are responsible for bacteriological relapses after the conclusion of therapy. It is likely that FQs and the 2LIs have some sterilising capabilities. High doses of the new FQs may very well also have potent sterilising activity, which would explain the success of short MDR-TB treatment regimens like the Bangladesh regimen described below. The sterilising action of the remaining SLDs is practically nil, as is that of E.

Persistent or totally dormant population

Because these bacteria lack metabolic activity, pharmacological treatment cannot destroy them. It is likely that only individual host defence mechanisms can exert some measure of control over this population. One hypothesis suggests that these bacteria are among the populations responsible for relapse in patients with severe immune deficiency. As a result, the second main premise of TB treatment in all its forms is to administer very prolonged treatments to give the drugs the ability to kill *M. tuberculosis* in its different growth phases and ranges of metabolic activity. The length of treatment will depend on the drugs that can be associated. If R can be included, treatment may be reduced to 9 months, and even to 6 if Z is also included. If R cannot be used, treatment may need to last at least 18 months, and perhaps even longer if H cannot be used. Note that recent work with MDR-TB patients (Bangladesh regimen) has shown excellent cure rates with a treatment programme of 9 months, likely because the high doses of new FQs end up playing a role similar to R.

Core versus companion drugs in the intensive and continuation phases

Once it is agreed that TB treatment must be prolonged and include a minimum of four drugs, it is necessary to discuss how the four drugs are needed when the bacillary load is quite elevated. This occurs when there is a high likelihood of selecting naturally resistant mutant bacilli (which exist in all naïve populations) if all the four drugs are not associated. When the bacillary load has been substantially reduced, fewer drugs are needed. All treatment programmes must have at their core a minimum of two very active drugs responsible for killing and sterilising *M. tuberculosis*, and two or more accompanying drugs that kill little but are responsible for protecting the core drugs so that the bacillus does not become resistant. If possible, the same core drugs should be used throughout the treatment unless toxicity becomes a problem.

The likelihood of cure depends on the core drugs that can be utilised in a given regimen, but also on the accompanying drugs used to protect the core drugs so they can perform their important actions. Accordingly, plans should be designed with two phases, an intensive phase that includes at least four drugs (two core and two accompanying) and continues until bacillary load had been reduced to a minimum, and a continuation phase, during which the accompanying drugs can be discontinued and which is prolonged until cure is ensured with minimum risk of relapse. The best indicator that the bacillary load has been reduced to a minimum and that a shift should be made from the intensive to the continuation phase is when the

acid-fast bacillus (AFB) smear comes negative. Although some authors prefer to associate the transition phase with conversion of cultures, the fact is that when the AFB smear is negative, the bacillary load is sufficiently reduced for the two potent drugs alone to kill the remaining bacilli. The continuation phase will thus depend on the sterilising capacity of the core drugs to be used until the end of treatment.

Based on the potential action of the drugs listed in Table 8.3, the best existing core drugs are H and R, which must therefore be administered during both TB treatment phases in initial cases. Other core drugs may be FQs, especially those of the new generation, and the injectables, which must be prescribed when H or R cannot be used. The FQs can be given throughout treatment but the injectables cannot due to the possible build-up of toxicity over months of use. There is consequently a tendency to suspend injectables at the end of the intensive phase. The remaining drugs can hardly be used as core drugs, although the thioamides and possibly Lzd could take on this role, albeit less potently, if no other possibilities exist.

Rationale for an ideal initial treatment regimen

As explained above, the combination of H+R+Z constitutes the ideal basis for a TB treatment regimen for the first 2 months of management, followed by H+R for another 4 months. This treatment regimen offers potent bactericidal and sterilising action with few relapses (less than 1%–2%) and few side effects. Z should only be administered for 2 months, because after this period the great majority of lesions and cells presenting in acid pH conditions (the preferred conditions of action for this drug) have disappeared. The sterilising action of Z is scarce or nil after the second month of treatment if R, with its potent sterilising action, has been included in the regimen. If a treatment plan does not include R, whether due to proven resistance or intolerance, Z could possibly continue to have sterilising action for much longer than the initial 2 months. This would explain why Z's behaviour was tremendously useful when it was administered for 18–24 months prior to the discovery of R.

To summarise, in all cases of initial TB where sensitivity to all drugs in the regimen can be assured, the ideal treatment is 2 months of H+R+Z followed by 4 months of H+R. Nonetheless, important determining factors—microbiological (possible initial resistance to some of the drugs), operative (impossibility of guaranteeing supervision of administration) and economic (some drugs are much more expensive than others)—make it necessary to consider different variations from this theoretically ideal management scheme.

Justifications for adding a fourth drug in the initial phase of treatment

H and S have been massively used worldwide for decades, unfortunately including in many cases with deficient criteria (involving frequent true or masked monotherapies), leading to high resistance rates to these two drugs in many parts of the world. This is particularly true for H, which remains the core for initial treatment. In the event of initial resistance to H, and considering the high proportion of natural mutants resistant to Z (Table 8.1), R stands very much alone for treating those with very large microbial populations. A fourth drug must thus be added to the initial treatment to protect R if the patient has been contaminated by a strain of H-resistant *M. tuberculosis*. Of course patients run the greatest risk with positive AFB smears and cavitations in chest X-rays because they have higher bacillary loads and hence a potentially larger number of mutants resistant to different drugs. Although patients with less extensive lesions or negative AFB smears would in theory not need this fourth drug, standardisation of patient management calls for all patients to receive it so that 'all bases are covered'.

Once the need to add a fourth drug in the first phase of TB treatment is accepted, the choice may centre on S or E. The latter is preferable for two important reasons, one bacteriological and the other operative. Bacteriologically, S has been used as massively as H, and its initial resistance rate is therefore also high in much of the world. Because the fourth drug is administered with the goal of protecting against the development of resistance, S should be rejected in favour of E, for which very few cases of initial resistance have been described. From an operative standpoint, S must be administered by a nurse via intramuscular injections. This complicates the administration of treatment at the most peripheral levels of health care (i.e., in areas where the person responsible for treatment may be a less qualified health-care worker or even someone from outside the health-care field such as a community leader or teacher). Furthermore, in very poor areas where disposable syringes are unavailable, the risk of human immunodeficiency virus (HIV) transmission must be taken into account.

Length of the intensive phase and continuation phase in initial tuberculosis treatment

With the previously discussed initial treatment (2 months H+R+Z+E followed by 4 months H+R), the majority of patients will be cured with a minimum of adverse side effects. However, this regimen is already 30 years old, and while it continues to be effective, resistance around the world has noticeably changed over this period. This can raise questions about the length of the intensive and continuation phases.

If there are negative AFB smears at the end of the second month of treatment, the length of the intensive phase should be unchanged because the TB patient could very possibly be sensitive to the entire administered drug regimen. In any event, the bacillary load will be so low that nothing will happen by moving to the continuation phase. However, if Z+E are systematically suspended when the intensive phase ends, regardless of the AFB smear result, questions arise about the fate of the more than 10% of patients who still have positive smears at the end of the intensive phase. It is possible that some patients will have positive AFB smears due to non-viable, dead bacilli or totally susceptible bacilli (delayed conversion). In both cases, there would be no effects. Another cause of such a presentation may be viable bacilli with initial resistance to H. These patients may be more likely to have a positive AFB smear at the end of the second month, because this drug has not been able to act with its powerful early bactericidal activity. However, the cause of the presentation would not be known until culture results became available, which can take several weeks. It is therefore advisable that, for this group of patients with positive AFB smears at the end of the intensive phase, the same treatment be maintained with the four drugs throughout the entire period of treatment. This ensures protection of R in all patients with initial resistance to H, a condition that customarily is not known until several weeks or months after treatment is started. Although this strategy can be controversial because there are no studies addressing the issue, adding E and Z (or at least E) for these patients is hardly ill-advised because R will always be protected. Although Z would not be necessary in the continuation phase for those with positive bacilloscopies at the end of the second month (E could be prolonged to protect R), the best way to facilitate management on the ground is 6 months of H+R+Z+E.

Ideally, a DST for H and R should be performed on patients who still have positive AFB smears at the end of the second month of initial treatment and a decision made when the results are received. If the culture is negative (indicating that the positive AFB smear is due to dead or non-viable bacilli), or if it is positive but the isolated bacilli are sensitive to H+R (indicating delayed conversion), the choice could be made to suspend the intensive phase and move to continuation with 4 months of H+R. For such patients, information provided by Xpert would not be valid because it only addresses possible R resistance, while the patient may be sensitive to R but resistant to H. In this case, we run the same risk of amplifying resistance to R by moving to the continuation phase with only H+R.

Although the continuation phase with 4–6 months of H+R usually suffices to cure most patients, several conditions have been identified in recent years that may facilitate relapses if the treatment lasts only 6 months. This has notably been seen with HIV infection, where it is more and more widely

accepted that to reduce the chance of relapse, the continuation phase should consist of at least 8–9 months of treatment with H+R (Chapter 11). Other conditions, such as extensively advanced or cavitary TB or delayed smear and/or culture conversion even in sensitive patients, seem to benefit from prolonged continuation phases. Standardised plans should always be administered under controlled programmed conditions but, in cases of delayed bacteriological conversion, it may be best to maintain the continuation phase for a minimum of 4 months after smear conversion.

Intermittent treatment regimens

Though daily treatment is the ideal scenario to ensure maximum effectiveness, numerous trials have demonstrated similar efficacy with intermittent treatments. As noted above, *M. tuberculosis* multiplies very slowly (approximately once every 14–24 hours), enabling efficacy when the anti-TB drug is administered in a single daily dose. It is known that a single dose of H inhibits bacterial growth for several days, meaning it is equally effective to administer either two weekly doses or one daily dose. However, efficacy decreases when the interval between doses exceeds 4 days. With R and E, growth inhibition also persists for several days, though the bactericidal behaviour of R makes the latter much more effective. In any case, the efficacy of these two drugs is similar whether administered daily or once a week. Similar considerations apply to Z, which at a pH of 5.6 inhibits mycobacterial growth for 9 days following 24 hours of bacterial exposure to the drug. These circumstances apply to H, R, E and Z but not to FQs, ethionamide (Eth) or thiacetazone (Th). Therefore, if regimens with H, R, E and Z are recommended, intermittent administration in the form of twice-weekly doses can be used with the same therapeutic safety margin as a daily dose, the only requirement being an increase in the amount of H, E and Z contained in each dose. The dose of R should not be increased. In order to achieve satisfactory efficacy, a minimum of two doses a week is required. Consequently, national tuberculosis programmes (NTPs) that recommend intermittent regimens should first ensure strict supervision of medication administration.

Some programmes recommend administration three times a week (even though it has been reasoned that twice is enough) for operative reasons only, because this recommendation also applies to the second phase of therapy when adherence to treatment decreases. No problems should be expected if a single dose is missed in the context of the thrice-weekly treatment scheme, because two weekly administrations effectively suffice to ensure therapeutic efficacy. However, if a dose is missed in a twice-weekly treatment scheme, the patient will in effect receive only a single weekly dose, creating a dangerous situation because R may inhibit mycobacterial growth for 3–4 days but H does so for 7–8 days. From a bacteriological perspective,

a single weekly dose of these two drugs means that the patient is actually receiving sequential monotherapy with H, with the risk of selecting for mutants resistant to H.

Use of these drugs in intermittent treatment regimens makes supervising administration more practicable (supervision is only needed twice a week instead of daily), the option is much less expensive (for R, the most costly drug, it is not necessary to increase the dose at each administration) and toxicity is similar to that associated with daily dosing. Moreover, it has been suggested that greater peak concentrations in blood make the selection of resistant mutants less likely. Although the drugs could be administered intermittently from the start (mycobacterial growth inhibition being achieved from the first dose), it is normally advised to commence therapy with a daily administration phase lasting 1–2 months, because maximum bactericidal action takes place in the first days of chemotherapy. Nevertheless, some studies have shown intermittent administration to be effective from the start, though four drug substances are used in the initial phase in such cases.

There has been controversy recently about whether these intermittent treatments cause more failures, relapses or amplification of resistance. Although the evidence is not very strong, if intermittent treatments are initiated at the beginning of therapy, the result may be more relapses in specific patient groups, such as those co-infected with HIV, with cavitation on chest X-rays or with initial resistance to H. The likelihood that more failures and amplifications of resistance in these three patient groups will occur is somewhat more controversial, but some trials have shown just such results. The best way to avoid these unfortunate occurrences is daily treatment for all phases. If this is not possible at field-level conditions, the intensive phase should be administered daily with the goal of moving to administration three times a week in the continuation phase. Patients infected with HIV should have daily treatments in both phases.

Rationale for an ideal drug-resistant tuberculosis treatment regimen

In most instances, MDR-TB results in a completely different treatment regimen and prognosis. Patients with R-resistant strains should be similarly managed even when the strain retains H susceptibility. In fact, the prognosis is very similar when there is resistance to R, with or without MDR-TB. Perhaps the definition of MDR-TB should be linked to R resistance. In the field, over 90% of R resistance is linked to H resistance, and the number is even higher in patients who have already been treated. This is not true of H resistance, which is linked to R resistance in a small percentage of patients that varies by region. Moreover, resistance to H, whether associated with S

resistance or not, can be overcome with a 9-month treatment with R and an FQ as core medications throughout treatment. The accompanying drugs could be two of Z, E or S, depending on the pattern of resistance. On the other hand, patients with strains resistant to R but susceptible to H should be managed like MDR-TB patients, who should also have H added to the treatment. This is because some cases are authentic MDR-TB (as the H susceptibility test is reliable, but not totally so), or because even with total H susceptibility (very rare in the field), management is quite similar, with a minimum treatment length of 18 months.

In these DR-TB cases, although the same premises discussed previously should be followed, it is necessary to associate several drugs for a prolonged treatment period and to assess the ideal number of drugs, the most rational use of the available drugs, the optimal length of treatment (intensive and continuation phases) and the benefits that surgery may offer. In all cases, assessments and treatment plans must address patterns of resistance for individual patients. Lastly, treatment should be as standardised as possible to simplify management of these complicated cases and reduce the chance of treatment errors and increased drug resistance. Each of these factors will be analysed thoroughly.

Approach to the diagnosis of a patient suspected of drug-resistant tuberculosis; reliability of drug susceptibility testing

Regarding drug selection for patients with drug resistance, the American Thoracic Society (ATS) guidelines published in 1966 stated: 'The selection of anti-tuberculosis agents is based upon the history of previous therapy and the results of reliable drug susceptibility tests.' In the 40 years since this publication, very little if any progress has been made on the subject. The major predictor of resistance to a particular drug is the demonstration of its prior use in monotherapy for more than 1 month. Obtaining such information requires a meticulous and directed history of antibiotic use in all patients suspected of DR-TB. This involves an accurate assessment of the dosage and combination of drugs to establish the precise sequence of drug introduction and withdrawal, which then enables evaluation of real or masked monotherapies previously received by the patient. Only then can one accurately predict resistance to particular drugs and avoid their inclusion in the retreatment plan. Surprisingly, if the treatment history is taken meticulously, it can not only prevent errors leading to failure but also direct the examiner to drugs with potential efficacy, despite prior use, if they were prescribed in sound combinations and led to culture conversions in the past. Of course, obtaining an accurate treatment history is sometimes problematic in that it relies on patients' ability to remember which drugs they took in the past or access to patient charts for previous TB episodes. For this

Patient: Year												
Drug	January	February	March	April	May	June	July	August	September	October	November	December
H												
R												
Z												
E												
S												
Kn												
Am												
Of												
Lf												
Mx												
Eth/Pth												
Pas												
Cs												
Cfz												
Lz												
*												
*												
Smear**												
Culture***												
DST****												
	H: Isoniazid	R: Rifampicin	Z: Pyrazinamide	E: Ethambutol	S: Streptomycin	Kn: Kanamycin	Am: Amikacin	Bm: Capreomycin	Of: Ofloxacin	Lf: Levofloxacin	Mx: Moxifloxacin	Eth: Ethionamide
	Pas: PAS	Cs: Cycloserine	Cfz: Clofazimine	Lz: Linezolid	*Others							
	Smear: Date and Result // *Culture: Date and result					****DST: Date and Result						

Figure 8.1 Model of drug history (from Caminero, *A Tuberculosis Guide for Specialist Physicians*, p. 208).

reason, the history should be obtained by experts in MDR-TB. To facilitate history taking for DR-TB patients, the ideal is to use a form with appropriate questions such as the one in Figure 8.1. One sheet should be completed per patient and per year. The analysis of all of a patient’s history sheets will provide relevant information for treatment formulation, especially for those who have had multiple rounds of treatments with exposure to various anti-TB drugs in the past.

Another possible approach to ascertaining the pattern of resistance is performing DST for FLDs and SLDs. This issue was addressed in depth in Chapter 7. Drug susceptibility tests have several weaknesses, including a problem with results that are delayed usually by more than 3 months after sampling (when carried out using conventional methods on solid media) and failure due to insufficient growth of cultures. In addition, it is important to realise that although in vitro and in vivo correlation of the DST is very reliable for H and R, reliability is lower for other drugs. Drug resistance, as detected by the antibiogram, reflects the inefficacy of a drug in culture media, but drug susceptibility does not necessarily reflect the efficacy of the drug within a new regimen. Even in wealthier countries, where multiple methods are available for performing DST for SLDs, interpretation of results requires careful analysis by experienced staff. Studies aiming to standardise DST results for SLDs are scarce and have yielded inconsistent results, as the concentrations employed for each drug and the definition of resistance vary

greatly even between the best performing laboratories. Today, DST for some SLDs like kanamycin (Km) and ofloxacin/ciprofloxacin could be of great help after considering the drug history of the patient, but not DST results for other SLDs.

Accordingly, the diagnosis of MDR should be based upon patient history (failure of standard regimens, exposure to patients with MDR-TB, etc.) and on the results of DST for H and R, for which reliability approaches 100%. Under NTP conditions, the history of drugs previously employed in the country and the epidemiological surveillance of DST for H and R after failures of standard regimens should be considered. For instance, in a country where cycloserine (Cs) and PAS have never been employed, susceptibility to these drugs is to be assumed for all patients. In all cases, DST for FQs and 2LIs should be performed if available for patients with confirmed MDR-TB, but the results must be considered in the light of an individual patient's drug history.

Number of drugs necessary to treat a patient with drug-resistant tuberculosis

One of the most controversial issues relating to DR-TB in recent years concerns the best drugs for patient treatment, mainly because of the absence of controlled trials validating specific regimens. It is in fact nearly impossible to gather samples from an adequate number of patients with a similar resistance pattern to carry out clinical trials that compare regimens with different numbers of drugs and different drugs. Moreover, efficacy is dissimilar among anti-TB drugs (Table 8.3), emphasising the need for a rational regimen design. Considering the basic activity of various drugs, it may prove more effective to prescribe a regimen with three or four bactericidal drugs rather than one with five or six bacteriostatic agents with weak activity. Hence, it is very important to properly classify the available drugs and associate them in a reasoned way (Table 8.4). This issue will be discussed in Chapter 9.

A comprehensive critical review of the literature points to several good studies from the pre-rifampicin period (also the pre-fluoroquinolone period), showing that treatment with only three drugs may ensure very favourable clinical outcomes in patients with resistance to S, H and PAS. These patients were very similar to the current XDR-TB (extensively drug-resistant TB) cases because neither R nor FQs were available. There were times when these resistant *M. tuberculosis* strains were totally sensitive to the remaining drugs, which, practically speaking, had not been used in the field. Consequently, we could conclude that in the event that all drugs to be administered were totally sensitive, just three drugs could suffice, though this is not currently the case. Meanwhile, other studies from the R period have

demonstrated good outcomes with more than four drugs. Many of these studies were performed in settings with very high rates of MDR-TB, where most patients, including those without a history of previous treatment, were resistant to many other drugs besides H and R.

Given that a major goal in preparing a set of recommendations is to ensure that they are suitable for the majority of patients, four points must be considered: 1) The use of three effective SLDs could be sufficient (natural resistant mutants per drug $> 1 \times 10^5$) from a bacteriological point of view. 2) In the field, however, some drugs often have compromised efficacy or very weak action. 3) For this reason, under NTP conditions, a SLD regimen should include at least four drugs. 4) Occasionally, when several drugs exhibit compromised efficacy or very weak action, prescribing more than four drugs may be justified.

Most rational use of effective drugs against tuberculosis in a patient with drug resistance

It is very important to bear in mind that not only is the number of drugs available to control TB quite limited, but their efficacy also differs and some exhibit cross-resistance. Based on their activity, efficacy, route of administration, tolerance, availability and cost, anti-TB drugs can be classified into five groups as shown in Table 8.4. The dosage of these different drugs is also presented. At least four drugs should be selected to design a regimen, starting from Group 1 (FLD for oral administration) and moving to the next group when no adequate drug is left in the previous group. It should be noted that one only drug should be selected from Groups 2 (FQs) and 3 (2LIs) because of documented total or partial cross-resistance within groups. It should also be stressed that all DR-TB patient regimens must include a new-generation FQ (high-dose levofloxacin or moxifloxacin), with the FQ drug counting among the four new ones that must form the framework of treatment in MDR-TB cases. On the contrary, an FQ should be given, but not relied on as one of the four new drugs, in cases where resistance is suspected or confirmed, such as in XDR-TB.

All patients with MDR-TB will need at least two drugs (plus the FQ and 2LI) from Group 4. The best one is ethionamide (Eth), and it should always be included in the regimens of patients with MDR-TB and XDR-TB when it can be susceptible. Other Group 4 drugs should be included in the MDR-TB regimen, preferable cycloserine (Cs). If Eth or Cs cannot be used, PAS may be considered.

Group 5 is composed of drugs for which anti-TB action has not been documented in clinical trials (except for Th). Their efficacy has been reported only in animal models or in vitro studies. These agents have been designated as reserve drugs (including Th) due to their low activity and high

toxicity, especially in HIV patients. This matter will be addressed in more depth in Chapter 9, where the role each drug can play for HIV patients will be reviewed.

A drug that has been employed for a patient within a failing regimen should not be counted in the total of four drugs for retreatment, even when the result of DST is encouraging, although if DST shows susceptibility to the drug, it may be added to supplement the regimen of at least four drugs. Lastly, a trend toward inclusion of Z in these regimens has been observed, but importantly, it is typically stopped before the emergence of resistance. Although this is a good argument for susceptibility to Z, confirmation by DST is very difficult (as it requires radiometric BACTEC technology). Therefore, if Z is added, it should not be counted as one of the four core drugs.

Suitable length of injectable drug administration during initial and continuation phases of treatment

During the initial phase (IP) and continuation phase (CP), different changes occur in DR-TB as compared to drug-sensitive TB. With the latter, the difference between the two phases is marked by the lack of need to continue with the accompanying drugs (E+Z) when the bacillary load has been reduced to a minimum. This is logical, and in this manner the core drugs may be administered throughout treatment. With DR-TB, the inability to use H+R means the core treatment drugs must be FQs (especially new-generation FQs such as levofloxacin or moxifloxacin) and 2LIs. In such cases, these two core drugs cannot be given throughout treatment, because of the accumulative toxicity of the 2LIs. The FQs are the best option (Table 8.3), and because they are generally well tolerated, they certainly should be maintained throughout treatment. 2LIs may cause more frequent adverse side effects as they are used over a longer period of time. Due to this, and the fact that their sterilising capacity is rather reduced, it is advised that they be suspended when the bacillary load has clearly been reduced. In other words, in DR-TB treatment, the main difference between the IP and CP is the suspension of the 2LI as a core drug. In this case, the CP must include an FQ and other accompanying drugs that will protect the FQ so it can do its job and not be selected by the naturally resistant mutants.

Once this matter is analysed, decisions should centre on the ideal length of time to administer the 2LI, and hence the length of the IP. Compelling evidence is also lacking in this regard. There have been no clinical trials comparing the efficacy of regimens with different lengths of parenteral drug administration in patients with drug-resistant strains of TB. In the pre-rifampicin period, several studies evaluated regimens containing an aminoglycoside, but the length of administration was not stated.

A review of the major guidelines reveals some controversy. The WHO and The Union recommend only 2 months of S in the standard retreatment regimen with FLD (called Category 2). For the WHO, which published specific guidelines for the treatment of patients with MDR-TB in 1997, the period of parenteral administration was extended to a minimum of 3 months, or until culture conversion. However, WHO guidelines from 2003, while maintaining the same length of dosing for the parenteral drug in the Category 2 regimen, recommended an extension to a minimum of 6 months for this parenteral drug for chronic patients. Additionally, the 2006 and 2008 WHO guidelines suggest 'at least 6 months and at least 4 months after the patient first becomes and remains smear- or culture-negative.' More recent recommendations from the WHO, published in 2011, increase the time to a minimum of 8 months, a fixed time that does not at all take into account bacteriological conversion, which should be the first premise to guide the change from the IP to the CP. This controversial recommendation has been classified as temporary and is accompanied by low-quality evidence. As such, each country should adapt the recommendations to its circumstances and patients.

The guidelines of the ATS from 1994 and 2003 state that in the absence of another therapeutic option, the maximum cumulative dose of S to be prescribed is 120 grams, due to its toxic effects. No reference is made to other 2LIs. In 1998, the British Thoracic Society (BTS) recommended the use of five or more drugs for MDR-TB patients and indicated that these should be employed until cultures become negative, after which three drugs should be continued. Although it is very likely that the 2LI would be one of the drugs withdrawn when cultures become negative, it is not specifically mentioned. Expert opinions are thus contradictory. Some tend to recommend a treatment length of between 3 and 6 months, while others suggest a minimum of 12 months after the cultures become negative, when susceptibility to only four drugs is likely, or even throughout administration if the patient presents with extensive lung damage or a high degree of resistance.

Considering that the site of action of this injectable drug may be exclusively extracellular, one could expect low efficacy once the cultures become negative. However, injectables can also have intracellular activity. If so, this group of drugs would be very likely to remain effective even after culture conversion. For this reason, the recommendation on the length of administration of the injectable drugs should be decided with regard to other drugs in the regimen, the patient's bacteriological status and close monitoring of adverse effects. If a regimen provides three effective drugs from Groups 1, 2 and 4 (Table 8.4) after withdrawal of the injectable agent, this agent can be safely withdrawn when the smear and/or cultures become negative.

Conversely, when there are fewer than three effective drugs, or if any of them belongs to Group 5, a longer administration of the injectable agent should be considered, depending on the efficacy of the remaining drugs, the bacteriological status of the patient and the presence/absence of undesirable effects.

To summarise, for patients with MDR-TB or those with DR-TB very likely to be FQ-susceptible, it may suffice to administer the injectable until AFB smear conversion is confirmed, which could be considered the case when the patient has two consecutive negative AFB smears at 1-month intervals. With a low bacillary load after the intensive phase, the FQ could be enough, without the need for an injectable, if supported by another companion drug. One may indirectly conclude that patients who present with early negative AFB smears (in the first 2–3 months of treatment) very possibly do so because the *M. tuberculosis* strain is susceptible to FQs and injectables, and that there should be no problems suspending the IP with the confirmation of negative AFB smears. This recommendation was followed in the successful 9-month treatment of the Bangladesh regimen (shortened with SLDs) for MDR-TB cases that had not previously received SLDs. The study showed a relapse-free cure approaching 90% with a regimen that included only 4 months of Km or until smear conversion. It is a logical and very practical recommendation, because it is based on the results of AFB smears, which are much more reproducible in the field than cultures. In terms of standardisation, 4 months of IP could be a good choice for patients with early smear conversion.

On the other hand, for patients in whom there are clear suspicions that the *M. tuberculosis* strain might be FQ-resistant (whether based on a history of FQ administration for TB or DST results), the administration of the injectable should be prolonged after the cultures have converted to negative because it would be the sole regimen core drug and the one that clearly increases the chances for cure. It is also very likely that these patients will convert to negative slowly, giving an indirect parameter for evaluating possible resistance to FQs. Thus, all XDR-TB cases should receive the injectable for 6–12 months after culture conversion. Because this involves many months of treatment, administration three times a week instead of daily could be evaluated. If circumstances permit, intravenous administration through long-term catheters should be considered.

The role of surgery in the treatment of patients with drug-resistant tuberculosis

Surgery may be indicated in concrete cases for managing sequelae or complications of pulmonary TB. For patients with extra-pulmonary TB, surgery

may be acceptable for obtaining samples for study and treating some situations such as constrictive pericarditis, vertebral abscesses compressing the spinal cord or superficial and accessible abscesses in cases of osteoarticular TB. Note that in pulmonary TB, surgery should not be considered as a viable option for therapy, in view of the excellent performance of pharmacological treatments.

A historical review of TB treatment during the first half of the twentieth century shows that surgery played a major role. Reduction of the bacillary burden achieved by the different surgical procedures in the pre-pharmacotherapy era produced a higher cure rate than that of the natural evolution of the disease. Surgery nonetheless fails to entirely eradicate bacilli from lesions and involves high morbidity and mortality. With the discovery of effective anti-TB drugs, the indication for surgery was progressively abandoned and had virtually disappeared from case management by the 1970s. The question then emerged again for patients with MDR/XDR-TB and resistance to multiple other drugs, when practically no available pharmacotherapy regimen ensured a cure. Under these circumstances, many patients today face situations very similar to those in the pre-pharmacotherapy era.

Despite the absence of randomised trials assessing the role of surgery in the treatment of patients with MDR-TB, virtually all available guidelines and specific recommendations on the subject mention surgery, although it is assigned only a secondary role. Surgery should be considered for treating DR-TB only in patients meeting the three following conditions: 1) a fairly localised lesion, 2) an adequate respiratory reserve, and 3) a lack of sufficient available drugs to design a regimen potent enough to ensure cure.

The strongest advocates of surgical treatment recommend scheduling surgery at the time of the lowest possible bacillary load, preferably after sputum smears and culture have become negative, and suggest continuing a predetermined pharmacotherapy regimen of 18 to 24 months. It would be useful to evaluate the clinical outcome of these patients with negative cultures if chemotherapy was continued without surgery, considering that pharmacological treatment has demonstrated efficacy in sputum conversion, bearing in mind that the bacillary load is already much lower. It should be kept in mind that surgery performed on these patients, even by the most experienced surgeons, has high rates of morbidity and mortality.

Consequently, surgery should only be considered for the management of MDR/XDR-TB for patients meeting the three conditions mentioned above and must be performed only by experienced surgeons with the support of efficient postoperative care units. Such settings are available mostly in developed countries. Of course surgery may be indicated more often in

patients with XDR-TB in settings where the third condition—a lack of sufficient available drugs—is seen more frequently.

Approach to the optimal regimen for drug-resistant tuberculosis: standardised versus individualised regimens

The guidelines of scientific societies in resource-rich countries have always advocated individualised case management. On the basis of these experiences with an abundance of resources, various authors have published important recommendations based on individualised criteria for the selection of the best possible regimen for each patient. The major principles of individualisation include choosing the treatment according to the results of DST and the development of aggressive therapeutic regimens in settings allowing for close follow-up by skilled professionals. Published studies have reported the efficacy of this strategy. This is nonetheless a very expensive approach that is difficult to implement in the majority of countries with moderate and low economic resources, which unfortunately bear the highest burden of MDR-TB. As many countries have barely employed SLDs during the past few years, one could expect the presence of microorganisms susceptible to most of the SLDs. For this reason, the WHO's specific recommendations for the treatment of MDR-TB from 1997 favoured the use of standardised treatments in many circumstances. Standard treatments for these patients facilitate management, decrease the number of specialist physicians needed and reduce the overall cost of treatment by a factor of five to ten. In the light of these advantages, various authors have advocated standard management, but only under specific conditions. Importantly, the efficacy of this strategy has been confirmed by reports in the literature.

To help resolve this controversy and simplify management of these cases, potential sources can be condensed into three categories: 1) Initial MDR-TB in patients without a history of receiving anti-TB drugs (or duration of less than 1 month), 2) MDR-TB cases having received only FLDs in the past, and 3) MDR-TB cases having received FLDs and SLDs in the past. The various management possibilities for these patients will be discussed separately for each category.

Initial multidrug-resistant tuberculosis in patients without a history of previous anti-tuberculosis treatment

Although there is some controversy, most studies have shown a high rate of incident MDR-TB in patients who had previous contact with known MDR-TB cases. In these cases, it is judicious to recommend that contacts of DR-TB cases be treated with the same regimens as index cases. If the index case is unknown, these initial MDR-TB cases should receive the standardised plan for the country (with SLDs). In both cases, the plan can be modified once DST results are complete.

Multidrug-resistant tuberculosis cases who have received only first-line drugs in the past

Even in countries with abundant resources, these patients could be treated with standardised SLD regimens because most will be susceptible to all SLDs. As shown in Table 8.4, the regimen for these patients might include a new FQ (high-dose levofloxacin or moxifloxacin), a 2LI other than S and two other drugs from Group 4 (preferably Eth and Cs, given their tolerance and efficacy). Z should be added because it sometimes retains susceptibility and because the DST for this drug is not reliable. E can be considered if the DST shows susceptibility, even if it has been used in the past, given its low toxicity and cost. This standard regimen fulfils all the requirements previously set forth and will avoid the great danger of improvised treatments and problems inherent in interpreting DST results for SLDs. Accordingly, the standardised regimen designed to benefit all patients with MDR-TB who have not received SLDs in the past would include an intensive phase with a new FQ (high doses of levofloxacin or moxifloxacin), a 2LI (capreomycin (Cm), Km or amikacin (Am)), a thioamide (Eth or prothionamide (Pto)), a fourth new drug and Z. This intensive phase comprising four new drugs and Z must be maintained until smear conversion is confirmed (two consecutive smears at 1-month intervals). Other programmes may choose to have the IP continue until some months after culture conversion or opt for fixed durations that do not take the bacteriological status of the patient into account, even though this is not advisable. Conversely, the CP should include all these drugs except the injectable and be maintained for a minimum of 12–18 months after culture conversion, more than enough time to ensure cure.

The plan discussed above has been used throughout the world over the last 10 years. The problem with this standardised regimen, which the great majority of countries are more or less following, is that it is very long, expensive and toxic, and clearly has potential for significant abandonment of treatment. Importantly, abandonment of course decreases chances for success, which barely exceed 60% in the field. This is why much shorter, cheaper and better tolerated regimens are needed. In this respect, the Bangladesh studies, in which a regimen of just 9 months with SLDs has achieved relapse-free cure rates approaching 90%, are encouraging. This promising 9-month regimen includes a 4-month IP (or until smear conversion) with high doses of gatifloxacin, high-dose H, Km, Pto, clofazimine (Cf), E and Z, and a 5-month CP with high doses of gatifloxacin, Cf, E and Z. Meeting all the basic recommendations for DR-TB regimen design described in this chapter, this regimen appears to portend a good future for MDR-TB patients who have not taken SLDs before, but it must be proven in other regions of the world. These Guidelines openly support this regimen. Of course such

standardised treatments are not indicated for carriers of XDR-TB strains of *M. tuberculosis*.

Multidrug-resistant tuberculosis cases who have received first-line and second-line drugs in the past

Management of these patients poses a most difficult problem as they have often suffered from a regrettably lengthy sequence of therapeutic errors with multiple regimens and drugs administered, which are very often hard to ascertain. The only solution in these cases is individualised management based on the premises presented in this document. However, certain situations may require standardised regimens. This is the case in many countries where only one or two SLDs are commercially available, for instance middle- and low-income countries where Km and FQs are the only reserve drugs. Following the logical sequence described above (Table 8.4), a regimen including Cm from Group 3 and the three drugs from Group 4 (Eth, Cs and PAS) could be recommended, in addition of course to a new FQ. Many other regions and countries have counted only on Km and Am as reserve drugs.

Such individualised treatment should always be offered to patients with XDR-TB strains. In addition, it is very difficult to find four new drugs from Groups 1–4 (Table 8.4) for most of these cases, meaning it is frequently necessary to add drugs from Group 5 (even though there is scant experience in TB for these drugs), and possibly other drugs with likely resistance to the regimens of these complex cases. These drugs will be extensively reviewed in Chapter 9. All of these patients should receive a new FQ that they have not previously received or to which the strain is known to be resistant, and a 2LI not previously administered. This recommendation is based on the fact that despite the existence of a high rate of cross-resistance among all the FQs and among all the 2LIs, this cross-resistance is not absolute. They should thus be given in case the strain is not totally resistant (of course not counting them among the four new drugs that form the treatment framework). Many of these patients are going to have to take six or seven, or even eight or nine drugs, in the hope that they all offer something towards possible cure. These are very expensive regimens and have many adverse side effects, some of which are very serious and must be aggressively addressed from the outset. At this time, they represent the most important clinical challenge in TB treatment, together with the recently described TDR-TB, a term that, although not officially accepted, would include those TB patients resistant to all the drugs in Groups 1–4 (Table 8.4). In these cases, it is clearly necessary to resort to numerous drugs from Group 5 (Table 8.4) to attempt cure. These patients may have a chance for cure if there are good resources for access to all Group 5 drugs and if clinical management is appropriate.

Other new drugs in study phase, such as TMC207, may also offer efficacy to help manage difficult cases. These drugs and their possible role in the management of all these patients are reviewed in Chapter 9.

Treatment of mono- or poly-resistant non-multidrug-resistant tuberculosis

The therapy focus for patients carrying mono- or poly-resistance who are not MDR is completely different than cases where the drug involved in the resistance is H or R. Patients with H mono- or poly-resistance but who retain susceptibility to R are fairly common in all NTPs. These patients are relatively easy to treat and cure with a drug combination regimen of 9–12 months that includes R and three other drugs, including an FQ. These three other drugs should be selected based on the rational categorisation illustrated in Table 8.1 and on the poly-resistant patient's pattern of resistance. The ideal treatment for a patient with H mono-resistance would be treatment length of 9 months with R+FQ+E and the initial support of Z during the first 2 months.

A completely different situation exists in patients with R mono- and poly-resistance retaining susceptibility to H. This situation is very rare because over 90%–95% of cases with R resistance are actually MDR-TB. Further, it must be remembered that while DST reliability for H is high, it is not 100%. So, under field conditions, all R mono- or poly-resistant cases must be managed like MDR-TB patients, of course adding H for its potential helpful effect. Accordingly, an MDR-TB plan must be designed following all the premises discussed in this chapter. H must be added, but preferably not counted among the four drugs forming the core of treatment. The patient will then have a high likelihood of cure, whether he is MDR-TB or R mono- or poly-resistant but with susceptibility to H. Because R cannot be used on these patients, treatment should last at least 18 months.

Conclusions

Despite the fact that the management of TB patients grows more complicated as patterns of resistance expand and change, with proper clinical and operational patient management, cure can be achieved even for patients with expanded patterns of resistance. The problem lies in the fact that the evidence on which the management of these patients is based is very scarce and of limited quality. Therefore, there is a great deal of controversy about many aspects of case management even today. Table 8.5 shows a summary of discussions in this chapter, with the most important recommendations to follow.

Table 8.5 Multidrug-resistant tuberculosis management, fundamental aspects

<i>Steps</i>	<i>Considerations</i>
1 Diagnosis	<p>Assess information from:</p> <ul style="list-style-type: none"> • History of drugs used: 1 month of monotherapy or single drug intake over a failure regimen could be a strong predictor of resistance • DST: Most reliable for R and H; also reliable for Km and FQs; less reliable for E and Z; very low reliability for Group 4 drugs • Perform HIV test. If positive, initiate cotrimoxazole prophylactic therapy and antiretroviral therapy as soon as possible
2 Number of drugs	“At least four effective drugs” never used in the past or proved susceptible by DST taking into account DST reliability and cross-resistance
3 Drug selection	<ul style="list-style-type: none"> • Use FLDs if still effective • One injectable • One new-generation FQ • Use Group 4 drugs until four effective drugs found • If necessary, use Group 5 drugs to strengthen the regimen or when four effective drugs are not found within the previous groups; count two Group 5 drugs as one effective drug
4 Length of injectable administration	<ul style="list-style-type: none"> • At least 4 months after smear or culture conversion • Longer if there are not three effective drugs during continuation phase or if they are from Group 5
5 Surgery	<p>Consider only if:</p> <ul style="list-style-type: none"> • Few effective drugs are available • Localised lesions • Sufficient respiratory reserve
6 Ideal regimen	<ul style="list-style-type: none"> • Standardised: If there has been no use of SLDs in the past • Individualised: Use of SLDs in the past or contact with MDR patient having used SLDs (treat with the effective regimen for the index case)

Source: Adapted from Monedero and Caminero, page 121.

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Anti-tuberculosis drugs: mechanisms of action and rationale for use

José A. Caminero

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-

The treatment of tuberculosis becomes more intricate as the resistance profile of mycobacteria broadens, particularly in the case of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB). In recent years, a number of basic rules for the management of these patients have been agreed upon, including the caveat that all patients should receive at least four drugs to which the Mycobacterium tuberculosis strain is susceptible and that anti-TB drugs should be categorised into five groups according to their importance. These agreements have not resolved the multiple issues concerning the best use of the five groups of drugs. After reviewing each group, on the basis of recently accumulated evidence, we have reached the following conclusions: 1) High-dose isoniazid (H) along with pyrazinamide (Z) and ethambutol (E) should be evaluated as an adjunct for the treatment of MDR-TB and XDR-TB. 2) The fluoroquinolone (FQ) of choice is levofloxacin (Lfx) at high doses (750–1000 mg/day) or moxifloxacin (Mfx). 3) The best sequence for the injectable drugs, depending on availability, is: capreomycin (Cm), kanamycin

(Km) and amikacin (Am). 4) The other second-line drugs should be used in the following order: thioamides always as the first choice, then cycloserine (Cs) and P-aminosalicylic acid (PAS). 5) With regard to the fifth group of adjuvant drugs, perhaps the best sequence would be: clofazimine (Cf), amoxicillin/clavulanate (Amx/Clv), linezolid (Lzd), carbapenems (imipenem and meropenem), clarithromycin and thiacetazone (Th).

The present chapter discusses the basis for these recommendations, which are crucial considerations in the treatment of MDR-TB, especially XDR-TB patients or those with a more extensive pattern of resistance. Among the new drugs being

tested for the treatment of TB, in addition to the role that Mfx may play in the initial treatment of TB, only TMC207 (Bedaquiline) and OPC-67683 (Delamanid) are in Phase III research, with studies underway on the former in MDR-TB and XDR-TB cases looking very promising. Testing is also being conducted on animal models with several new combinations of existing drugs. Some of the areas addressed in this chapter need further clinical studies to elucidate the actual role of each drug in the treatment of these patients.

Introduction

The period between 1950 and 1970 marked a turning point in the battle against TB, because it was during this time that most of the current anti-TB drugs were discovered and the therapeutic regimens that made TB a curable disease were designed. Unfortunately, initial optimism progressively gave way to a pessimistic perspective, due to the appearance of increasingly resistant forms of TB and the fact that in the last 45 years, only FQs have been incorporated to the anti-TB arsenal. The concept of patients with incurable TB is thus regularly being discussed once again. Although the probability of cure decreases as the resistance profile of *M. tuberculosis* broadens, rational use of the available drugs will always provide significant chances of cure in patients with drug-resistant TB (DR-TB), even those with MDR-TB (resistance to at least H and R) or XDR-TB (MDR-TB plus resistance to FQs and at least one second-line injectable drug (2LI)). This rational use of anti-TB drugs always improves chances for cure.

Appropriate use of the available drugs becomes crucial in treating MDR-TB and XDR-TB. The regimen should combine a minimum of four drugs to which the patient's organism may still be susceptible, and this choice should be based on rational introduction according to their recommended categorisation into five groups (by order of importance, see Table 8.4). Important issues have emerged in recent years with regard to optimising the use of these five drug groups, including possible cross-resistance. Decisions must be made by analysing each of the five groups individually and determining what each might bring to the management of DR-TB patients despite possible or proven resistance on the susceptibility test.

There are patients whose strain of *M. tuberculosis* has such an extensive pattern of resistance that even with the availability of all Group 5 drugs, there is no adequate treatment plan that meets the basic assumptions reviewed in the previous chapter. Investments must therefore be made in the development of new drugs that can support the treatment of these quite complex cases and also to assess their possible role in the treatment of drug-sensitive TB.

Other important questions arise in the management of patients with MDR-TB and XDR-TB, such as how to approach the possible susceptibility

or resistance of each drug against *M. tuberculosis*. MDR-TB should not be diagnosed unless resistance to H and R (at least R) has been documented by drug susceptibility testing (DST), implying that there is some capacity for this test at sites where MDR-TB is being diagnosed and treated. Moreover, in countries with capacity to perform DST for the other first- and second-line drugs (FLDs and SLDs), the information regarding FQs and injectables must be considered together with the history of drugs taken by the patient in the past. This issue was addressed in Chapter 7 of these Guidelines.

Anti-tuberculosis drugs: mechanisms of action

As indicated in Chapter 8, the success of a TB treatment plan will depend as much on combining an appropriate number of drugs (generally at least four new ones or those with proven susceptibility) as on selecting one with the ability to kill *M. tuberculosis* in its various stages of growth. Knowledge of the mechanisms of action of the various anti-TB drugs is therefore fundamental when designing a treatment plan. Ideally, a regimen should combine the greatest number of bactericidal drugs with others that have a sterilising action. Bactericidal drugs will kill many bacilli in a short time and so should always be part of the core treatment. This will rapidly reduce the patient's capacity for infectiousness and increase the chances for survival. Conversely, sterilising drugs kill *M. tuberculosis* in its latent or semi-latent phases, allowing for shorter treatment duration. The different bactericidal and sterilising actions of the anti-TB drugs and their chances of causing adverse side effects are summarised in Table 8.3 and extensively reviewed in Chapter 8. We will also review here the site of action for killing *M. tuberculosis*. This review of all anti-*M. tuberculosis* drugs follows the classification of the five groups discussed in Table 8.4 to further discern the role each can play in treating DR-TB (Table 9.1).

Role of first-line oral anti-tuberculosis drugs in the management of drug-resistant tuberculosis

The first group in Table 8.4 includes the four main drugs that make up the ideal regimen for initial treatment: H, rifampicin (R), Z and E. The role that H and R can play in non-MDR-TB patients with mono- or poly-resistance is addressed in detail in Chapter 8. Clearly, the therapy focus for non-MDR-TB patients with mono- or polydrug-resistant strains is entirely different if resistance is to H or R. Patients with H mono- or poly-resistance but retained susceptibility to R are relatively common in all NTPs. As expected, R should be kept as a fundamental drug in regimen design and included among the four that make up the basic regimen. By using R, the length of treatment

Table 9.1 Role of the different groups of drugs in MDR-TB and XDR-TB treatment

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- 1 First-line oral anti-tuberculosis drugs
 - High-dose isoniazid along with pyrazinamide and ethambutol should be evaluated as an adjunct for MDR-TB and XDR-TB treatment
 - Not to be counted as one of the four basic drugs of the regimen
 - 2 Fluoroquinolones
 - A fluoroquinolone should always be used in MDR-TB or XDR-TB treatment
 - Preferably use levofloxacin in doses of 750 to 1000 mg/day; moxifloxacin may also be a good choice
 - The fluoroquinolone should be counted as one of the four basic drugs of the regimen in patients with MDR-TB, but not in XDR-TB patients (possible cross-resistance)
 - 3 Injectable anti-tuberculosis drugs
 - An injectable drug should always be used in MDR-TB and XDR-TB treatment
 - Never use streptomycin
 - Ideally, give preference to the sequence capreomycin → kanamycin → amikacin
 - The injectable should be counted as one of the four basic drugs of the regimen in patients with MDR-TB, but not in XDR-TB patients (possible cross-resistance)
 - 4 Other less effective second-line drugs
 - Use all the necessary agents to have four active basic drugs; always start with ethionamide/prothionamide, followed by cycloserine and then p-aminosalicylic acid
 - 5 Other less effective drugs or drugs with limited clinical experience
 - To be counted as 0.5 drug → It will be necessary to use a minimum of two drugs from this group, when needed
 - Introduce according to availability in the following order: clofazimine, amoxicillin/clavulanate, linezolid, imipenem/meropenem, clarithromycin and thiacetazone
 - Evaluation is required before adding high doses of isoniazid
-

can be reduced to 9–12 months. A completely different situation exists if a patient with R mono- and poly-resistant strains retains susceptibility to H. This situation is quite rare in the field, because more than 90%–95% of cases with R resistance are actually MDR-TB. Thus, although H should always be given in these cases, R should not be included, and the designed plan should be the same as if the patient were suffering from MDR-TB.

Accordingly, the great majority of MDR-TB and XDR-TB patients have already received and failed one or several cycles of combined drugs, including Z and E. Given this, and the low reliability of the susceptibility tests for E and Z, resistance to them should often be suspected, meaning Z and E

should never be considered among the four essential drugs in regimens for these patients. In recent years, however, some evidence has been published on the value of these FLDs (including H) in the treatment of MDR-TB and XDR-TB cases.

Isoniazid: mechanism of action and role in the treatment of drug-resistant tuberculosis

It is a shame that a drug that is so good and has such potent bactericidal activity has already been lost to an important percentage of patients around the world due to proven resistance. First, H is only active against mycobacteria. Within the genus, its effect is mainly against *M. tuberculosis complex* and to a lesser extent against a few species of environmental mycobacteria, e.g., *M. kansasii*. H has the most potent early bactericidal activity of all anti-TB drugs, and adding other drugs does not increase this activity. Thus, the rapid reduction in infectiousness following initiation of chemotherapy is most likely attributable in large part to the bactericidal activity of H. It also seems logical that it will have a decisive influence on improving chances of survival in the early days/weeks of treatment and on earlier conversion to negative of sputum smear microscopies and cultures.

Early reports suggest that H affects cell wall integrity. Acid-fastness is lost shortly after treatment with H begins. This drug inhibits the synthesis of mycolic acids in the cell wall. When acting on the mycobacterial cell wall of continually replicating bacilli, there must be active bacilli replication for the drug to exert its potent bactericidal action. This is why its bactericidal action declines in the early weeks of treatment and nearly disappears when the sputum smears become negative, i.e., when most of the remaining bacilli are in latent or semi-latent growth phases. Interestingly, the sterilising action of H is very poor. With these important characteristics, its good tolerance and low price, it is regrettable that H is already lost to over 10% of patients worldwide due to resistance acquired over years of misuse.

H is a prodrug that is activated by catalase-peroxidase synthesised under the control of the *katG* gene. It is thus virtually devoid of action against *M. tuberculosis* unless it is converted to its active form by the *katG* gene. Hence, mutation of the *katG* gene results in a very high level of resistance to H (greater than 1 mg/L). In the absence of the *katG* mutation, activated H acts upon several genes of the bacillus, of which the *inhA* gene is most important. The *inhA* gene is also the genetic target of ethionamide (Eth) and prothionamide (Pto), and mutation of this gene results in a low level of resistance to H (0.2 mg/L) and concurrent cross-resistance to Eth. Therefore, strains with low and high levels of resistance to H by DST are usually fully resistant to H, but probably susceptible to Eth. Conversely, strains resistant to low levels of H (0.2 mg/L) but susceptible to high levels of the drug

(1 mg/L) are usually resistant to Eth (*inhA*) and susceptible to high doses of H (10–15 mg/kg). The latter could be true for up to 10%–15% of TB patients with resistance to H, in whom high doses of this drug may be useful (in spite of demonstrated *in vitro* resistance) to overcome the potential problem of cross-resistance to Eth.

This controversial issue was recently evaluated in a randomised clinical trial by Katiyar et al., which concluded that “after adjustment for potential confounders, . . . subjects who received high-dose H became sputum-negative 2.38 times (95%CI 1.45–3.91, $P = 0.001$) more rapidly than those who did not receive it, and were 2.37 times (95%CI 1.46–3.84, $P = 0.001$) more likely to be sputum-negative at 6 months. These subjects displayed better radiological improvement without an increased risk of H toxicity.” Although the results of this clinical trial are very valuable, the study was too small to control for other outcome predictors in any realistic way.

We therefore conclude that adding high doses of H to the treatment of MDR-TB and XDR-TB could be a sound recommendation and should be evaluated as part of regimen design. Ideally, this recommendation should be followed only in selected patients with proven susceptibility to high-dose H or with an LPA test (GenoType) showing no mutation in the *katG* gene. However, it often takes at least 2–3 weeks to obtain the results in many settings. Thus, in countries with a high MDR-TB burden and no facilities to provide such information, systematically adding high-dose H to the DR-TB regimen should be considered. The use of high doses of H and Eth should ensure the presence of one active drug. In these cases, vigilance for hepatotoxicity and neurotoxicity should be exercised, especially in an at-risk population.

Rifampicin and other rifamycins: mechanism of action and role in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis

Discovered over 40 years ago, R remains the most effective drug against *M. tuberculosis*. It has the ability to kill *M. tuberculosis* in all its growth phases. R works on mycobacterial RNA, enabling good bactericidal action (though not as good as H) and sterilising action (Table 8.3). Its powerful sterilising action makes it the most influential drug for shortening TB treatment. A regimen with R can cure in 9 months, whereas a regimen without it needs 18 months at minimum, at least according to classical studies (although the new generations of FQs may have a similar sterilising action at high doses and thus the ability to shorten MDR-TB treatment). It appears that the other rifamycins have the same effect as R in TB treatment, though there is little solid evidence to support this.

Contrary to H, R is active against a wide range of microorganisms including *Mycobacterium leprae*, *Staphylococcus aureus*, *Neisseria meningitidis*

and *Legionella pneumophila*. Like all naphthalenic ansamycins (the class to which rifampicin belongs), R is a specific inhibitor of DNA-dependent RNA polymerase. R acts by interfering with the synthesis of mRNA by binding to the RNA polymerase. Three different rifamycins are currently commercially available: rifampicin, rifabutin and rifapentine. *M. tuberculosis* develops resistance to all of these by means of a mutation in the 81 bp region of the RNA polymerase β -subunit (*rpoB*) gene. However, analysis of the diverse mutations of this gene has revealed that even if most of the isolates resistant to R are also resistant to rifapentine, about 15%–20% could be susceptible to rifabutin. This has also been observed in some clinical studies. Potential susceptibility to rifabutin is based on the current recommended cut-off for its DST. This cut-off has never been clinically validated, and therefore, clinical response to rifabutin should not be expected in patients whose isolates are susceptible to rifabutin but resistant to other rifamycins. Moreover, the possible use of rifabutin in MDR-TB and XDR-TB patients is limited by its high cost and the lack of availability of the drug and corresponding DST in many countries. For these reasons, the use of R or other rifamycins should not be systematically recommended in MDR-TB and XDR-TB cases. It should be considered only in isolated cases where rifabutin can be tested, and then only if results show sensitivity. It should not be among the four basic regimen drugs, but rather an addition to the core drugs.

Pyrazinamide: mechanism of action and role in the treatment of drug-resistant tuberculosis

Z is essentially a weak drug with very limited activity only on bacilli that are intracellular and dividing in an acidic environment. Z is also only active against mycobacteria, and among the genus, mycobacteria other than *M. tuberculosis* (including *M. bovis*) are naturally resistant. It was recognised early on that Z acts only in an acid environment. The active derivative of Z is pyrazinoic acid, which preferentially accumulates in an acidic pH. Z is not active against intracellularly growing *M. tuberculosis*; only the accumulation of pyrazinoic acid through the action of the amidase pyrazinamidase by susceptible *M. tuberculosis* triggers its intracellular bactericidal action. Relatively little is known about the actual drug target, although the nicotinamide adenine dinucleotide metabolic pathway has been postulated as a potential target. Mutations in *pncA*, a gene encoding pyrazinamidase, causes resistance to Z. Resistance against Z appears to develop rapidly if it is given as a single drug.

Therefore, while the bactericidal ability of Z is very poor, it has powerful action on bacilli that divide very little in the presence of an acidic medium unfavourable to bacilli. This acidic environment unfavourable to bacilli is the same for most anti-TB drugs, including H and R. The difference is that Z

does not lose its action in the acidic environment surrounding the bacilli when it is inside the macrophage or when there is much inflammation. On the contrary, when the acidic environment disappears, the action of Z should in theory be nil. Thus, it is recommended only during the first 2 months of initial treatment plans. This reasoning may be valid when R is kept in the regimen with its potent sterilising action, but it is very likely that if R is not present, Z may continue working after the first months of treatment. In conclusion, Z has very good sterilising action but poor to no bactericidal capacity.

Z was commonly used between 1950 and 1970 to treat patients carrying bacilli poly-resistant to H+S (similar to today's XDR-TB patients, because R and FQs did not exist). Three interesting articles were published during that time, reporting excellent cure and/or bacteriological conversion rates for the combination of Eth+Cs+Z. Presumably, Z had a major role in this regimen and remained active for the entire duration of the treatment. Moreover, a relatively frequent situation in MDR-TB patients is continued maintenance of original susceptibility to Z. This is the case for patients with initial treatment regimen failure who develop MDR-TB, but with a strain initially resistant only to H. This could explain the results reported in two articles published recently on MDR-TB and XDR-TB patients demonstrating that adding Z, E or S to the treatment of patients who remain susceptible to these drugs improved their prognosis.

Taking into account the unknown reliability of the Z susceptibility test and its low cost and moderate to low toxicity, it seems reasonable to consider adding Z to all treatment regimens for MDR-TB, although it should not be counted as one of the four basic drugs. Evaluation should be individualised and consider that the risk of hepatotoxicity may be increased for elderly and alcoholic patients. The current common practice of using Z for patients with MDR-TB (regardless of susceptibility results) needs to be critically examined to determine if there are clinical benefits to such treatment and whether the benefits justify the possible increases in toxicity.

Ethambutol: mechanism of action and role in the treatment of drug-resistant tuberculosis

E is a somewhat controversial drug. Based on its theoretical mode of action (on the mycobacterial cell wall), it should have significant bactericidal capacity and be very potent. Yet it seems to behave as a far weaker drug than expected; its actual important properties correspond to its excellent tolerability and ability to prevent the selection of resistance to major drugs like H and R. E is also only active against mycobacteria and, theoretically, is bactericidal on both extracellular and intracellular tubercle bacilli. Specifically, it inhibits biosynthesis of the mycobacterial cell wall and acts on the

biosynthesis of arabinogalactan, the major polysaccharide of the mycobacterial cell wall. E inhibits the polymerisation of cell wall arabinogalactan and lipoarabinomannan, indirectly inhibits mycolic acid synthesis (by limiting the availability of arabinan for the mycolic acids to attach to) and triggers a cascade of changes in lipid metabolism of mycobacteria, leading to the disaggregation of bacteria clumps into smaller clusters.

The main benefits of E are its excellent tolerance and very low initial resistance rate in most countries. Furthermore, as mentioned for Z, patients with initial regimen failure who have MDR-TB but whose organisms were originally resistant only to H are likely to remain susceptible to E. This explains the benefit of E for MDR-TB and XDR-TB patients, although there are other plausible explanations for the improved results that have been observed. Given the uncertain clinical reliability of the E susceptibility test and the low cost and toxicity of the drug, it seems reasonable to evaluate the addition of E (dose: 15 mg/kg) to the treatment of MDR-TB. However, for patients who previously received E and for whom DST shows resistance, the addition of E is not advised. Further, E should not be counted as one of the four basic drugs and its inclusion as an additional drug in an already large pill burden needs to be carefully considered in the light of its potential detrimental effect on adherence.

Fluoroquinolones: mechanism of action and role in the treatment of drug-resistant tuberculosis

The FQs represent the mainstay of treatment for MDR-TB and XDR-TB patients and deliver the best outcomes. Importantly, they also hold potential in the treatment of drug-susceptible TB. FQs currently available are ciprofloxacin (Cfx), ofloxacin (Ofx), Lfx and Mfx. The latter two are called new-generation FQs to distinguish them from the second generation, which includes Cfx and Ofx. FQs inhibit DNA gyrase of *M. tuberculosis* and thus have acceptable bactericidal and sterilising action in combination, although action varies widely between them. This dual action, together with good tolerance and affordable cost, make FQs the best option among all SLD options. Given that all FQs share the same genetic target (*gyrA* gene), the use of only one per regimen is justified. Three questions relating to them are discussed below.

Are all fluoroquinolones equally effective?

Evidence is limited in this regard. It seems that Cfx is somewhat less effective and therefore should not be recommended. There is only one clinical study comparing Ofx and Lfx (Yew et al.). Lfx has been clearly proved to be more effective in patients whose *M. tuberculosis* shows confirmed susceptibility to Ofx, as well as in patients with *M. tuberculosis* resistant to this drug. The latter

finding suggests that there is not complete cross-resistance among FQs. Despite the lack of clinical studies, the pharmacodynamic data showed that Cfx is the least effective and that the effectiveness of FQs has increased with the new-generation agents. Lfx was superior to Ofx, but Mfx and gatifloxacin (Gfx) were even better than Lfx. The early studies used Lfx at doses of 500 mg/day. More recent studies using Lfx at 1000 mg/day demonstrated the best early bactericidal activity among the FQs (even a little better than Mfx and Gfx), but with the highest area under the concentration-time curve (from 0 to 24 h)/minimum inhibitory concentration (AUC₂₄/MIC), even a little higher than Mfx. Other studies have shown that Mfx and Gfx are better than Ofx, but without comparison against Lfx. To date, there have been no studies comparing high-dose Lfx with high-dose Mfx or Gfx. High doses of Gfx were used in the successful Bangladesh trial (short MDR-TB regimen), where nearly 90% of MDR-TB patients who had never before received SLDs had successful outcomes with a treatment regimen of just 9 months (van Deun et al.). With practically no evidence of relapses in this 9-month regimen, one may postulate that these high doses of Gfx have potent sterilising activity, probably very similar to R.

Is there cross-resistance between all the fluoroquinolones?

This was initially thought to be the case, as they all act upon the same *gyrA* gene. However, subsequent analyses of these gene mutations have demonstrated that approximately half of the isolates resistant to Ofx could remain susceptible to Mfx and to high-dose Lfx. These findings may account for the reported efficacy of Lfx in patients with resistance to Ofx. Furthermore, an interesting recent meta-analysis by Jacobson et al. analysed the outcomes of XDR-TB patients treated in 13 different settings. Although the favourable outcome rate was low (43.7%, while 20.8% died), favourable outcomes totalled 59% in settings where a new-generation FQ was systematically used for verified XDR-TB cases. In settings where this new generation of FQs was not used, the favourable outcome rate was just 31%. The most pertinent fact here is that studies in which a higher proportion of patients received a later-generation FQ reported a higher proportion of favourable treatment outcomes ($P = 0.12$), presenting new evidence that cross-resistance among the FQs is not absolute, especially with the new-generation drugs.

Which is the best fluoroquinolone to recommend in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis?

In the light of this discussion and the cost of Lfx, the ideal doses of FQ may be 750–1000 mg/day. The slightly better profile for Lfx (at the higher dose) compared with Mfx and Gfx is not likely to be clinically significant, and has

not been studied clinically. Therefore, Mfx and Gfx can be good options as well. Given the low toxicity of these new FQ generations and the available evidence, it is justifiable to always include one in the treatment of MDR-TB and XDR-TB. In the case of MDR-TB, the FQ is counted as one of the four basic drugs, but not in the case of XDR-TB due to the risk of cross-resistance to Ofx. Again, the question of which FQ to use (and at what dose) needs further clinical study, including an evaluation of possible long-term side effects.

Injectable anti-tuberculosis drugs: mechanism of action and role in the treatment of drug-resistant tuberculosis

Another mainstay in the treatment of DR-TB is the group comprising injectable drugs: the aminoglycosides—streptomycin (S), Km and Am—and the polypeptides, Cm and viomycin (Vi). The injectables are bactericidal and have strong extracellular activity, but some intracellular action has also been demonstrated, which could be explained by their mode of action. The aminoglycosides inhibit protein synthesis through irreversible binding to the 30S ribosomal subunit. The polypeptides appear to inhibit translocation of peptidyl-tRNA and block the initiation of protein synthesis. Cm has a different chemical structure and mechanism of action than the aminoglycosides, but the mechanism of antibacterial and metabolic activity is similar. As mentioned for the FQs, there is no reason to use more than one injectable in the treatment of DR-TB. Although similar efficacy and adverse side effects have been assumed for all 2LIs, they have not been demonstrated in the literature. In fact, there are no studies that compare the efficacy of these three injectables, although the pharmacokinetic and pharmacodynamic parameters are somewhat better for Am than for Km and Cm. This may lead to the assumption that Am could be somewhat better than the other two, although again, this has not been demonstrated in clinical studies. Nor are there studies comparing adverse effects, although it appears that side effects involving the eighth cranial nerve and renal damage occur less frequently with the use of Cm and that it should be the only one recommended for pregnant women due to its lower risk for teratogenic effects. With Cm, problems have been described with the control of ions such as magnesium, calcium and sodium. Further, in studies using all these 2LIs, there appears to be a slightly higher rate of adverse side effects with Am than with the others. Still, there is currently no strong evidence showing that one is superior to another in terms of efficacy or adverse effects. Because all 2LIs display very similar effectiveness and adverse reactions, this group of drugs raises the following questions.

Is there cross-resistance between all the injectables?

Here again, the evidence is scarce. Forty years ago, Tsukamura reported that isolates resistant to low concentrations of Km were susceptible to Cm and Vi

(this was not observed with the isolates resistant to high concentrations of Km, which were often resistant to Cm as well), while isolates resistant to Cm were susceptible to Km and resistant to Vi. Subsequent articles from the same author presented multiple indications of the likelihood of unidirectional cross-resistance between the injectables and therefore of the importance of the choice of injectable. Analysis of more recent publications studying the MIC of each 2LI and genetic mutations determining their resistance has led us to conclude that:

- 1 Isolates acquiring resistance to S are usually susceptible to Km, Am and Cm. However, rare strains with apparently single-step mutations conferring resistance to both S and Km have been observed.
- 2 Isolates acquiring resistance to Cm can be susceptible to Km and Am. However, a diverse proportion (dependent on setting) may be resistant to Km and even to Am.
- 3 Isolates acquiring resistance to Am almost always acquire resistance to Km and Cm.
- 4 Isolates acquiring resistance to Km show different levels of cross-resistance to Am and Cm.

Hence, while available evidence seems to demonstrate that Cm causes less cross-resistance than the others, this is not the case in all *M. tuberculosis* cultures, and results seem to vary according to setting. Moreover, the susceptibility test for all these 2LIs is not very reliable. Whenever one is used and shows resistance, possible cross-resistance to the other two must be suspected, a factor that must be kept in mind when designing treatment regimens.

What is the best sequence of use of the injectable drugs in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis?

To avoid cross-resistance that may interfere with the activity of other injectables in subsequent treatment regimens, the most reasonable sequence would be the following: S, Cm, Km and finally Am. However, S should never be used in the treatment of MDR-TB or XDR-TB, even if DST indicates a sensitive isolate (because DST is not reliable for these), because the rate of primary resistance is extraordinarily high and increases significantly in scenarios with resistance to H as in MDR-TB and XDR-TB patients. Moreover, there are other injectables available to ensure the efficacy of this mainstay group of drugs. The injectable of choice would hypothetically be Cm, except that it lacks large-scale availability at global level, has a short shelf life (24 months) and is more expensive than Km. In many countries, of necessity and practicality, Km is the first option in the field, as it is much more readily available and cheaper. In recent years, though, there have also been Km supply

problems, meaning that many countries have no other option but to use Am. Indeed, Am is the most widely available injectable drug in all hospitals because of its excellent activity against other bacteria. Given the good efficacy and low/moderate toxicity of these 2LIs, the treatment of MDR-TB and XDR-TB should always include one of them, with the choice dependent on the history of previous use for each one and the likelihood of resistance, particularly in XDR-TB patients. In the case of MDR-TB, the 2LI must be counted as one of the four basic drugs, but not in the case of XDR-TB due to the risk of cross-resistance. Again, the question of which 2LI to use (and at what dose) needs further clinical study.

Group 4—thioamides, cycloserine/terizidone and p-aminosalicylate: mechanism of action and ideal sequence of introduction in a drug-resistant tuberculosis regimen

This group encompasses agents from three drug classes extensively evaluated in clinical efficacy studies: the thioamides (Eth and Pto), Cs or its derivative terizidone, and PAS. As these drugs belong to different drug classes with diverse genetic targets, it is reasonable to use more than one if necessary. The drugs should be introduced in the above-mentioned order, especially the thioamides, which are much better drugs than the others in the group. Indeed, thioamides are more bactericidal than Cs and PAS, have a better toxic-therapeutic ratio and are less expensive. As a group, these drugs are considerably less effective than the previous groups.

Thioamides

Thioamides are by far the best of the Group 4 drugs, as documented by numerous studies showing their efficacy and ability to cure, even when only associated with weak drugs such as Z and Cs. Due to their mechanism of action, they are somewhat like a slightly weaker H, but when all is said and done their action is similar, meaning there obviously may be cross-resistance with H. Following the discovery of the pyridine-containing H, numerous pyridine derivatives were tested, and the activity of thio-isonicotinamide against *M. tuberculosis* was noted by several groups. Eth was one of these thioamides. Thioamides are active against *M. tuberculosis* and, to a lesser extent, against other mycobacteria.

Although the mechanism of action of thioamide drugs has not been fully elucidated, like H, they appear to inhibit mycolic acid biosynthesis. Pto is rapidly absorbed and excreted. Both thioamides show excellent penetration into cerebrospinal fluid. Resistance develops rapidly if used alone and cross-resistance is complete between Eth and Pto. Thioamides are generally good drugs except for low gastric tolerance and, as mentioned before, the

risk of cross-resistance to H. As such, they often become a basic anti-TB drug in MDR-TB and XDR-TB treatment regimens and are in fact included in the great majority of standardised MDR-TB regimens. Reliability of DST for Eth is very poor, so it is advisable to use it empirically and not rely on DST. Results for Eth DST must be interpreted with caution, always considering previous use of the drug. Modern LPA (GenoType Plus) techniques are able to test for the *inhA* gene, a target of thioamides (and of H, as noted above), and if the mutation is present, a possible resistance to thioamides must be suspected.

Cycloserine

There are similarities between Cs and Eth. It is surprising that Cs is such a weak drug, because its mechanism of action involves the mycobacterial cell wall and it is derived from a streptomycete. Cs is only bacteriostatic and competitively blocks the enzyme that incorporates alanine into an alanyl-alanine dipeptide, an essential component of the mycobacterial cell wall. Cs is active against *M. tuberculosis* and several species of gram-positive bacteria. Among the advantages of Cs are its high gastric tolerance (compared with the other two drugs in this group) and lack of cross-resistance to other agents. The two main drawbacks of Cs are adverse psychiatric reactions (psychotic reactions with suicidal tendencies), which necessitate a psychiatric interview prior to treatment initiation, and a short shelf life (24 months). Terizidone is a combination of two molecules of Cs, potentially causing fewer adverse events, although reports concerning this drug are scarce and not always relevant. Cs has become a basic drug in MDR-TB and XDR-TB treatment regimens in spite of its lower activity and adverse effects. The reality is that Cs is used extensively worldwide only because there are no better drugs to include in MDR-TB regimens and because at least four drugs are needed to ensure the highest probability of therapeutic success. Its only contribution may be that it protects the core pharmaceuticals in these treatment plans (FQs and 2LIs) from resistance selection. Replacing Cs with Cf as the fourth drug seems to have been a good choice in the Bangladesh (short MDR-TB) regimen.

p-Aminosalicylate

There are very few arguments for using PAS. It is quite weak, has scant activity (just bacteriostatic), is very poorly tolerated (particularly gastric adverse effects) and is very expensive. It is therefore relegated to the last level for drug selection for DR-TB treatment plans. Analogous to the observation that benzoic acid inhibits respiration of tubercle bacilli, PAS might be built into coenzyme F of the bacterium instead of para-aminobenzoic acid and thereby inhibit growth. The first PAS compound used in various studies was the acid

salt. The use of p-aminosalicylate sodium (PAS sodium), requiring doses 30% higher than the PAS acid, became progressively widespread in the 1950s and 1960s. From the 1970s until nearly 2000, PAS sodium was used in most countries, despite its well known gastric intolerance. However, over the last 10 years, thanks to global demand for MDR-TB and XDR-TB treatment, PAS was re-introduced, particularly in the form of enteric-coated PAS granules, and is now gradually replacing PAS sodium. Nonetheless, many countries still use the sodium formulation, because experience around the world has demonstrated its efficacy. Significant current demand for this agent has led to the use of both formulations of PAS. The main advantage of enteric-coated PAS acid seems to be better gastric tolerance and lower dose requirement, although it needs to be kept refrigerated (4°C), therefore requiring cold chain transport that is not always available in developing countries. In contrast, the major advantage of PAS sodium is its simple storage requirements with no need for a cold chain. In any case, PAS displays very low effectiveness and poor tolerance with high costs, which relegate it to the last place in Group 4.

Most effective drugs in Group 5 and recommended sequence of use

This is a very heterogeneous group that includes drugs for which experience is very limited in human TB treatment and which display very low efficacy or a high toxicity profile. As a consequence, the drugs in Group 5 are considered minor or adjuvant drugs and each should be counted only as 0.5 within the total of four core drugs for treatment of MDR-TB and XDR-TB. When it is necessary to resort to this group, at least two compounds should thus be chosen. The mechanism of action of the great majority of these drugs has not been clearly defined. Based on effectiveness, potential adverse reactions and cost, the sequence of introduction of drugs in this group should be as follows.

Clofazimine

Although experience with Cf in TB treatment is limited, it may turn out to be a much better drug than believed to date, with potential intracellular and extracellular activity. Adequate dose management facilitates control of adverse reactions, in particular photosensitivity and gastric intolerance. Low cost is another advantage, but current availability in the market is not assured as this drug has been almost exclusively restricted to treatment for leprosy. Some countries where Cf is available include it in standardised regimens because of its benefits and low cost. This is the case for the shortened MDR-TB Bangladesh regimen, in which Cf is used for just 9 months with a

success rate approaching 90% and included in the plan throughout treatment (see Chapter 8). In addition, one of the most promising lines of new drug studies and new plans associates Cf with other drugs like Mfx and/or Z. It appears that regimens with Cf clearly work better than those not using this drug, so it is possible that it acts as a facilitator for other drugs. Given these qualities, an initiative should be undertaken to facilitate global availability of Cf.

Amoxicillin/clavulanate

Beta-lactams antibiotics have not been regarded as useful drugs for TB treatment because *M. tuberculosis* is naturally resistant to most of them in vitro. Resistance is thought to be mediated by a class A β -lactamase which hydrolyses penicillins and cephalosporins. Resistance may be overcome by 1) inhibition of the β -lactamase or 2) use of an antibiotic that is not a substrate for it. An example of the former strategy is the use of a combination of a β -lactam and a β -lactamase inhibitor like Amx/Clv, which is active in vitro and has early bactericidal activity in patients with pulmonary TB. Anecdotally, Amx/Clv combined with other SLDs has been successfully used in selected patients infected with MDR strains. This approach has been met with considerable scepticism and the role, if any, of Amx/Clv remains unclear. In any case, the lack of effective drugs for the treatment of MDR-TB and XDR-TB, the good tolerance and the low toxicity profile of this drug have made Amx/Clv a drug of choice from Group 5.

Linezolid

More than 10 years ago, studies on a mouse model demonstrated the effectiveness of Lzd and other oxazolidinones against *M. tuberculosis* despite its possible low bactericidal activity. This activity had been confirmed in a number of reports concerning patients with MDR-TB and XDR-TB, though most of them included a limited number of cases. Lzd and the other oxazolidinones researched to date (see below) are new orally administered antibiotics that act by interfering with early protein synthesis. They have a very broad spectrum of activity on aerobic and anaerobic gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*, *Staphylococcus epidermitis* and *enterococcus*. Lzd would be a drug of choice in the management of MDR-TB and XDR-TB (not only from Group 5, to which it is currently assigned) were it not for the fact that it displays a high toxicity profile in the long term (25%–45% rate of severe anaemia and/or thrombocytopenia and peripheral and optic neuropathy) and is expensive. Costs and toxicity would clearly decrease, without decreasing efficacy, by reducing the initial dose (600 mg/12 h) by 50% (600 mg/day). There are some studies using 300 mg/day. Although the ideal dosage to use in TB treatment has not been clearly defined, there

is near unanimous agreement on recommending 600 mg/day. Some recent publications also demonstrate that the rate of adverse side effects is not so important or serious if they are addressed early on and aggressively, and that cost problems are very much linked to manufacture and distribution, because in countries like India the drug may be even cheaper than Km or Cm. Two recent meta-analyses found a therapy success rate near 70% in complicated DR-TB cases in which Lzd was systematically included in the treatment regimen. In any case, countries that can afford the drug and control the adverse reactions end up using Lzd (600 mg/day) as a basic drug against XDR-TB and probably in many cases against MDR-TB.

Carbapenems

Following the rationale invoked for Amx/Clv, the carbapenems offer a second approach to overcoming the β -lactam resistance of *M. tuberculosis*. They are poor substrates for both class A and class C β -lactamases, and two carbapenems, meropenem and imipenem, are active in vitro against *M. tuberculosis*. Effectiveness has been demonstrated in some reports on MDR-TB and XDR-TB patients treated with imipenem and meropenem combined with clavulanic acid. Though experience with the drug is very limited to date and involves very isolated XDR-TB patients who have an even more extensive pattern of resistance, outcomes appear to be rather successful. Still, limited experience, unknown long-term toxicity and high costs make carbapenems a group to be used only in extreme situations.

Clarithromycin

The effectiveness of clarithromycin against *M. tuberculosis* is very weak and no role has been demonstrated for it in the treatment of TB. Based on the isolated reports that have been published with a restricted number of patients receiving multiple other drugs, only a minor anti-TB role can be assigned to clarithromycin. The sole advantage of this agent is relatively good tolerance and a low toxicity profile. It is of doubtful and low effectiveness against *M. tuberculosis*. Clarithromycin is only used when no other drug is left, and then with more scepticism than hope.

Thiacetazone

This is one of the oldest and most widely used drugs in the treatment of TB, even though its action has always been considered very weak and is only bacteriostatic. Due to its high toxicity, particularly in patients infected with human immunodeficiency virus (HIV), entailing an even higher mortality rate, it has been almost eliminated from the anti-TB therapeutic arsenal. Moreover, Th exhibits partial cross-resistance to Eth. The use of this agent should be restricted to cases with an extensive profile of drug resistance,

with close follow-up for adverse reactions and exclusion of patients co-infected with HIV because of documented incidents of Stevens Johnson syndrome and toxic epidermal necrolysis. Given all of its weaknesses, this agent is hardly ever used in practice.

Cross-resistance among anti-tuberculosis drugs

As noted earlier in this chapter, some of the anti-TB drugs may present cross-resistance among the various drugs. This is especially important among all the FQs and 2LIs, because acquired resistance to one of the drugs in the group often makes the others useless. This is particularly important for FQs and 2LIs because, as explained in Chapter 8, they will clearly offer a greater probability of curing the patient when properly associated. Possible cross-resistance between each of the FQ and 2LI components has been analysed and discussed because practically all plans for TB patients with some degree of drug resistance include a new-generation FQ and a 2LI. While of less relevance to prognoses, possible cross-resistance should also be noted between H and the thioamides and between these thioamides and Th, both of which have been analysed in detail in this chapter.

Potential new drugs for drug-resistant tuberculosis treatment

In recent years, considerable research has been conducted in the hunt for new medicines/derivatives of existing compounds and new forms of therapy that will improve TB treatment and accelerate disease control. Four principal avenues are under study: 1) new anti-TB drugs, 2) new uses of existing antimicrobials, 3) immunomodulators, and 4) new routes of drug administration. For DR-TB management, we are interested in the first two avenues of study.

Unfortunately, as with most pharmacotherapeutic development, the discovery process of a new anti-TB drug takes 10 to 15 years. Some 10000 substances must customarily be analysed, at a cost of many millions of dollars, to find a single promising compound for clinical use. To be accepted as a new medication, it must go through complex stages of validation in experiments on animals and humans, which usually entails 10–15 years of research. Despite these obstacles, several dozen new chemical compounds are currently in varying stages of development. We analyse below those for which full development appears to be the most promising. Of all the drugs under study for DR-TB treatment, only TMC207 (Bedaquiline) and OPC-67683 (Delamanid) are in Phase III trial. We may therefore be able to turn to these two compounds in the near future. For many of the compounds below, it is too early to discern the potential role they might play in the initial treatment of drug-sensitive TB.

Diarylquinolines (TMC207 [Bedaquiline])

There are currently high expectations here due to publications showing that a derivative of the diarylquinolines, R-207910 (TMC207), acting on both sensitive and resistant bacilli and in active growth and latent phases, could cut TB treatment time in half. It is more bactericidal than H (its initial early bactericidal activity is less than H and R but equals it at 14 days), and when combined with R or Z, it enhances the sterilising power of these drugs. In rats, the combination of TMC207, rifapentine and Z administered once a week was much more effective than the standard regimen of H+R+Z five times a week. It appears to be synergistic with Z. The appeal of TMC207 is that it is the first anti-TB drug in the last 40 years with a totally new mechanism of action: it acts by inhibiting the *M. tuberculosis* ATP synthase. This drug is currently in Phase III trials for the treatment of MDR-TB patients and has generated high expectations. There are already publications on its use in MDR/XDR-TB patients showing very promising results. In a Phase IIb study in MDR-TB, the addition of TMC207 to a treatment regimen with SLDs versus placebo plus SLDs administered over 8 weeks showed sterilised sputum in 48% of the patients versus 9% for the placebo group. After 2 years of treatment, 81% of patients who received TMC207 + the standard regimen were cured vs. 57% of those who received only the standard regimen. We must be cautious, however, because it appears that it may have unfavourable interactions with R, although it appears to lose no bactericidal activity.

Nitroimidazopyrans (PA-824 and OPC-67683 [Delamanid])

A series of nitroimidazopyrans originally investigated as radiosensitisers for use in cancer chemotherapy were shown to have *in vitro* and *in vivo* activity against *M. tuberculosis*. Newer derivatives showed substantial activity against *M. tuberculosis* and lacked mutagenicity shown previously with bicyclic nitroimidazoles. There is considerable *in vivo* activity (in mouse studies) against *M. tuberculosis*, comparable to that of H. Their action involves inhibition of fatty acid and mycolic acid synthesis. Similar to the nitroimidazoles (to which metronidazole belongs), these drugs show substantial *in vitro* bactericidal activity against bacilli held in a hypoxic stationary phase.

A series of nitroimidazoles, related to metronidazole, have shown to be bactericidal against *M. tuberculosis* both *in vitro* and *in vivo*. Experimental studies with a nitroimidazopyran called PA-824, which proved to be the most active metronidazole, showed action similar to H, with a spectrum of action very specific to TB. Like H, PA-824 acts on the biosynthesis of cell wall lipids but in different metabolic states, and also inhibits protein synthesis. Also like H, PA-824 acts on the bacilli in the exponential multiplication phase, although in an anaerobic culture model it also appears to act on

latent bacilli. It has shown effectiveness against strains of *M. tuberculosis* that are resistant to the usual drugs. More study is needed, but it may become a good alternative first-line drug. Otsuka Pharmaceutical is testing a new compound from the nitroimidazoles series, a dihydroimidaze-oxazol (OPC-67683 (Delamanid)), on patients that appear to have great anti-mycobacterial activity. It is already in Phase III testing and showing very promising results.

Derivatives of the oxazolidinones (linezolid, PNU-100480 and AZD5847)

A role for Lzd in TB treatment has been extensively analysed, as this is the only drug marketed from this group of new orally administered antibiotics. Recent studies show that PNU-100480 is more potent than Lzd and significantly improves the bactericidal activity of several anti-TB combinations, including Mfx, suggesting that it may be a new candidate to shorten TB treatment. Tests still in Phase I-II suggest that AZD5847 may be even more potent.

Ethylendiamines (SQ109)

SQ109, the most potent compound from among 2,796 similar preparations, demonstrates anti-TB activity. Although it is a diamine that began study as an analogue to E, its chemical structure and mechanism of action are not the same, and it in fact appears to have no cross-resistance with E. SQ109 acts by inhibiting synthesis of the mycobacterial cell wall and enhances the action of H and R, shortening the treatment time in a mouse model of TB. It appears to be synergistic in the murine TB model with H, R and TMC207.

Pyrroles (LL3858)

Various pyrroles have shown notable action against specific sensitive and resistant strains of *M. tuberculosis*. Their mechanism of action is unknown. The new LL3858 compound sterilises the lung and spleen of infected rats in a shorter time than conventional pharmacotherapy. It also appears to act intermittently, so a LL3858+rifapentine+Z regimen administered once a week has the same efficacy as H+R+Z administered five times a week in rats. It is currently in Phase II trials for evaluation in human TB.

New drugs from already known families

These include new rifamycins (rifabutin, rifapentine and rifalazil) and the new FQs (Lfx, Mfx and Gfx), the role of which in the treatment of DR-TB has already been largely reviewed and discussed above. Conversely, other macrolides like clarithromycin have shown a very reduced effect in DR-TB treatment. While clarithromycin and other macrolides, such as roxithromycin

and azithromycin, have demonstrated anti-mycobacterial activity with good MIC in vitro, in reality, this does not happen in all cases and there is insufficient clinical experience to recommend its use. On the other hand, both clarithromycin and azithromycin are very active against mycobacteria other than tuberculosis, and are thus the basis for treatment of many of these mycobacterioses.

New drug combinations

There is a growing conviction that, in addition to the properties of each individual drug, an evaluation must be made of their most effective combinations, because therapeutic success depends more on the treatment regimen than the activity of each component taken separately. Combined treatments were initially proposed to prevent the development of bacterial resistance. Today, we are also seeking to augment efficacy through the benefits of varying drug combinations. For example, many combinations under study show that Cf may have great value when combined with other drugs, possibly facilitating their mechanism of action. Of the various associations currently known to be under study, a combination of Cf with Z and Mfx looks like it may have excellent bactericidal and sterilising activity.

Conclusions

Every case of TB, including those bearing *M. tuberculosis* with an extensive profile of drug resistance, has a probability of cure assuming rational use of the currently available anti-TB drugs. Drug availability is not the only requirement, however: effective treatment also demands a sound understanding of which agents should be introduced as the resistance profile broadens. We have presented here an up-to-date analysis of the rational and adequate use of anti-TB drugs, a crucial issue for MDR-TB and XDR-TB treatment. Most areas addressed in this chapter require further clinical studies to definitively elucidate the actual role of each drug in TB treatment.

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Adverse reactions to anti-tuberculosis drugs: practical approaches and appropriate management

Chen-Yuan Chiang

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-

The high frequency of adverse drug reactions represents one of the major challenges in drug-resistant tuberculosis (DR-TB) treatment. Common adverse drug reactions include: nausea, vomiting, diarrhoea, dizziness, hearing disturbances, headache, electrolyte imbalance, anorexia, peripheral neuropathy, depression, tinnitus, allergic reactions, etc. Adverse drug reactions are related to the type, number, duration, dosage and frequency of drugs used. Although adverse drug reactions are common, the majority are minor and do not require withdrawal of drugs from the treatment regimen. Adverse drug reactions resulting in permanent termination of DR-TB treatment are relatively rare (1%–2%). However, if health-care workers are not familiar with the adverse effects of anti-TB drugs or not well trained in managing adverse drug effects, frustration can result when

dealing with patients who may have multiple reactions and complaints. Drugs may then be stopped unnecessarily or treatment may be terminated prematurely by inexperienced health workers, resulting in a high proportion of failure. On the other hand, patients may refuse to continue treatment if discomfort caused by adverse drug reactions is not properly addressed by health-care workers. Identification and management of adverse drug effects in a timely manner are thus critical in a successful DR-TB programme.

Introduction

Studies on outcomes of multidrug-resistant tuberculosis (MDR-TB) have reported a high proportion of loss-to-follow-up, likely due to the large pill burden, a high frequency of adverse drug effects and the long duration of

treatment. A high frequency of adverse drug reactions is one of the major challenges in the treatment of MDR-TB. Adverse drug reactions that frequently or occasionally occur during the treatment of DR-TB include nausea, vomiting, diarrhoea, anorexia, gastritis, abdomen pain, hepatitis, arthralgia, dizziness, general discomfort, hearing disturbances, headache, sleep disturbance, electrolyte imbalance, peripheral neuropathy, depression, hypothyroidism, tinnitus and allergic reactions. Adverse drug reactions are related to the type, number, duration, dosage and frequency of drugs used. Patients may experience several adverse drug reactions simultaneously or sequentially.

Although adverse drug reactions are common, the majority are manageable and do not require withdrawal of drugs from the treatment regimen. Adverse drug reactions resulting in permanent termination of MDR-TB treatment are relatively rare (1%–2%). However, if health-care workers are not familiar with the adverse effects of anti-TB drugs or not well trained in managing adverse drug effects, there can be frustration in dealing with patients who have multiple discomforts and complaints. Drugs may be stopped unnecessarily and treatment may be terminated prematurely by inexperienced health workers, resulting in a high proportion of failure. During technical assistance missions for programmatic management of DR-TB (PMDT), it has been observed in many settings that health workers discontinue drugs unnecessarily for non-specific clinical or laboratory findings due to fear of litigation. It is also a fact that patients may refuse to continue treatment if adverse drug reactions are not properly addressed. To tackle the challenge of the high frequency of adverse drug reactions in MDR-TB treatment, a strong commitment to achieving a high cure rate, sound knowledge of adverse drug reactions and careful attention to patients' suffering from adverse drug effects are critical.

Adverse reactions to first-line anti-tuberculosis drugs

Regimens used in the treatment of new TB patients consist of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). In general, first-line anti-TB drugs (FLDs) are well tolerated with a relatively low frequency of major adverse effects that result in withdrawal of drugs from the regimens. Gonzalez Montaner and colleagues reported that the frequency of interruption of treatment due to adverse effects was 0.9% for H, 2.3% for R and 4.9% for Z. Ormerod and Horsfield assessed 1317 patients and reported that 5.1% of patients had adverse reactions to anti-TB drugs requiring modification of treatment regimens. Reactions occurred in 4.9% of patients treated with Z, 4.5% with streptomycin (S), 1.8% with R, 0.5% with H and 0.2% with E. A meta-analysis reported that the overall proportion of adult

patients treated with regimens containing both H and R who developed clinical hepatitis was 2.7%, but there was substantial variation between settings. Yee and colleagues reported that 9% of patients had major adverse drug effects and that overall incidence of major adverse effects of Z (6%) was higher than H (4%) or R (3%). The proportion of patients with MDR-TB who experienced one or more adverse drug reactions was 69.2% in Turkey, 71% in Bangladesh, 72% in Nepal and 79% in Latvia. The proportion of MDR-TB patients who required discontinuation of one or more anti-TB drugs during treatment was substantial: 21.4% in Taiwan (Taipei), 28.7% in Russia (Tomsk), 30% in the United States (Denver), 34.2% in Peru (Lima), 42.6% in Estonia, 43.5% in Latvia, 49.4% in the Philippines (Manila) and 55.5% in Turkey (Istanbul). Several factors are associated with increased risk of hepatotoxicity during anti-TB treatment: old age, extensive TB disease, malnutrition, excessive use of alcohol, chronic hepatitis B infection, chronic hepatitis C infection and human immunodeficiency virus (HIV) infection. Fernández-Villar and colleagues reported that drug-induced hepatotoxicity occurred in 5.8% of patients without prior risk factors for the condition and in 18.2% of patients with prior risk factors.

Isoniazid

Abnormally high liver enzymes (transaminase) are relatively frequent among patients treated with H. Hepatitis and peripheral neuropathy occur occasionally. Seizures, hallucinations, psychosis, optic neuropathy, pellagra, anaemia, metabolic acidosis, lupus erythematosus, agranulocytosis, alopecia, asthma and dermatitis are rare.

Rifampicin

Among patients treated with R, transient elevation of bilirubin, orange discoloration of urine and tears and increased liver enzymes are relatively frequent. Hepatitis, pruritus and drug fever occasionally occur. Interstitial nephritis, glomerulonephritis, renal failure, toxic epidermal necrolysis, oligomenorrhoea, amenorrhoea, anaphylactic shock, thrombocytopenia, neutropenia, hemolytic anaemia, pseudomembranous colitis, lupus erythematosus and myopathy are rare.

Pyrazinamide

Among patients treated with Z, arthralgia and hyperuricemia are relatively common. Z interferes with the metabolism of purine, resulting in decreased excretion of uric acid. Allopurinol is not recommended in the management of Z-induced hyperuricemia because it increases plasma concentration of pyrazinoic acid, which inhibits renal urate secretion. Hepatitis, nausea and rash occasionally occur. Anaemia, lupus erythematosus, convulsions and

photodermatitis are rare. Among the first-line anti-tuberculosis drugs, Z is the most frequent offending drug in cases of drug-induced hepatitis.

Ethambutol

Among those treated with E, the most important adverse effect is ocular toxicity, which fortunately is uncommon. Aplastic anaemia, eosinophilic pneumonia, thrombocytopenia and hyperuricemia are rare.

Streptomycin

The main adverse drug effects of S are vestibular-cochlear toxicity and renal toxicity, both of which are typically dose-dependent. Hypersensitivity reaction occurs relatively frequently. S may in rare cases cause neuromuscular blockade.

Adverse reactions to second-line anti-tuberculosis drugs

Treatment for MDR-TB requires the use of second-line drugs (SLDs). The frequency of adverse drug effects among MDR-TB patients treated with SLDs is much higher than that among new patients treated with FLDs. The SLDs most commonly used in the treatment of DR-TB include fluoroquinolones (FQs), second-line injectable drugs (2LIs; i.e., kanamycin (Km), amikacin (Am) and capreomycin (Cm), ethionamide (Eth), prothionamide (Pto), cycloserine (Cs) and P-aminosalicylic acid (PAS). Table 10.1 shows the common adverse effects of these SLDs.

Table 10.1 Common adverse effects of second-line drugs

<i>Drug</i>	<i>Adverse effects</i>
Ethionamide, prothionamide	Gastrointestinal disturbance, hepatitis, hypothyroidism
P-aminosalicylic acid	Gastrointestinal disturbance, hepatitis, hypothyroidism
Cycloserine/terizidone	Neurological and psychiatric disturbances: headache, irritability, depression, seizures, suicidal ideation
Kanamycin, amikacin, capreomycin	Pain at injection site, hypokalaemia and hypomagnesaemia, nephrotoxicity, ototoxicity, peripheral neuropathy
Ofloxacin, levofloxacin, gatifloxacin, moxifloxacin	Generally well tolerated, occasional gastrointestinal disturbance, joint pain

Source: Adapted from World Health Organization, 2008 Guidelines.

Fluoroquinolones

Among SLDs, FQs have a relatively low frequency of adverse reactions and are generally well tolerated. Gastrointestinal intolerance, headache, malaise, restlessness, dizziness, allergic reactions, diarrhoea, elevation of liver enzymes, photosensitivity, tendon rupture, peripheral neuropathy and QT prolongation are occasional or rare.

Second-line injectable drugs

2LIs, including Km, Am and Cm, may cause pain at the injection site, renal insufficiency/failure, vestibular toxicity (nausea, vomiting, vertigo, ataxia, nystagmus), auditory damage, electrolyte imbalance (hypokalaemia and hypomagnesaemia) and peripheral neuropathy. As most adverse drug effects of 2LIs are usually dose-related, adverse drug effects rarely occur at the early stage of treatment, except pain at injection site and hypersensitivity. These drugs are usually administered daily initially and may be reduced to three times a week after a few months of treatment to enhance tolerability and reduce the risk of adverse effects.

Thioamides

Among patients treated with Eth and Pto, severe gastrointestinal intolerance (nausea, vomiting, diarrhoea, abdominal pain, metallic taste and/or anorexia) frequently occurs from the outset or later during treatment. Further, allergic reactions, psychotic disturbances, drowsiness, dizziness, restlessness, headache and postural hypotension, hepatitis, gynaecomastia, menstrual irregularity, arthralgia, leucopenia, hypothyroidism, peripheral neuritis, optic neuritis, diplopia, blurred vision and a pellagra-like syndrome (reactions including rash, photosensitivity, thrombocytopenia and purpura) may occur. Of 218 MDR-TB patients treated with Pto in a Taipei study, 23 (10.6%) had Pto discontinued (15 within 1 month), of which 14 (6.4%) due to intolerable nausea/vomiting (10 within 1 month). Figure 10.1 shows the proportion of MDR-TB patients who had Cs, Eth/Pto or PAS withdrawn from treatment regimens due to adverse drug reactions, as reported in different settings.

P-aminosalicylic acid

Like Eth/Pto, PAS also frequently causes severe gastrointestinal intolerance (nausea, vomiting, diarrhoea, abdominal pain), presenting difficult challenges in the use of this drug. Of the 209 MDR-TB patients treated with PAS in Taipei, 19 (9.1%) had PAS discontinued (9 within 1 month), of which 13 (6.2%) due to intolerable nausea/vomiting (6 within 1 month) (Figure 10.1). PAS granules are a delayed-release granule preparation with an acid-resistant

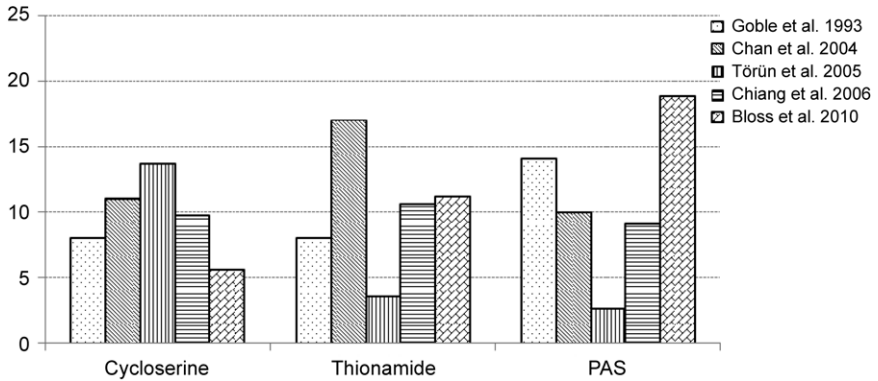


Figure 10.1 Proportion of MDR-TB patients who had cycloserine, a thioamide (ethionamide or prothionamide) or p-aminosalicylic acid withdrawn from treatment regimens due to adverse drug reactions.

coating that protects against degradation in the stomach. Under neutral conditions in the small intestine, the acid-resistant coating dissolves rapidly. PAS granules should be taken with mildly acidic food and may result in less gastrointestinal intolerance than other PAS preparations. However, diarrhoea remains an adverse effect and empty capsules may appear in the stool. Other adverse effects of PAS include hypothyroidism, hepatitis, allergic reactions, thyroid enlargement, malabsorption syndrome, increased prothrombin time, fever, haemolytic anaemia and hypoglycaemia in diabetes.

Cycloserine

Unlike Eth/Pto and PAS, the major adverse reaction of Cs is not gastrointestinal intolerance but rather neurological and psychiatric disturbances including headaches, irritability, sleep disturbance, aggression, tremors, depression, confusion, dizziness, restlessness, anxiety, nightmares and drowsiness. Further, gum inflammation, pale skin, visual changes, skin rash, numbness, tingling or burning in hands and feet, jaundice, eye pain, seizures and suicidal thoughts may occur.

Clofazimine

Adverse effects of clofazimine (Cf) are generally dose-related and mainly affect the skin, eye and gastrointestinal tract. Pink to brownish-black discolouration of skin, cornea, retina and urine occur in a high proportion of patients within a few weeks of treatment. Other skin problems include ichthyosis, dryness, rash and pruritus. Gastrointestinal disturbances include abdominal pain, nausea, vomiting and diarrhoea.

Linezolid

Diarrhoea and nausea are common in patients treated with linezolid (Lzd). Administering Lzd for a prolonged period of time is associated with haematological and neurological toxicities. Haematological adverse effects are mostly reversible and include myelosuppression manifesting as anaemia, leucopenia, pancytopenia or thrombocytopenia. Peripheral and optic neuropathies have been reported. The adverse drug effects of Lzd are generally dose-related.

Initiation of multidrug-resistant tuberculosis treatment

Successful initiation of MDR-TB treatment is the first step to successful MDR-TB treatment. As FQs are generally well tolerated and adverse drug effects of 2LIs usually occur after a period of treatment, successful initiation of MDR-TB treatment largely depends on administering Eth/Pto, PAS and Cs. Armed with knowledge about the adverse drug reactions, all drugs in a MDR-TB treatment regimen may be administered from the beginning at full dose. However, it is essential to acknowledge that a substantial minority may not be able to tolerate Eth/Pto, PAS and Cs (Figure 10.1). Strategies must be in place to support such patients and to avoid potential refusal of treatment due to adverse drug effects.

If adverse drug effects occur, ancillary drugs may be helpful. As gastrointestinal disturbance is common, some experts routinely include an anti-emetic drug such as metoclopramide or prochlorperazine from the beginning. If ancillary drugs do not solve the problem, offending drugs should be identified. Reducing the dosage of the drug at issue may be helpful, but dosage must be gradually increased to an adequate level at a later point in time if the patient can tolerate it. Alternatively, potential offending drugs could be stopped temporarily and re-challenged after symptoms minimise.

Commonly, there may be more than one suspected drug causing adverse effects. Gastrointestinal disturbance might be due to either Eth/Pto or PAS. In some cases, patients may be able to identify which drug is causing trouble. In a PMDT technical assistance visit in Asia, one MDR-TB patient taking both Eth and PAS granules was able to clearly establish that Eth was tolerable but PAS granules were not. The patient explained that she mixed PAS granules with water and chewed, resulting in the granules running in her mouth, followed by intolerable nausea and vomiting. Consequently, she refused to continue MDR-TB treatment a few days after initiation. Her nausea and vomiting completely disappeared when she was advised to take PAS granules together with orange juice, without chewing. For others, it may not always be possible to identify which drug is causing trouble. In

these circumstances, there are two approaches. The first is to reduce dosage or completely stop drugs one by one to identify offending drugs. This might be applicable in the management of gastrointestinal disturbance. The second approach is to discontinue all possible offending drugs and re-challenge them one by one to identify the offending drug(s). The latter is usually preferred in cases with severe adverse reactions such as drug-induced hepatitis.

Knowing that a substantial proportion of patients will experience intolerable adverse drug reactions, the alternative is to add drugs step by step when beginning treatment to maximise tolerability, especially if Eth/Pto, PAS and Cs are included in the regimen.

At the initiation of MDR-TB treatment, an FQ, a 2LI and one SLD oral agent (either Eth/Pto, Cs or PAS) could be introduced from the beginning, together with Z and E (if these drugs are included in the treatment regimen). If treatment begins with Eth, an FQ, Km and Z, and gastrointestinal disturbance occurs, it is usually caused by Eth, and rarely due to the FQ or Z. Daily doses of Eth can be given in 2–3 divided doses. Administering an antiemetic drug, such as metoclopramide or prochlorperazine, may be helpful. If gastrointestinal disturbance persists after administering an antiemetic drug, reducing the dosage of Eth to 250 mg per day can be attempted temporarily. If a patient can tolerate 250 mg Eth, the dosage can be increased to 250 mg twice per day then escalated to full dose. As soon as patients can tolerate Eth, another oral SLD (Cs or PAS) can be added. Dose escalation may be considered for PAS and Cs as well.

It is essential to closely monitor patients' reaction to drugs to ensure that they can tolerate the treatment regimen. A short period of hospitalisation at the initiation of treatment can be helpful and allow health-care workers to closely monitor patients' tolerance of the treatment regimen. If ambulatory treatment is provided from the beginning, directly observed treatment (DOT) support, either facility- or community-based, must also be provided. Daily contact with patients by health workers provides opportunities to closely monitor patients' tolerance of regimens, identify adverse drug effects and address adverse effects in a timely manner. It is difficult for patients to self-administer SLDs and deal with adverse drug effects on their own.

Monitoring of adverse drug reactions

It is essential to monitor adverse drug effects in a systematic and timely manner. There are two categories of adverse drug effects: clinical symptoms that patients can feel and effects that are occult in the beginning and require laboratory screening. At every DOT encounter, health workers should pay attention to clinical symptoms of common adverse effects including skin rashes, gastrointestinal disturbance, psychiatric disturbance

(headache, anxiety, depression, irritability, behaviour change), jaundice, ototoxicity (hearing loss), vestibular toxicity (nausea, vertigo, ataxia), peripheral neuropathy and symptoms of electrolyte wasting (muscle cramping, palpitations). Patient education on potential adverse drug reactions is essential. This should be done at the initiation of treatment and at follow-up. If patients are not informed about potential adverse drug effects, they may not report such symptoms. Delay in identification of adverse reactions may result in life-threatening events or irreversible damage of vital organs. Further, patients may be afraid or anxious if they are not informed of or do not know how to deal with adverse drug effects, which may result in treatment interruption or refusal.

Laboratory screening should be performed regularly for occult adverse effects, including serum creatinine abnormalities (screen at baseline and monthly if possible when receiving a 2LI); potassium (at baseline and monthly if possible when receiving a 2LI); thyroid stimulating hormone (at baseline and every 3 months if receiving Eth/Pto or PAS); liver enzymes (every 1–3 months if receiving H, Z, Eth/Pto or PAS); haemoglobin, white blood count, platelet count; and others depending on the drugs used.

Management of adverse drug reactions

The key principles in the management of adverse drug effects in MDR-TB treatment are:

- 1 If minor adverse effects occur, be supportive, consider administration of ancillary drugs and reassure patients.
- 2 In case of major adverse effects that are life-threatening or can potentially cause damage to vital organs, identify and discontinue the offending drugs.

Once adverse drug reactions are identified, they must be addressed promptly and effectively:

- 1 Ancillary drugs (such as metoclopramide for gastrointestinal disturbance, vitamin B6 for peripheral neuropathy, non-steroidal anti-inflammatory drugs for arthralgia and headaches, antihistamines for hypersensitivity reactions, levothyroxine for hypothyroidism, potassium and magnesium replacement for electrolyte wasting) may be helpful.
- 2 If ancillary drugs do not solve the problem or are not useful (i.e., cases of hepatitis or renal failure), the suspected drug(s) should be identified. At times, reactions may not be caused by anti-TB drugs. Other potential causes must be dealt with as well. Careful clinical assessment and differential diagnosis is critical. For example, depression

may be due to chronic TB or socioeconomic issues rather than to Cs. In such cases, suspending Cs may not be helpful.

- 3 Reducing the dosage of the offending drugs may resolve the problem in some cases, such as with gastrointestinal disturbance, but the dosage must be increased to adequate levels gradually at a later point in time if the patient can tolerate it. In other cases, suspected agents should be temporarily or permanently stopped. Drugs that are completely intolerable or cause major adverse effects that are life-threatening or damaging vital organs (such as hepatitis, renal toxicity, optic neuritis, severe neurological and psychiatric disturbance) should be discontinued. In cases where there are two or more suspected agents, a procedure re-challenging with these suspected agents one by one after symptoms minimise should be conducted to identify the offending drugs.
- 4 Permanent discontinuation of one or more drugs may be required. However, discontinuation of drugs, especially FQs and injectables, may compromise the efficacy of the regimens. Permanent discontinuation of FQs is rarely needed. The decision to permanently discontinue FQs should be made only after very careful clinical assessment, as it may substantially increase the risk of treatment failure. Second-line injectables are also critical in the intensive phase and should not be discontinued too early. An average 10% of patients (5%–15%) cannot tolerate Eth/Pto or Cs or PAS (Figure 10.1). If a higher proportion of patients (25% or higher) has Eth/Pto withdrawn from the treatment regimen due to adverse drug effects, investigation is required to ensure that health-care workers have not unnecessarily stopped Eth/Pto due to minor adverse effects. This also applies to PAS and Cs.
- 5 Replacement with other drugs should be considered if discontinuation of one or more of the drugs may compromise the efficacy of the regimen. This is particularly important in the intensive phase.
- 6 Permanent discontinuation of MDR-TB treatment due to adverse drug effects is rarely required. If 5% or more patients have permanent discontinuation of MDR-TB treatment due to adverse drug effects, assessment is needed to find out whether this can be improved.

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Drug-resistant tuberculosis and human immunodeficiency virus: update and management

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-

Tuberculosis (TB) and human immunodeficiency virus (HIV) infection are conditions that may cause challenges in diagnosis and treatment. TB can present in HIV-infected individuals with a range of atypical symptoms. In addition, diagnosis with front-line tests, such as sputum smear microscopy and chest X-rays, is not always reliable when the immune system is compromised. Without treatment, TB may evolve rapidly in people living with HIV (PLH) due to immunosuppression, and may frequently result in meningeal, miliary or disseminated TB. These types of TB are associated with poor prognosis. Additionally, HIV-infected patients are more likely to be affected by multidrug-resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB) outbreaks. Drug-resistant TB (DR-TB) treatment in PLH and HIV-negative individuals is, in principle, the same. Certain challenges can none-

theless arise when managing PLH with DR-TB. They include high pill burden, TB-immune reconstitution inflammatory syndrome (TB-IRIS), drug-drug interactions and overlapping toxicities and other opportunistic infections or conditions. DR-TB-HIV patients need prompt diagnosis and commencement of anti-TB treatment, co-trimoxazole preventive therapy and antiretroviral therapy (ART).

Drug-resistant tuberculosis and HIV: reasons for and consequences of association of the two diseases

HIV infection leads progressively to extensive destruction of the immune defence mechanisms of the body. HIV grows mainly in certain cells called

CD4+ T lymphocytes (CD4 cells). These cells are an important part of the immune defence mechanisms responsible for protecting individuals against various infections and cancers. As a result, PLH become ill with severe and often deadly infections to which HIV-negative persons are not usually vulnerable. These are called opportunistic infections. When the immune system weakens, *Mycobacterium tuberculosis*, either from a new infection or previously dormant state of infection, may begin to multiply, causing TB disease. TB is the most common opportunistic infection in PLH in countries with a high TB prevalence, and also the leading cause of death among PLH in these communities. It follows that, in these settings, PLH should be regularly screened for TB. All patients who do not know their current HIV status should be routinely offered HIV testing and counselling.

Although HIV infection is the strongest known risk factor for TB to develop in persons with latent TB infection, HIV is not currently considered as a risk factor for developing DR-TB. Nonetheless, PLH are prone to infection by *M. tuberculosis* and development of active TB disease, whether drug-susceptible or resistant. There is also evidence that PLH may have decreased anti-TB drug absorption, especially for rifampicin (R). Low drug levels in the blood may eventually lead to the acquisition of drug-resistant strains of *M. tuberculosis*. In fact, there are many documented examples of MDR- and XDR-TB thriving among PLH. It follows that preventing the spread of TB bacilli in health, congregate and other settings that may be frequented by PLH is an essential step towards preventing DR-TB. There is no doubt that the combination of DR-TB and HIV puts patients at great risk: not only are their lives threatened, but TB control also faces severe challenges in high HIV burden countries.

Drug-resistant tuberculosis and HIV: clinical facts and typical and atypical tuberculosis presentation

Symptoms and signs suggestive of TB do not differ among patients with drug-susceptible or drug-resistant-TB. However, the clinical presentation of TB in PLH depends largely on the degree of immunosuppression. In early HIV infection, when the immune defence mechanisms of the body are almost normal, TB presents with symptoms and signs similar to those in HIV-negative persons, with a high proportion of adult cases being smear-positive. When the body's immune defence mechanisms weaken, clinical presentation of TB becomes atypical. Patients with pulmonary disease may present with no respiratory complaints and may have extreme fatigue, fevers, night sweats, loss of appetite and weight and anaemia. Extra-pulmonary forms of TB occur more frequently in PLH. TB should be suspected whenever a person living with HIV has any of the following symptoms: cough of any duration, fever, weight loss or night sweats.

Diagnosing tuberculosis and drug-resistant tuberculosis in persons living with HIV

All TB patients should be offered testing for HIV unless they already know their recent HIV status. As explained above, diagnosis of TB is more difficult in persons with severe immunosuppression, where sputum microscopy and chest X-rays are less sensitive. The steps for early diagnosis of TB in PLH include:

- **Step 1: Clinical presentation.** The first step in the diagnosis of TB or DR-TB is to suspect the presence of TB. Clinical staff should always maintain a high degree of clinical suspicion and conduct symptomatic TB screening at every contact with PLH. The best symptom screening to date includes evaluation for presence of the aforementioned four clinical symptoms (cough of any duration, fever of any duration, weight loss and night sweats). The presence of any one of these four symptoms has TB diagnostic sensitivity of more than 90% and specificity of almost 35%. If a patient does not have any of these symptoms, a TB diagnosis can be reasonably but not completely ruled out.
- **Step 2: Sputum smear examination.** This step plays a vital role in the diagnosis of infectious TB cases, even in countries where HIV infection is prevalent. For known HIV-positive patients, induced sputum, sputum concentration methods and LED microscopy may increase the sensitivity of microscopy. Note that many TB-HIV patients will be acid-fast bacillus smear-positive if their immune and nutritional statuses are satisfactory.
- **Step 3: Chest X-ray (CXR).** CXRs remain relevant in PLH because their sensitivity is greater than that of sputum microscopy. Unfortunately, specificity is much reduced with atypical radiological patterns and the possible presence of several other conditions. As CD4 count declines, the diagnostic value of CXRs also is reduced.
- **Step 4: Detection of TB lipoarabinomannans (LAMs).** LAMs are membrane glycolipids present in the cellular wall of *M. tuberculosis*. They can be detected in the urine of patients with disseminated TB disease. There is a novel test for their detection that consists of a strip that reacts with LAMs in a urine specimen. Simple and fast, this test provides results in less than 30 minutes. There is no need for processing of specimens, laboratory equipment or a trained laboratory technician. The test can be performed by any appropriately trained health-care worker. In this regard, the test resembles rapid HIV tests. Test sensitivity and specificity are approximately 56% and 91%–95%, respectively. Low sensitivity increases in patients with decreasing CD4 cell counts, who may be at greatest risk of dying without prompt start of anti-TB treatment. At the same time, LAM-positive patients may

experience episodes of TB-IRIS and have poor prognosis. The fact that TB LAMs detection represents a simple and inexpensive point-of-care test may increase access to TB diagnosis in PLH.

- **Step 5: Molecular technologies.** The introduction of molecular technologies may lead to improved diagnosis of both drug-susceptible and drug-resistant-TB in PLH. These techniques are highly specific and sensitive diagnostic tests for detecting *M. tuberculosis*, especially in smear-negative persons. They can also provide results rapidly. If resources allowed, molecular techniques could become first-line investigations for TB in PLH. Results indicating R resistance are proxy measures for MDR-TB diagnosis.
- **Step 6: Bacteriological tests.** Culture and drug susceptibility testing (DST) are the next steps in assessing the possibility of DR-TB. Unfortunately, these tests are not routinely available in many resource-limited countries. Results may also take several weeks and, because rapid clinical decisions may be vital in TB-HIV patients, their role is frequently limited. However, culture and DST are essential in confirming the diagnosis of DR-TB.

Management of HIV-positive patients with drug-resistant tuberculosis

HIV-infected TB patients (with drug-susceptible or -resistant strains) may face an accelerated course of HIV infection and even die without appropriate early treatment. Presence of TB in an HIV-positive patient indicates the need to start treatment with antiretroviral (ARV) medicines. Pulmonary TB in PLH leads to the World Health Organization (WHO) clinical stage 3, and extra-pulmonary TB is indicative of WHO clinical stage 4. This classification is also applicable to patients with DR-TB. Severely immune-compromised patients may have other concomitant conditions, both infectious and non-infectious, making their management complicated.

The following steps are recommended:

- 1 *Immediate initiation of anti-TB treatment.* Regardless of whether TB is of a susceptible or resistant strain, the patient needs anti-TB treatment as soon as possible to prevent death.
- 2 *Co-trimoxazole preventive therapy should be offered for at least the duration of the anti-TB treatment.* Co-trimoxazole is a well-tolerated and inexpensive fixed-drug combination consisting of trimethoprim and sulfamethoxazole. It has been shown to considerably reduce morbidity and mortality among symptomatic PLH.
- 3 *Consideration of diagnosis and treatment of any other opportunistic diseases, especially those affecting the central nervous system (CNS), prior to*

the start of ART. In patients with neurological symptoms, it is important to carry out investigations for an opportunistic CNS infection such as TB meningitis, cryptococcal meningitis or toxoplasmosis and defer ART until the condition has been treated. This reduces the risk of life-threatening IRIS in patients whose immunity starts improving as a result of ART.

- 4 *Start ART as soon as the patient tolerates the anti-TB treatment and no later than at completion of the intensive phase of anti-TB treatment.* New evidence confirms better survival in patients who were commenced early on ART, that is, within 2 weeks of anti-TB treatment start. This is particularly important in severely immune-suppressed persons with CD4 < 50/ml. In PLH with higher CD4 cell counts, benefits of a very early ART start remain unclear. However, ART started within the first 8 weeks of anti-TB treatment leads to better survival in patients with all forms of TB except TB meningitis.

Treatment of MDR-TB is more complex, more toxic and less effective than treatment of drug-susceptible TB. Treatment interruptions can occur due to a high pill burden, drug-drug interactions and toxicities in patients who receive concomitant treatment for both HIV infection and MDR-TB. Patients must be counselled, and they and their families should be offered information and support regarding the importance of taking medications as scheduled, possible adverse medication effects, and how to take the medication. Patients must also be informed about the possibility of TB-IRIS (see below) to prevent treatment interruption.

Management of drug-resistant tuberculosis in persons living with HIV

Initiation of anti-TB treatment is a priority when TB has been diagnosed. If DR- or MDR-TB is suspected, empiric MDR-TB treatment may be a suitable option due to possible long delays in receiving definitive results (2–6 months in many settings) and the risk of death in immunosuppressed patients. The anti-TB treatment regimens are in principle the same for patients with and without HIV infection and the recommendations made in the previous chapters should be followed. It is important to include R throughout the entire treatment in patients with an R-susceptible *M. tuberculosis* strain, especially in PLH.

Antiretroviral therapy in drug-resistant tuberculosis patients

The WHO MDR-TB guidelines state: 'Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-tuberculosis drugs [SLDs], irrespective of CD4 cell-count, as early as possible [within the first 8 weeks, see above] following initiation of

anti-tuberculosis treatment.’ Evidence confirms the beneficial effects, even though mortality remains high. Recent evidence indicates that the earlier ARVs are introduced in PLH with TB, especially in severely immune compromised patients, the higher the survival rate. ART is a life-long treatment for all PLH.

ART, also called highly active antiretroviral therapy (HAART), is a combination of at least three medicines administered with the goal of restoring and maintaining immune defence mechanisms by restoring immunity and slowing the replication of HIV in the body, thereby decreasing the occurrence of opportunistic infections and cancers. As in anti-TB treatment, ART regimens consisting of at least three ARV medicines decrease the risk of developing drug resistance. ARV medicines improve anti-TB treatment outcomes and also enhance quality of life in PLH. ART reduces the persistent inflammatory process caused by HIV, and this is associated with better long-term cardiovascular health. Lastly, by decreasing the HIV load in plasma and other body fluids, efficacious ART can decrease the risk of HIV transmission to a sexual partner and from an infected mother to baby during pregnancy, delivery or breastfeeding.

Good ART adherence is very important and it is advisable to use fixed-dose combinations (FDCs) where possible to simplify the dosing of medicines and lighten the pill burden.

Problems with co-treatment

Several issues and challenges can arise when treating TB-HIV patients. The following may complicate TB-HIV patient management.

TB-immune reconstitution inflammatory syndrome

IRIS is an exaggerated immune response against living or dead pathogens, and occurs when the immune system returns to normal after having been depressed. IRIS is one of the most frequent complications in TB-HIV patients. They may develop IRIS after commencement of anti-TB treatment and/or ART, especially when ART follows soon after the start of anti-TB treatment. HIV-infected patients whose immune status is very low are at a higher risk of developing this syndrome than those with better immune status. A short interval between the start of anti-TB treatment and initiation of ART increases the risk of IRIS, though this must be weighed against delaying ART, which increases the risk of death. Additionally, patients with disseminated TB disease are prone to develop IRIS. Patients with secondary or acquired MDR-TB are more likely to develop IRIS after the introduction of ART because they have had the disease for a longer period and have widely dispersed bacilli in their bodies.

There are two main types of TB-IRIS:

- *Paradoxical TB-IRIS* develops mainly in PLH with TB receiving anti-TB treatment who later receive ART. Initially, their clinical condition improves but after 2 to 4 weeks of ART, paradoxical worsening of previous lesions (of TB or other opportunistic disease) occurs. Patients develop fever, enlarged lymph nodes, pulmonary infiltrates, meningitis and other symptoms. In other words, previously subclinical or latent opportunistic infections become symptomatic due to better functioning immune mechanisms. The immune system reacts with inflammation not only against living pathogens but also against antigens of unviable pathogens. Paradoxical TB-IRIS is thought to happen in at least 10% of PLH starting ARVs and especially among those with severe immune suppression.
- *Unmasking TB-IRIS* occurs in patients who have been started on ART with undiagnosed TB. Patients may initially have few or no symptoms at all, but then present with fulminant symptoms and signs suggestive of TB. This can be explained by the fact that the recovering immune system is suddenly able to 'reveal' or 'unmask' an existing TB. Patients with unmasking TB-IRIS require anti-TB treatment as soon as the condition is suspected and, without it, their prognosis may be poor.

TB-IRIS is a clinical diagnosis. The differential diagnosis consists of:

- 1 Recent history of irregular intake of anti-TB or ARV medicines
- 2 Progression of TB, HIV infection or a new opportunistic infection/disease
- 3 Drug-resistant TB; this is a frequent condition in certain southern African countries
- 4 Adverse drug effects of anti-TB and/or ARV medicines.

Management of TB-IRIS

The currently recommended management strategy for TB-IRIS includes non-steroidal anti-inflammatory drugs and other support measures, such as an abscess aspiration. A short course of oral corticosteroids is also recommended for patients with severe IRIS. Prednisone at a dose of 1.5 mg/kg/day for 2 weeks followed by 0.75 mg/kg/day for another 2 weeks is recommended for adults. Anti-TB treatment and ART should be continued. ARVs can be discontinued in life-threatening situations, especially if severe neurological symptoms appear. Anti-TB treatment should not be stopped.

TB-IRIS may lead to multiple visits to emergency departments, hospital admissions and frequent treatment default.

Drug-drug interactions and toxicities

Concomitant management of TB and HIV infection requires multiple medicines. This frequently leads to occurrence of adverse drug effects and overlapping toxicities, especially when SLDs are used. Vigilant monitoring is recommended. It is also important that patients be informed to prevent treatment interruption. Other conditions, such as malnutrition, dehydration and advanced HIV wasting or opportunistic infections may complicate management further.

The classical drug-drug interaction occurs between R and several ARVs. R induces the cytochrome P450 enzymes and reduces the serum concentration of protease inhibitors, nevirapine, efavirenz and others. This is a lesser problem in patients with MDR-TB because, by definition, the strains are resistant to R, so it is not included in the treatment regimen. However, for all drug-susceptible cases, daily treatment with R remains the cornerstone of TB treatment, and therefore the ART regimen should consist of ARV medicines with lesser or no interaction with R. New medicines, such as TMC207, may be also metabolised by cytochrome P450. Clarithromycin, sometimes used in XDR-TB patients, can also produce cytochrome induction.

Unfortunately, limited information is available on drug-drug interactions between SLDs and ARVs, though some evidence has recently started to emerge (see Table 11.1). The vast majority of toxicities and side effects of SLDs in the immune-competent patient are disturbing but not life-threatening (see Chapter 10). Currently used ARV combinations present considerably fewer side effects than medicines that were commonly used some years ago.

Problems arise whenever there are major side effects, such as hypersensitivity or severe skin reactions, severe hepatitis or severe neurological reactions. In these situations, it is difficult to determine the medicine(s) that is/are responsible for interactions and adverse reactions. Clinical diagnosis is complicated with the possibility of TB-IRIS, non-response to anti-TB or ARV medicines or presentation of an unsuspected opportunistic infection or disease. Careful evaluation of adverse drug events and other conditions should be given priority to prevent adverse treatment outcomes.

The following life-threatening circumstances caused in TB-HIV patients by SLDs should be noted:

- Hypokalaemia and electrolyte wasting can occur in severely immune-compromised PLH who are dehydrated due to diarrhoea or vomiting when ethionamide (Eth) or capreomycin is used with tenofovir (Tdf). Patients may present with muscle pain and are at risk of lethal arrhythmia. Potassium and sometimes magnesium levels must be replenished intravenously in the most severe cases. A component of renal insufficiency might also be present in these patients.

Table 11.1 Potential overlapping toxicity from antiretrovirals and anti-tuberculosis medicines

<i>Potential toxicity</i>	<i>Antiretroviral therapy</i>	<i>Anti-tuberculosis therapy</i>
Peripheral neuropathy	Stavudine, didanosine	Cycloserine, isoniazid, ethambutol, fluoroquinolones, streptomycin, kanamycin, amikacin, capreomycin, viomycin, ethionamide/prothionamide, linezolid
Psychiatric symptoms	Efavirenz	Cycloserine, isoniazid, fluoroquinolones, ethionamide/prothionamide
Hepatitis	Nevirapine, ritonavir-boosted protease inhibitors, efavirenz, etravirine, maraviroc	Pyrazinamide, isoniazid, rifampicin/rifabutin, p-aminosalicylic acid, ethionamide/prothionamide, fluoroquinolones
Gastrointestinal intolerance	Zidovudine, protease inhibitors, didanosine	Ethionamide/prothionamide, p-aminosalicylic acid, pyrazinamide, isoniazid, rifampicin, ethambutol, clofazimine
Renal toxicity	Tenofovir, indinavir, capreomycin	Streptomycin, kanamycin, amikacin, viomycin, rifampicin
Bone marrow toxicity	Zidovudine	Linezolid, rifampicin/rifabutin
Lactic acidosis	Stavudine, didanosine, zidovudine	Linezolid
Stevens-Johnson syndrome	Nevirapine, efavirenz, etravirine	Thiacetazone, cycloserine, linezolid, ethambutol, streptomycin
Arrhythmias/QT prolongation	Atazanavir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir	Fluoroquinolones
Rash/pruritus	Nevirapine, efavirenz, etravirine, abacavir	Rifampicin/rifabutin, pyrazinamide

Source: Adapted from World Health Organization, Guidelines for the programmatic management of drug-resistant tuberculosis, 2011.

- Peripheral neuropathy, which may be disabling, in malnourished PLH taking stavudine and cycloserine (Cs) or isoniazid (H) in high doses. High doses of vitamin B6 and switching stavudine to zidovudine or Tdf, for example, is frequently indicated. Treatment with carbamazepine, amitriptyline or gabapentin may also be necessary.
- Commonly, the presence of a psychiatric disorder may be exacerbated by efavirenz or Cs, or both. Again, vitamin B6 is recommended in addition to management of the psychiatric condition. Depression is very common and apart from medical treatment, psychosocial support to alleviate difficult circumstances is indicated.
- PLH frequently have chronic hepatitis B or C infection. In these patients, pyrazinamide (Z) or H at high doses and hepatotoxic ARV medicines, such as efavirenz or nevirapine, significantly increase the risk of drug-induced hepatitis, especially in patients who also consume large quantities of alcohol. Tdf and emtricitabine can be helpful in treating chronic hepatitis B infection. It is also advisable to consider the hepatotoxic profile of the anti-TB drugs that are used. Patients should receive support to stop or reduce alcohol intake.

Presence of other opportunistic infections, treatment adherence, high pill burden

In TB-HIV patients, mortality during the early months of treatment is considerable, even in patients with drug-susceptible TB. Anti-TB treatment may not be fully effective if other frequent conditions such as malnutrition are not properly addressed. The extraordinarily high pill burden that MDR-TB-HIV patients may face also merits attention. Some patients may be taking levofloxacin+kanamycin+Eth+Cs+Z for MDR-TB, EFV-3TC-TDF for HIV infection and co-trimoxazole and possibly fluconazole preventive treatments. These treatments could amount to more than 30 pills a day. Even if a person wishes to take all medicines as instructed, it may be difficult to understand when and how to do that. Directly observed treatment (DOT) is essential to ensure proper ingestion of medicines. The use of FDCs and treatment simplification are highly recommended.

During follow-up visits, active screening of possible adverse drug events and provision of constant support are crucial to avoid defaulting and dying. The role of health-care workers and psychosocial support of patients by their families and communities throughout treatment is indispensable. Many of these patients may be facing not only the two diseases but loss of employment, reduced income, stigma, discrimination, gender violence, family separation, etc. This means that additional resources may be required, especially in settings with a high burden of both HIV infection and DR-TB, to achieve good DR-TB-HIV treatment results.

Particularities of multidrug-resistant tuberculosis management in the co-infected

Special care must be taken when treating MDR-TB-HIV patients:

- During DR-TB treatment, most patients will receive an injectable medication daily. Strict observation of the principles of the universal precautions for HIV infection control is essential. These include the use of a sterile needle and syringe for each injection in each individual patient, followed by destruction of the syringe and needle, and appropriate management of clinical waste.
- Among all in-patients, there is a high risk of nosocomial transmission and MDR-TB outbreaks. This is especially true for HIV-infected patients. Avoid placing HIV-positive patients in MDR-TB wards after cure, as they may become reinfected (see infection control chapter for more information).
- After TB cure, patients on ARVs should be screened regularly for the presence of any symptoms suggestive of TB, because the risk of TB relapse and reinfection may be greater in PLH than immune-competent persons.
- Considering the higher risk of non-tuberculous mycobacteria (NTM) in HIV-positive populations, all TB suspects should undergo species identification or at least species differentiation. For countries with low-resource laboratories, Runyon's classification is sufficient to differentiate TB from NTM for the purposes of treatment. New molecular techniques are able to differentiate and identify NTM, marking a great advance in early identification and proper treatment.

Collaborative TB/HIV activities

Given the complexity of managing TB-HIV patients, and particularly PLH with DR-TB, clinical activities alone are likely to fail if not guided by national policies and guidelines and supported by national TB and AIDS control programmes. Strong political commitment is also required.

The WHO recommendations on collaborative TB/HIV activities provide a well-established framework to guide national programmes in their response to HIV-related TB. The objectives of collaborative TB/HIV activities, outlined in the 2012 WHO guidelines on collaborative TB/HIV activities, are to:

- Establish mechanisms between AIDS and tuberculosis programmes for the delivery of integrated TB and HIV services at the same place and time whenever possible.

- Decrease the burden of TB for PLH, their families and communities by ensuring the delivery of the Three I's (intensified case finding, infection control, isoniazid preventive therapy) to HIV/TB patients and through earlier initiation of ART.
- Decrease the burden of HIV in presumptive and confirmed TB patients, their families and communities through the provision of HIV prevention, diagnosis and treatment.

With the exception of isoniazid preventive therapy, all HIV-positive MDR-TB patients and their contacts benefit from the implementation of the above measures (see Table 11.2). The International Union Against Tuberculosis and Lung Disease has also published a TB/HIV programmatic guide to the best ways to make these policies operational in the field, based on its country-level experiences.

Table 11.2 Recommended collaborative TB/HIV activities

-
- A Establish and strengthen the mechanisms for delivering integrated TB and HIV services
 - A.1 Set up and strengthen a coordinating body for collaborative TB/HIV activities functional at all levels
 - A.2 Determine HIV prevalence among TB patients and TB prevalence among people living with HIV
 - A.3 Carry out joint TB/HIV planning to integrate the delivery of TB and HIV services
 - A.4 Monitor and evaluate collaborative TB/HIV activities
 - B Reduce the burden of TB in people living with HIV and initiate early antiretroviral therapy (the Three I's for HIV/TB)
 - B.1 Intensify TB case-finding and ensure high quality antituberculosis treatment
 - B.2 Initiate TB prevention with isoniazid preventive therapy and early antiretroviral therapy
 - B.3 Ensure control of TB infection in health care facilities and congregate settings
 - C Reduce the burden of HIV in patients with presumptive and diagnosed TB
 - C.1 Provide HIV testing and counselling to patients with presumptive and diagnosed TB
 - C.2 Provide HIV prevention interventions for patients with presumptive and diagnosed TB
 - C.3 Provide co-trimoxazole preventive therapy for TB patients living with HIV
 - C.4 Ensure HIV prevention interventions, treatment and care for TB patients living with HIV
 - C.5 Provide antiretroviral therapy for TB patients living with HIV
-

Source: World Health Organization, WHO policy on collaborative TB/HIV activities, 2012.

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Management of drug-resistant tuberculosis in special situations

Ignacio Monedero, Gilles Cesari

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- DR-TB management during pregnancy
 - Fundamentals of DR-TB treatment during pregnancy
 - Pregnancy and anti-TB drugs
 - DR-TB treatment during pregnancy
 - Special care to be taken after birth and during breastfeeding
 - DR-TB management in children
 - Main differences in diagnosis of DR-TB in children
 - Initial management of children suspected of having or presenting with DR-TB
 - DR-TB regimen for children
 - Monitoring and follow-up of children with DR-TB
 - DR-TB management in DM patients
 - Main differences in diagnosis of DR-TB in the diabetic patient
 - Management of DR-TB with DM
 - DR-TB management: other frequent co-morbidities
 - Renal dysfunction
 - Liver dysfunction
 - Vulnerable and marginalised populations
-

In this chapter, we present a variety of drug-resistant tuberculosis (DR-TB) cases with special situations, a frequent occurrence especially as DR-TB treatment becomes more widely available. These special cases require a slightly different approach from the clinical or social perspective to achieve positive outcomes. For DR-TB in pregnant women and children, most management rules follow the same rationale as for men and non-pregnant women. Diabetes induces a relative immunodeficiency status that makes TB appear in an atypical presentation, complicating diagnosis and sometimes treatment. Renal dysfunction requires changes and adjustments in anti-TB drug dosages. The best way to manage DR contacts is still being actively debated; nonetheless, the number of potential DR contacts can be extraordinarily high, and appropriate care is key. Lastly, we will address, with examples, how to best approach DR-TB patients from vulnerable groups. Often excluded, vulnerable groups represent a considerable proportion of DR-TB patients. Increased access to prompt diagnosis and correct TB treatment, and follow-up of outreach especially in excluded populations, is essential to prevent and cope with the ongoing DR-TB epidemic. DR-TB management typically presents more controversies than evidence, and this is especially true for special cases. Flexibility and extra care are needed in these cases.

is essential to prevent and cope with the ongoing DR-TB epidemic. DR-TB management typically presents more controversies than evidence, and this is especially true for special cases. Flexibility and extra care are needed in these cases.

Drug-resistant tuberculosis management during pregnancy

TB mainly affects young people, and DR-TB is seen frequently in women of childbearing age. Managing DR-TB during pregnancy creates anxiety not only for patients but also for clinicians, especially considering the toxicity of the drugs used. Nonetheless, aggressive management of gestational DR-TB may benefit both mother and child. All women of childbearing age who

are diagnosed with DR-TB should be tested for pregnancy and human immunodeficiency virus (HIV) prior to treatment start. If testing is negative, family planning is highly recommended for the entire length of treatment and all patients should be informed about potential problems and risks of pregnancy while receiving DR-TB treatment.

If the pregnancy test is positive, all routine prenatal care used in the particular country should be followed. Pregnancy is not a contraindication for DR-TB management. Moreover, not treating DR or susceptible TB during pregnancy would put the mother and foetus at risk. Clinical presentation of TB during pregnancy does not differ from typical presentations, and pregnancy does not increase the likelihood of resistance or worsen treatment outcomes. However, if TB remains untreated, maternal mortality increases, as do low birth weight, premature births, foetal loss and transmission to children after delivery. When DR-TB is adequately treated, these risks for mother and child are much reduced.

Table 12.1 U.S. Food and Drug Administration classification on drug safety during pregnancy

Safety class, interpretation

- A** Adequate, well-controlled studies in pregnant women have not shown an increased risk of foetal abnormalities in any trimester of pregnancy.
 - B** Animal studies have revealed no evidence of harm to the foetus; however, there are no adequate and well-controlled studies in pregnant women.
OR
Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the foetus in any trimester.
 - C** Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women.
OR
No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
 - D** Adequate and well-controlled or observational studies in pregnant women have demonstrated a risk to the foetus; however, the benefits of therapy may outweigh potential risk. For example, the drug may be acceptable in a life-threatening situation or in serious disease for which safer drugs cannot be used or are ineffective.
 - X** Adequate and well-controlled or observational studies in animals or pregnant women have demonstrated positive evidence of foetal abnormalities or risks. The use of the product is contraindicated in women who are or may become pregnant
-

Source: Adapted from Mukherjee et al., page 37.

Fundamentals of drug-resistant tuberculosis treatment during pregnancy

After the diagnosis of DR-TB in a pregnant woman, treatment strategy decisions must weigh risks and benefits for mother and foetus. There is vast experience in the use of first-line drugs (FLDs) during pregnancy, but limited knowledge regarding the safety of second-line drugs (SLDs). DR-TB treatment should preferably be started during the second trimester of pregnancy in the HIV-negative patient if clinical conditions are stable. Deferring treatment reduces the risks of teratogenesis or toxicity, which are greater during the first trimester of pregnancy, and allows enough time during the second and third trimesters for the mother to achieve sputum or culture conversion prior to delivery. The risk of transmission from mother to child is thus reduced. In life-threatening situations (respiratory failure, advanced disease, HIV-positive, etc.), TB treatment is recommended immediately, even in the first trimester, given the risks that exist for both mother and foetus. The patient should be informed and the risks and benefits of treatment vs. lack of treatment must be thoroughly explained. The mother should understand and be involved in all clinical decisions.

Pregnancy and anti-tuberculosis drugs

There is vast evidence on the safe use of FLDs during pregnancy, showing that all but streptomycin (S) are permitted and recommended. Based on the current knowledge, most SLDs are also quite safe during pregnancy with the exception of the aminoglycosides.

Aminoglycosides, namely S, kanamycin (Km) and amikacin (Am), are potentially teratogenic drugs and care is required when used during pregnancy. These drugs are pregnancy safety class D according to the U.S. Food and Drug Administration classification (see Tables 12.1 and 12.2) and are

Table 12.2 Safety of drugs during pregnancy: current anti-TB drugs by U.S. Food and Drug Administration class

Safety class, drug

A —

B Ethambutol, amoxicillin/clavulanate

C Rifampicin, isoniazid, pyrazinamide, FQs, capreomycin, cycloserine, p-aminosalicylate, ethionamide/prothionamide, clofazimine, clarithromycin, linezolid

D Streptomycin, amikacin, kanamycin

X —

not recommended during pregnancy, especially within the first 20 weeks. In approximately 10% of cases for which S was prescribed, ototoxicity and malformation in the foetus were seen. Km and Am probably induce similar teratogenic effects to S. If there is no other option, these can be used, but preferably after the 20th week and always taking risks and benefits into account with the patient. Their use should be limited to patients whose poor clinical state and resistance pattern justify such risk.

Capreomycin (Cm) is an injectable drug (a polypeptide, not an aminoglycoside) and has a similar action to S but no teratogenic effect. Cm is a positive alternative to aminoglycosides as the toxic profile is much reduced in terms of ototoxicity and it presents as safety class C (like most of the FLDs and SLDs used). Cm has no documented teratogenic effect for the foetus and is commonly used in pregnant DR-TB women around the world.

Fluoroquinolones (FQs) are considered safety class C and have no documented teratogenicity in human studies, although the average treatment duration was 2–4 weeks in such studies. Data on prolonged use in pregnancy are limited, but FQs are currently used in approved DR-TB programmes in all Green Light Committee countries. As these are the best drugs for DR-TB given their high bactericidal activity, benefits are likely to exceed risks.

All drugs from Group 4 (ethionamide (Eth), cycloserine (Cs) and p-aminosalicylate (PAS)) are safety class C with no evidence of foetal toxicity. Nonetheless, Eth administration can result in significant vomiting and exacerbate the nausea and vomiting usually associated with pregnancy.

Group 5 drugs are all considered safe with no documented foetal toxicity, but here again evidence is limited.

Drug-resistant tuberculosis treatment during pregnancy

Pregnant DR-TB women should receive a similar regimen to other patients, combining at least four effective drugs with one FQ as a core drug. The main difference relates to the use of Cm as the injectable of choice. If this is not possible or Cm is not available, Km should be used, but preferably starting during the second trimester. The use of Km three times weekly instead of daily can be considered during the first trimester. Overall, it is a mistake not to add an injectable, even during pregnancy. Not doing so can compromise treatment efficacy and increase the likelihood of DR amplification, making curative treatment virtually impossible (see Table 12.3). Vitamin B6 (pyridoxine) should be used in all pregnant women with TB in doses not higher than 150 mg. Higher doses may interfere with FQ absorption and, after birth, the child may experience vitamin B6 withdrawal manifesting as seizures and other neurological presentations.

Table 12.3 Recommendations for the management of drug-resistant tuberculosis and pregnancy

Initial pregnancy and HIV screening for all women of childbearing age

- Encourage family planning if not pregnant

If pregnant:

- Close follow-up of the pregnancy with regular care (at a minimum)
 - Patient involvement in therapeutic decisions
 - Individualised management
 - Ideally, avoid treatment during first trimester, but consider treatment regardless of trimester if life-threatening conditions are present
 - During first 20 weeks, avoid injectables if possible or use capreomycin preferentially
 - Initiate DR-TB therapy during second or third trimester to achieve smear conversion prior to delivery
 - Consider risks and benefits to mother and foetus
 - Use pyridoxine (50–100 mg) in all patients on ethionamide and/or cycloserine or isoniazid
-

Special care to be taken after birth and during breastfeeding

During and after delivery, one of the most important issues is the risk of TB transmission from mother to child. Unlike HIV, transmission from mother to child of congenital TB may occur haematogenously or during delivery, but this is extraordinarily rare. Infection via breast milk is also extremely rare. The most common source of contagion by far is airborne transmission. If the mother is not undergoing appropriate treatment or still has positive cultures, contacts between mother and child should be limited for the well-being of the child. Contact should occur in an open-air space if possible, with the mother wearing a surgical mask or N95 respirator.

Breastfeeding is permitted especially when the mother is smear-negative (and ideally culture-negative). If the mother is smear-positive, she should be separated from the child (different bedrooms) and preferably use formula feeding or extracted (pumped) breast milk to avoid close contact. Breast milk will present some level of anti-TB drugs but not high enough to be deleterious for the child (or to protect him/her against TB infection). All children born to a mother with TB should be closely monitored to ensure that no TB symptoms ensue and be given early TB treatment if they do.

Drug-resistant tuberculosis management in children

DR-TB in children is most often primary DR-TB, meaning it is usually a resistant TB transmitted from an adult. As with susceptible TB, children tend

to have paucibacillary forms of TB, which makes diagnosis more difficult given the higher number of paucisymptomatic diseases and atypical presentations. Culture can be negative in 50% of children with active TB. Hence, while children are able to develop patterns of resistance the same way adults do, they are less likely to do so due to the reduced number of TB bacilli, even with inappropriate disease management. DR amplification only occurs in grown children with cavitory forms (high number of bacilli) of TB and failed previous treatment. In this sense, the number of children with DR-TB indirectly reflects the transmission of drug resistance in the community. Infection control at the family level is crucial for children and even more important for families in high HIV settings. Despite the reduced evidence of TB, prognosis in DR children is similar to or better than in adults when treatment is adequate and there is complete treatment adherence.

Main differences in diagnosis of drug-resistant tuberculosis in children

Several issues make the confirmation of TB more difficult in children. Lower bacillary loads, less forceful coughs and more extra-pulmonary cases are seen, especially in children under 5 years of age. Considering that DR-TB is mainly a bacteriological diagnosis through culture and drug susceptibility testing (DST), a complete diagnosis is sometimes unavailable. For children, other less specific but more sensitive diagnosis tools achieve greater relevance. Chest X-rays and CT scans may also support the diagnosis process. Medical imaging results inform about the likelihood of presenting TB but cannot discriminate whether the TB is resistant or susceptible. In this sense, clinical symptoms, together with the existence of a close contact with TB or DR-TB, become highly significant. New tools like Xpert may, in the near future, support the diagnosis of TB and DR-TB, even in extra-pulmonary samples. Based on current evidence, in a high proportion of cases, child contact with a known DR-TB index case is often the scenario in presenting DR-TB. If a child does not improve with regular TB treatment and is a contact of a high-risk group (failure of Category 1 regimen or other conditions), DR-TB should be always considered.

Initial management of children suspected of having or presenting with drug-resistant tuberculosis

Despite difficulties, attempts must be made to definitively diagnose DR-TB whenever possible, though this should not delay treatment for the child. Management should preferentially take place at a DR-TB speciality clinic, and parents should understand the risks of the disease and the importance of completing DR-TB treatment. Because they will support the treatment

of the children, parents should be involved in all clinical decisions, and support should be offered to them. In this sense, directly observed treatment (DOT) and parental involvement are fundamental.

Drug-resistant tuberculosis regimen for children

With little evidence, the same principles for adult DR-TB treatment should be applied in children, with some minor differences (Table 12.4):

- Given the lower bacillary load and reduced risk of drug resistance acquisition, three effective drugs may be sufficient.
- Use the DST pattern of the adult index case's isolate if no isolate is available from the child. Most often, the treatment that cures the index case will work well in the child.
- Use the highest possible number of FLDs to which the child's organism may be susceptible.
- Injectables and FQs should remain as core drugs for DR-TB treatment. Despite showing a teratogenic effect in the murine model, FQs have not demonstrated toxicity in the developmental process for children and are currently used for long periods in those presenting with DR-TB and cystic fibrosis.
- Add one or two drugs from Group 4 (Eth, Cs), paying attention to the different drug groups and cross-resistance.

Table 12.4 Recommended dosages for anti-tuberculosis drugs in children

<i>Drug</i>	<i>Daily dose mg/kg</i>	<i>Frequency</i>	<i>Maximum daily dose</i>
Streptomycin	20–40	Once daily	1 g
Kanamycin	15–30	Once daily	1 g
Amikacin	15–22.5	Once daily	1 g
Capreomycin	15–30	Once daily	1 g
Ofloxacin	15–20	Twice daily	800 mg
Levofloxacin	7.5–10	Once daily	750 mg–1 g
Moxifloxacin	7.5–10	Once daily	400–800 mg
Ethionamide	15–20	Twice daily	1 g
Prothionamide	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

Regarding ethambutol, a recent comprehensive review showed ocular complications to be rare in children with doses up to 25 mg/kg/d; the currently recommended dosage for children is 15 mg/kg/d.

Treatment can be given 6 days a week for 12–18 months. The optimal duration of treatment in children is still uncertain, but for cavitary or extensive pulmonary TB, the proposed length is similar to that for adults. For primary, non-cavitary DR-TB, treatment periods of 12 months or less are probably sufficient. Currently, there is no evidence regarding the effectiveness of the Bangladesh regimen of 9 months of treatment in children, but it may appear soon; from a bacteriological point of view, there is no reason why it should work in adults but not in children. Reluctance to use FQs, injectables and ethambutol has been seen in children with DR-TB. Nonetheless, all have proven to be safe and necessary for the cure of adults and children.

Monitoring and follow-up of children with drug-resistant tuberculosis

For paediatric patient monitoring, use clinical symptoms, chest X-rays, cultures, sputum sampling and regular blood tests whenever possible. Children should be very closely monitored. Monthly visits during the intensive phase are recommended to check for side effects, record patient weight and counsel parents about possible adverse events and the importance of adherence. Doses must be adjusted as the child gains weight. Treatment regimen changes made necessary by adverse reactions appear to be less frequent with children than adults, but reactions may be more difficult to assess.

Drug-resistant tuberculosis management in diabetes mellitus patients

Diabetes mellitus (DM) creates a state of relative impairment of the immune system. To some extent, and with many similarities, DM and TB interact in milder but similar ways to what is seen with HIV and TB. The precise mechanisms by which DM predisposes to TB are still not clear, but it is thought that high blood sugar levels interact with the activation of macrophages, monocytes and lymphocytes that play a pivotal role in combating the TB pathogen. In fact, the risk of developing TB is 2–3 times higher in DM patients than those without it. DM patients with poorer glycaemic control appear to be at higher risk for TB, demonstrating a dose-response relationship between the degree and duration of hyperglycaemia and vulnerability to TB, in a way that is again similar to that observed with HIV and TB with the decreasing number of CD4.

The combination of these two diseases is highly relevant and will be even more so in the future as the burden of DM is continuously increasing in developed and developing countries alike. Currently, there is not enough evidence to confirm that DM patients are at higher risk for treatment failures,

meaning they are not at greater risk for development of DR-TB. They are probably more prone to present with primary DR-TB. In fact, the proportion of patients with DM among the DR-TB cohorts is higher than the overall populations in many middle-income countries. Few precise studies exist for DR-TB/DM outcomes to date, although for susceptible TB, studies have shown that there is an increased risk for poor outcomes and the risk of TB relapse or recurrence is almost four times higher.

Main differences in diagnosis of drug-resistant tuberculosis in the diabetic patient

As with HIV-infected individuals and children, relative immune impairment in DM patients creates a decreased inflammatory response to TB bacilli. Hence, the typical symptoms of TB may be milder or even nonexistent. Classical screening diagnosis tests like acid-fast bacillus (AFB) smears can be less sensitive, leading to delayed diagnosis. Prompt diagnosis and initiation of adequate therapy are key in immunocompromised patients. In fact, poorer glycaemia control makes presentation with atypical symptoms (AFB smear-negative, atypical chest X-ray findings and extra-pulmonary dissemination) more likely. Importantly, most diabetic patients in developing countries do not know their disease status, making it likely that their glycaemic control is poor.

A cough lasting more than 2 weeks and a smear test may not be enough to diagnose TB in the diabetic. An approach that includes querying for a cough of any duration, fever, weight loss and night sweats may be more sensitive. Evaluation that includes smears, a chest X-ray and culture, along with new technologies (e.g., molecular techniques), might be ideal when patients present with the symptoms above. Regarding DR-TB, DM should be considered as an additional risk factor when presented with a DR-TB contact or if the patient is not responding as expected to the standard therapy. The usefulness of culture and DST probably does not differ from non-DM patients.

Management of drug-resistant tuberculosis with diabetes mellitus

For susceptible TB, some authors suggest increasing the length of treatment to 8 or 10 months to reduce the risk of relapse, though there is still no evidence in this regard. The International Union Against Tuberculosis and Lung Disease and the World Health Organization (WHO) still recommend 6 months of treatment until sound evidence guides otherwise. Initial DR-TB management does not differ from the non-DM patient, and the same criteria and recommendations apply. Whether the optimal length of DR-TB treatment should be similar to non-DM patients is still uncertain, and more evidence is needed to establish the most appropriate DR-TB treatment length

and regimen for DM patients. On the other hand, management of these DR-TB/DM cases can be challenging and more complicated given the increased risk for toxicities from anti-TB drugs. Neuropathy, renal failure and older age are conditions frequently found in advanced DM patients and can complicate TB treatment. In addition, glycaemia control may become an important issue to increase or maintain immune system capacity and avoid further complications. Some authors support DOT not only for anti-TB medication but also for anti-diabetic medication (oral or injectable) in order to improve patient outcomes. Close monitoring for adverse effects, especially renal failure and glycaemia, are highly recommended. Whenever possible, creatinine and potassium levels should be monitored (weekly for the first month and then at least monthly thereafter).

Drug-resistant tuberculosis management: other frequent co-morbidities

Drug-resistant tuberculosis management in renal dysfunction

Renal dysfunction may lead to decreased immunity and also to an atypical TB presentation. Renal dysfunction occurs frequently in DM, and the aforementioned complications may overlap. Nonetheless, the main problem related to renal failure is that drug levels in the blood might remain high as the kidneys are unable to adequately filter them. Drug levels may increase to toxic levels, leading to worsening of the renal condition and the likelihood of other toxicities. In addition, aminoglycosides have adverse effects on kidney function. Tenofovir (Tdf), an ARV commonly used concomitantly with anti-TB medications, can create renal toxicity especially in the deteriorating TB patient infected with HIV. In cases of acute renal failure, consider stopping nephrotoxic medication. In a patient with advanced HIV, the combination of Tdf and Cm can lead to an electrolyte wasting syndrome with life-threatening hypokalaemia. Drugs should be stopped until the patient recovers and potassium should be replaced. Most anti-TB drug dosages will need to be adjusted in patients with renal dysfunction and, whenever possible, consultation with a nephrologist is recommended. The integrity of the SLD regimen should be maintained as much as possible to avoid compromising the efficacy of the anti-TB treatment and death from TB. In the absence of a specialist, one approach recommended is shifting the daily treatment to a thrice-weekly schedule while monitoring renal function and potassium.

Drug-resistant tuberculosis management in liver dysfunction

Hepatotoxicity is a significant issue regarding the toxicity of FLDs. Isoniazid (H), rifampicin (R) and pyrazinamide (Z) are all associated with hepatotoxicity. Of the three, Z is the most hepatotoxic (associated with liver

destruction) and R the least (associated with cholestatic jaundice). For SLDs, the most hepatotoxic might be Eth/prothionamide due to the similarities to H. PAS and FQs are also potentially hepatotoxic, but much less so than FLDs. DR-TB patients presenting with liver dysfunction should receive anti-TB treatment but with closer monitoring of liver enzymes and other liver function tests and active evaluation for classical liver dysfunction in clinical presentation (e.g., nausea, vomiting, fever, jaundice, dark urine, abdominal pain, increased liver size and confusion). The source of potential previous liver disorders should be treated or addressed (virus, alcohol consumption, etc.) to avoid further complications during treatment. Whenever severe chronic liver disease or acute viral hepatitis is present (especially in the HIV patient), consultation with a liver expert, or at least screening for hepatitis B and C, is recommended. Special care regarding prescribed drug use is needed for patients with acute liver failure or pre-existing liver dysfunction. In severe hepatitis or dysfunction, if the clinical condition allows, remove the most suspicious responsible drug and allow time for liver function to be restored or improve before anti-TB treatment re-initiation. Defer anti-TB treatment until acute hepatitis has been resolved. The combination of four non-hepatotoxic drugs is the safest option, but whenever possible in DR-TB, an FQ should be included to ensure the efficacy of the regimen.

Management of drug-resistant tuberculosis in vulnerable and marginalised populations

If TB is a disease of the poor, DR-TB is certainly a disease of the poorest of the poor and those most marginalised or discriminated against. The existence of DR-TB is intrinsically linked to difficulties in accessing appropriate TB treatment and/or proper follow-up. Socially neglected or excluded populations present higher rates of TB and have less access to treatment and health-care assistance for a variety of reasons. With an adequate approach to improving access to TB treatment, many of these DR-TB cases can potentially be prevented. Considering the large numbers of TB patients in high-burden countries, the absolute number of TB cases in marginalised groups may appear low (excluding regions where girls and women are discriminated against in terms of access to health care). Note too that the proportion of DR-TB cases tends to be much higher in these vulnerable groups than in the general population. Untreated or inappropriately treated patients evolve into remaining pockets of disease. If there is no government agenda to correctly treat susceptible TB patients, DR-TB will surely emerge and be transmitted to others. As recommended by the WHO, intensified case finding should be performed to increase the case detection rate. In sum, these marginalised populations cannot be ignored. Migrants (internal, legal, undocumented or refugees), indigenous and outcast populations usually face

difficulties in accessing TB treatment and care. When they do gain access, treatment and care are often administered inconsistently given their high mobility. Meanwhile, other vulnerable patients who try to access treatment through established channels are sometimes denied the care they need. When men who have sex with men, transgendered persons, ethnic minorities, sex workers, drug users, persons living with HIV (and in some settings women and children) are diagnosed, they may be treated rudely or otherwise suffer discrimination at the hands of health-care workers or others. Hence, they present an increased risk of default and DR-TB development. Disease stigma is added to social stigma in this case, making treatment completion even more complicated. Further, after experiencing such discrimination, these patients may return to their communities and discourage others from seeking diagnosis and treatment when sick. This results in individuals remaining infectious and untreated at the community level. In such scenarios, the default rate and DR-TB increase, and the case detection rate decreases (those potential cases lost), resulting in overall increased TB incidence.

Failure to reach these populations is usually attributed to logistics and difficulties in accessing them. If national tuberculosis programmes (NTPs) wish to reach these patients, then structures, guidelines and procedures need to be more flexible to properly address these particular populations. On the other hand, lack of human resources is a real limitation for NTPs in developing countries. The cost of neglecting these groups will nonetheless be economically and socially higher in the end if discrimination and stigma are amplifying the DR-TB epidemic.

TB and DR-TB diagnostics and treatment are not different for vulnerable groups than for the general population. The key issue is how to make these patients come to health centres when they are sick and to ensure medication adherence in the long run. Obviously, responses vary widely from population to population and country to country, depending on socioeconomic circumstances and the level of stigma and discrimination these groups face. Taking this into account, accessing vulnerable populations may be simply a question of negotiation, flexibility and health-care worker education.

An example of how slightly changing the 'one size fits all' strategy can increase access to vulnerable groups was recently presented in Namibia. The country was finding high rates of DR-TB among the indigenous San population, a nomadic group practising a hunter-gatherer lifestyle in the wilderness with a very traditional and unique social structure. Many DR-TB patients were put on treatment and hospitalised (in accordance with the national guidelines) in the district TB ward situated in a town more than 300 kilometres from their conservancy. There were very high defaulter rates among the San when this treatment approach was used because in their

culture, separation from the family entity was considered a form of punishment. Once this was acknowledged, the NTP negotiated with group representatives and trained the local community members in DOT and treatment delivery. Adherence improved remarkably and cure rates increased considerably.

For bacteriological, ethical and public health reasons, susceptible and DR-TB treatment should be available for ALL vulnerable populations, even if this requires more flexibility from NTPs. Increased access to appropriate TB treatment, care and follow-up of outreach to excluded populations is essential to prevent and address the ongoing DR-TB epidemic.

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An optimised cascade of treatment regimens

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The recommended approach to anti-TB chemotherapy in the context of national tuberculosis programmes (NTPs) is through a 'cascade of treatment regimens'. Based on an individual patient's treatment history, a specific standard treatment regimen is selected for that patient with on average a probability of successful outcome of 90% or more. Patients with no history of prior anti-TB treatment lasting as much as 1 month are given the standard 6-month treatment regimen based on first-line drugs (FLDs) and established as the most efficacious over the past several decades. Patients who have received this regimen and then relapse, or fail based on mi-

croscopy criteria, are given an extended version (second-line regimen, based on the same FLDs) because the microscopic definition of true failure (multidrug-resistant, or MDR disease) is uncertain and relapsing patients may in fact relapse with the same strain and not a drug-resistant strain. Whenever practicable, drug susceptibility testing (DST) for rifampicin (R) should be carried out as soon as possible in such patients to determine whether a third-line regimen for MDR-TB is indicated. The latter regimen lasts 9 months and is based on the core drug moxifloxacin (Bangladesh regimen). This regimen will also be 90% effective if the fluoroquinolones (FQs) and second-line injectable drugs (2LIs) are still active, which is the case in the majority of patients in most countries. Patients whose organism shows FQ resistance obviously cannot be treated successfully with a regimen that is based on an FQ. While there are many treatment options for patients with FQ-resistant organisms, compounded or not by 2LI drug resistance, treatment is complex and results are generally poor. Discussing such 'fourth-line regimens' is beyond the scope of this chapter, and readers are referred to specialised literature.

Definitions

In line with the proposed cascade of regimens, the terms first-line, second-line, and third-line regimens denote respectively the sequence of regimens

that are used in patients without a history of prior treatment for as much as 1 month, patients requiring retreatment after failure, and patients who relapse or return after absconding from the first-line or second-line regimen. Distinct from the designation of regimens, the anti-TB drugs are also, by common agreement, classified into 'first-line drugs' (FLDs) and 'second-line drugs' (SLDs). The former comprise the five drugs isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) and streptomycin (S) (and formerly thiacetazone, Th), these being the drugs on the basic Essential Medicines List of the World Health Organization (WHO). SLDs comprise all other anti-TB drugs.

Rationale for a cascade of treatment regimens

The history of anti-TB chemotherapy has consistently demonstrated that the probability of treatment error is smallest if a standard, clinical trial-established regimen is utilised for the first treatment, rather than 'individualised' regimens. Tailoring a first-line regimen according to DST results has several shortcomings, most notably delays in treatment start until test results are available and reliance on laboratory results that are neither 100% sensitive nor specific. In fact, the Global Project on Anti-Tuberculosis Drug Resistance Surveillance has demonstrated in its proficiency testing rounds that even among the most commonly used drugs, only H and R give more or less uniformly reliable DST results, while DST results for E and S are often poor even in the best laboratories. No attempt has been made to conduct similar tests for Z. Furthermore, laboratories may demonstrate reproducibility for some other drugs used in DR-TB, and seemingly demonstrate a reasonable level of specificity and sensitivity, but few studies have correlated this with clinical status. The luxury of clinical trial efficacy is sorely lacking for patients in need of a retreatment regimen, and it has therefore been advocated by some experts that individualised treatment based on DST results is then required. This argument may seem questionable given the considerable potential for laboratory results to be false, in which case patients might be deprived of an efficacious drug or given a drug that is potentially toxic and without efficacy.

Both the International Union Against Tuberculosis and Lung Disease (The Union) and the WHO thus recommend a standardised series of regimens that are based on a prior likelihood of efficacy in given situations. Such approaches obviate the need for costly and often inadequate or inaccurate DST services and reduce the requirement for such services for clearly defined indications and a limited number of key drugs.

At the population level, drug resistance emerges with increased and widespread use of a given drug. Considering the three most important anti-

TB drugs or anti-TB drug classes, H, R and FQs were sequentially introduced into routine treatment and their introduction was separated by decades. It is thus not surprising that the most common type of drug resistance is to H. R resistance is much less common, and resistance to the most recently introduced class of FQs is even more rare. The construct of a 'cascade' of regimens makes use of this knowledge. A first-line regimen should be designed to be effective in the majority of patients and to overcome H resistance in most cases. The *Mycobacterium tuberculosis* strains of patients who fail on such a regimen may or may not also have R resistance, whether it was initially present or acquired during treatment. Before embarking on the next regimen in the cascade expected to be efficacious against a strain resistant to R, there should be some certainty that the strain is indeed resistant to R and that the lack of response is not due to adherence failure, a false-positive microscopy result or another reason. Once it is established that the strain is resistant to R, a regimen based on a core FQ drug must be given. This FQ must have companion drugs that assure prevention of acquisition of resistance against itself and amplification of resistance in a combination that effectively reduces the risk of treatment failure and also guards against future relapse. The rationale behind the sequence of regimens recommended by The Union is explained in this chapter. Regimens must provide high effectiveness in each step of the cascade and minimise the frequency of adverse drug effects sufficiently for management to be decentralised. Further, regimens must make treatment logistically feasible through NTPs and acceptable to patients.

Principles for the choice of first-line drug regimens

The first-line regimen is given to any patient who has never received prior treatment or who received treatment for less than 1 month. It is the same regardless of site and form of disease and other patient characteristics (although minor modifications might be made in young children, e.g., omitting E as the fourth drug in the intensive phase), and total treatment duration is the same for central nervous system presentations (particularly meningeal tuberculosis) and other special clinical situations.

The first-line regimen of choice is a modification of the 6-month regimen first published by the Singapore Tuberculosis Service and the British Medical Research Council in 1979, which proved to be efficacious up to 8 years against treatment failure and relapse following cessation of treatment. The efficacy of this 6-month regimen with daily H+R throughout, supplemented by Z+S during the first 2 months, has never been surpassed by any other regimen in a head-to-head comparison. Because of the desirability of a fully oral regimen, the British Thoracic Association (now 'Society') compared this regimen with a similar one, but with E substituted for S.

The E-containing regimen was slightly but not significantly inferior to the S-containing referent regimen. This fully oral 6-month regimen, given daily throughout the treatment period, is now considered the standard against which all new regimens are measured, and is the recommended regimen for any new patient without a history of prior treatment unless the strain is known to be R-resistant. The regimen remains highly effective even in the presence of initial H resistance.

Daily versus intermittent treatment

Directly observed treatment (DOT) reduces relapse and acquisition of drug resistance. The effect on regimen efficacy of replacing daily with intermittent treatment (to facilitate DOT by health-care personnel) has long been studied. Interpretations of results with intermittent therapy vary considerably, with some opposed to any intermittent treatment, some advocating starting intermittent treatment only after a daily intensive phase, and some recommending intermittent treatment throughout. When intermittent treatment is selected, the spacing of doses has also been the subject of debate. In the United States, twice-weekly dosing (during the continuation phase) is a recommended option, while the WHO recommends a minimum of thrice-weekly administration for intermittent regimens (albeit only for the continuation phase and only if each dose is directly observed). In India, a thrice-weekly regimen from the outset is recommended, and a case is made for its equal efficacy compared to a daily regimen. The contested issue lies probably more with effectiveness than efficacy: where direct observation of every single dose is truly assured, effectiveness might approximate trial efficacy. Unfortunately, in most low-income settings with a large number of patients in treatment, actual DOT by a health-care worker in the continuation phase is more likely to be the exception than the rule. The argument for the use of any intermittent regimen then becomes moot. Recommending an intermittent regimen in such settings is more likely to promote acquired drug resistance, as irregularity with it seems to have a more profound negative impact than occasionally missing a dose from a daily regimen.

Special situations in the treatment of tuberculosis

Basically, the preferred standard regimen is recommended for any new patient without a history of prior treatment for as much as 1 month. Several exceptions should be considered.

Young children

In children, particularly those younger than school age, the bacillary load is commonly so small that it does not contain a sufficiently large number of

bacilli that are spontaneously resistant to even a single drug. If there is initial H resistance, given that Z is active only in an acidic milieu (i.e., not in the multibacillary linings of a cavity), only R and E are effectively active in the intensive phase. Among patients who are not young children, a four-drug combination should be mandatory. In pre-school children, the risk of selecting an R-resistant mutant seems small enough to justify dropping E from the regimen. Although retrobulbar neuritis is rare, paediatricians are sometimes reluctant to give E to children who cannot report early signs of colour weakness, an impending sign of more serious toxicity. For these reasons, the 6-month regimen is often modified in pre-school children by omitting E.

Meningeal tuberculosis

Extra-pulmonary TB is treated with the same regimen, but pharmacokinetic considerations (poor penetration of R and/or non-penetration or penetration of only protein-bound portions of E or S) reduce the potential bactericidal and sterilising activity of the regimen. Although rare (if high drug dosages are given), relapsing meningeal TB is certainly an undesirable outcome. Therefore, some experts call for prolongation of the regimen to 9 months and possible supplementation with S (rather than E) during the intensive phase.

Underlying renal and hepatic insufficiency

In patients with reduced renal function, E may accumulate to toxic levels if creatinine clearance is not taken into account for dosage adjustment. Thus, either creatinine clearance has to be known or, alternatively, E should be omitted altogether in such patients. Other drugs have an alternative metabolism pathway through the hepatic system and dosage adjustments are thus not mandatory for these drugs in cases of renal insufficiency.

H, R and Z are all potentially hepatotoxic and may potentially exacerbate pre-existing liver damage or accumulate because biliary excretion is reduced. An increased risk of additional drug-induced liver injury is documented for hepatitis C and, to a lesser extent, for hepatitis B. Patients with a history of alcohol abuse and pre-existing liver disease are at increased risk of at least H-induced liver injury, particularly in the first 2 months of treatment, and close monitoring is thus indicated.

Concomitant antiretroviral therapy

R is a potent inducer of hepatic enzymes and thus interacts with numerous other medications by lowering their serum levels. Because concurrent antiretroviral therapy (ART) is frequently required in many countries, particularly in sub-Saharan Africa, specific recommendations have been developed

either to adjust the anti-TB regimen by replacing R with rifabutin where available or to adjust the dosage of ART drugs, or to use alternative ART regimens incorporating drugs less prone to be affected by R. The latter approach is recommended.

Second-line treatment regimens

The earliest collaborative TB programmes of The Union used an 8-month regimen as the first-line regimen, consisting of a four-drug, 2-month intensive phase followed by a 6-month continuation phase with H and Th. Patients who failed on this regimen were likely to have had an H-resistant strain and acquired Th resistance. The second-line regimen was thus based on R throughout and strengthened to minimise the risk of both failure and relapse. It used all (except Th) of the then-available essential drugs, as this was the last chance of curing the patient. This cascade was highly effective in that the first-line regimen worked for more than 90% of patients and the second-line regimen was similarly effective for the 10% who needed it. Thus, only about 1% (and frequently considerably less) of all patients became chronic excretors of bacilli presumably resistant to both H and R.

For reasons of superior efficacy, recommendations by both the WHO and The Union now give preference to the 6-month regimen based on R throughout as the first-line regimen. This makes the original second-line regimen obsolete for patients with true failure due to R resistance, as both regimens are based on R throughout. However, patients 'failing' on the currently recommended first-line regimen do not necessarily have MDR-TB (resistance to both H and R) and should thus not empirically be given a more complex MDR-TB treatment regimen unless resistance to R has been demonstrated.

The definition of treatment failure in low-income countries is commonly based on sputum smear microscopy results at 5 months after treatment initiation or later. While finding a single acid-fast bacillus (AFB) in a diagnostic specimen is quite specific for live *M. tuberculosis* in countries where TB is highly prevalent, the same is not true for a follow-up result, as non-viable but otherwise intact bacilli are still stainable. The problem of acid-fast, non-viable bacilli has become even more acute with regimens containing R throughout, as shown in Figure 13.1.

When treatment was based on H but did not contain R, a positive microscopy result was an excellent predictor for culture positivity at any time during treatment. Once R was incorporated throughout, the proportion of positive microscopy results that also predicted a positive culture and thus bacteriological failure decreased rapidly after 3 to 4 months of treatment, and the proportion of acid-fast but non-viable bacilli increased steeply with

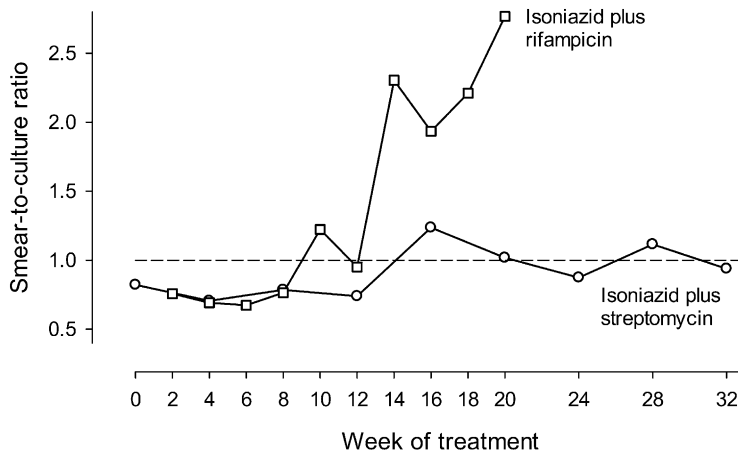


Figure 13.1 Smear-to-culture ratio during chemotherapy according to treatment regimen in U.S. Public Health Service clinical trials. (Data from Newman et al. and Mount and Ferebee.)

the duration of treatment. As bacteriologic response is currently assessed at 5 months or later, a considerable proportion of patients with positive sputum smears will thus not have failed bacteriologically. The problem is almost certainly compounded if the cut-off for a positive sputum smear during treatment is low (as in diagnostic specimens), as it is likely that dead bacilli will not be numerous. Positive sputum smears, particularly of low grade, should thus always be confirmed.

For this and other reasons, The Union also recommends that second-line treatment for failures diagnosed by microscopy should not be MDR-TB regimens unless the presence of MDR bacilli is proven by other means. DST for R (as a minimum, though it is perhaps the only drug that really needs to be tested) is mandatory before placing a patient on treatment for MDR-TB. Conventional phenotypic testing can be cumbersome and often fails, as the viability of bacilli may diminish during prolonged transport. This type of situation is a clear indication for a molecular test such as Xpert MTB/RIF. As positive results are to be expected even if bacilli are no longer alive, the positive result in itself is meaningless. What is meaningful is the result of R DST: if the result indicates R resistance, the patient should be given the third-line regimen for MDR-TB, unless the microscopy result can be safely assumed not to indicate failure due to resistance but perhaps due to non-adherence or indeed just non-viable bacilli.

While awaiting R DST results, second-line treatment is recommended, with first-line drugs. This treatment is reserved for failure cases and also for relapses and patients returning to treatment after absconding from the

first-line regimen. The second-line treatment, lasting 8 months and using R+H throughout, is strengthened during the intensive phase by adding S as a fifth drug. The rationale for this choice is several-fold.

First, a positive sputum smear result is not necessarily indicative of true failure. It may indicate failure to adhere or demonstrate dead bacilli (see above). In neither case is a more complex regimen for MDR-TB indicated. Second, patients may have a slower treatment response due to H-resistant bacilli that could eventually be overcome by an R-based regimen given for a longer period of time (8 months). If H resistance is present, the additional strengthening of the intensive phase with S should further reduce the bacillary load and thus reduce the likelihood of emergence of R resistance during the intensive phase. Third, the patient may indeed have an MDR-TB strain. In that case, S resistance could be acquired during the intensive phase. This is of little consequence, as the regimen for MDR-TB will not make use of S because the recommended choice of injectable is kanamycin (Km), an aminoglycoside that rarely exhibits cross-resistance with S. Some experts have recommended adding E to the continuation phase of this second-line regimen. The Union does not do so as there is no evidence that it really strengthens the regimen and protects R in the continuation phase; in fact, E is preferably reserved for the third-line regimen for MDR-TB.

The proposed second-line regimen should be stopped as soon as there are results showing that the patient indeed has MDR-TB. Every effort should be made to determine absence or presence of R resistance as swiftly as possible. The emphasis here is on determining R susceptibility, whereas susceptibility to any other drug is irrelevant at this point in time: R alone determines the likelihood of success or failure with the second-line regimen. The ideal and fastest test is thus a molecular test for R resistance with high sensitivity and specificity such as the Xpert MTB/RIF assay. If R resistance is confirmed, the second-line regimen is stopped and the patient is given a third-line regimen using SLDs with a high likelihood of effectiveness for cure in patients with MDR-TB.

Third-line treatment regimens for multidrug-resistant tuberculosis

In 1996, Sir John Crofton and collaborators produced guidelines on behalf of the WHO for the management of DR-TB, with an emphasis on MDR-TB treatment. There were no clinical trial data available pointing to a single efficacious regimen; instead, evidence was gathered from numerous sources and existing knowledge about available drugs. Among the potent drugs available at the time were ofloxacin (Ofx) and ciprofloxacin, from the second generation of FQs, now surpassed by the third (e.g., levofloxacin) and fourth generations (e.g., gatifloxacin (Gfx) and moxifloxacin (Mfx)). The

recommendations made at the time considered the various drug classes and proposed a composition of drugs and drug classes likely to be efficacious. Because of the recognised weakness of many of these drugs, the recommended treatment duration was 21 months. An acceptable regimen that was proposed in the absence of DST consisted of 21 months Ofx and the thioamide ethionamide (Eth), supplemented during the first 3 months by Z plus an aminoglycoside or a polypeptide. Obviously, no field study had yet shown the operational effectiveness of the various possible regimens for MDR-TB. A decade later, in 2006 and 2008, the WHO published revised guidelines for the management of MDR-TB. Generally, these revised guidelines have complicated treatment by systematically adding toxic drugs such as cycloserine to all recommended regimens, requiring a large number of consecutively negative cultures, prolonging the period of the initial phase with an injectable drug, etc. Unfortunately, these recommendations have not proven practical in the majority of NTPs in low-income countries.

The third-line regimen recommended here was developed in Bangladesh more than a decade ago for MDR-TB treatment, and is not complicated by additional FQ resistance. This regimen, modelled after the original WHO recommendations, was introduced in the Damien Foundation projects in Bangladesh in 1997. It was soon recognised that inclusion of the thioamide and the long duration of treatment made it impossible for many patients to complete the regimen, as nausea and vomiting occurred in more than 70% of patients, virtually forcing them to terminate treatment prematurely of their own accord. As a result, treatment effectiveness was very low: drug efficacy did not translate into programme effectiveness. The regimen was later sequentially adapted to find a balance between efficacy, as measured by failure and relapse, and overall effectiveness, largely measured by adherence to treatment until completion. Another key factor at the time was keeping regimen costs affordable. While several sequential adjustments to the original regimen improved effectiveness, the major breakthrough was only achieved when the fourth-generation FQ Gfx came off patent (Figure 13.2).

The regimen has a minimum duration of 9 months, with the intensive phase lasting 4 months but prolonged if sputum smear microscopy is still positive. The continuation phase is fixed at 5 months (Figure 13.3).

The choice of some of these drugs might appear unusual, but there is a sensible rationale for each. Km is used because it is the least expensive of all 2LI drugs and there is a low probability of cross-resistance with S. H is included despite laboratory-confirmed resistance for two reasons. First, strains resistant to H because of mutations in the *katG* gene show a wide variation in the level of resistance that might be declared as 'resistant' by the laboratory but with a minimum inhibitory concentration still below what can be achieved with a moderately high dosage in a certain proportion of patients.

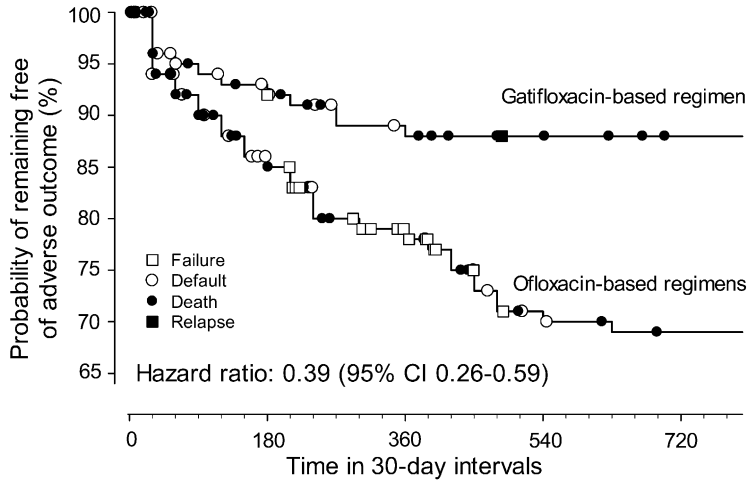


Figure 13.2 Kaplan-Meier analysis of adverse effect-free outcome with a gatifloxacin-based regimen compared to ofloxacin-based regimens. (Data from Van Deun, Kya Jai Maug et al., p. 690.)

Resistance conveyed by mutations in the *inhA* gene is generally of low level and almost always overcome with current therapeutic levels. Importantly, the latter type of resistance is a major mechanism for thioamide resistance, and a drug of that class would therefore be ineffective. Thus, combining H and a thioamide in the intensive phase makes it likely that at least one of the two drugs will be effective. Notably, the regimen in Bangladesh that did not contain any H gave the poorest results. E is likely still active after

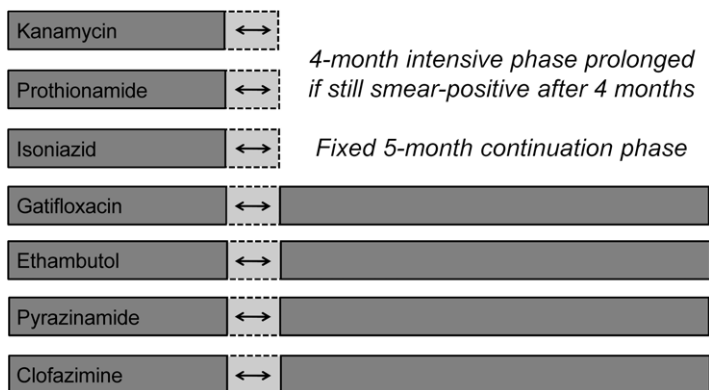


Figure 13.3 Bangladesh regimen: minimum duration of 9 months with drugs used in the intensive phase and throughout. (Data from Van Deun, Kya Jai Maug et al.)

the first- and second-line regimens, and its laboratory test results are commonly inaccurate. Its use may also be justified by the potential and unexpected efficacy exhibited in combination with other drugs, even if given at sub-inhibitory concentrations, and its excellent tolerance. Z susceptibility is difficult to test accurately by standard methods in the laboratory, and there is some evidence (A Van Deun, unpublished data) that it contributes to the sterilising activity of the regimen. There is observational evidence from Bangladesh and accumulating experimental and laboratory evidence that clofazimine is active not only against *M. leprae* but also against *M. tuberculosis*. It was also recommended as a possible adjunct drug in a review by the Global Alliance for TB Drug Development.

The Union thus recommends this regimen, the results of which were published in a prominent biomedical journal, as the third-line regimen. It offers high effectiveness against MDR-TB strains that are not also resistant to fourth-generation FQs (10% of patients in Bangladesh had resistance to Ofx but an uneventful failure- and relapse-free outcome) and is inexpensive enough (€220) to be affordable for many countries. The regimen may need modification due to the fact that Gfx has come into disrepute because of reports of dysglycaemic adverse effects in Canadian octogenarians. While this is of concern in industrialised countries, where substitution by Mfx is a viable and rational solution, the situation in low-income countries is quite different because: 1) drug costs are an important consideration; 2) patients in need of a third-line regimen have a life-threatening condition, are typically young, and diabetes is rare amongst them; and 3) monitoring of urine glucose and swift action in case of an anomaly is simple and feasible.

Remaining issues

In an increasing number of countries, misuse of FQs has led to a rise in FQ resistance. While the critical level is unknown, it is clear that where FQ resistance is highly prevalent, the recommended third-line regimen will rapidly lose its value. The third-line regimen is perfectly adapted to countries and NTPs where there has been little or no abuse of SLDs. The proposed cascade of regimens can thus be summarised as shown in Figure 13.4.

The figure illustrates another remaining issue, i.e., that the proposed cascade offers no solution if there is resistance to fourth-generation FQs or injectable drugs, or indeed to both of these classes (extensive drug resistance). The *M. tuberculosis* strains of the majority of patients with MDR-TB do not have additional resistance to either FQs or injectable drugs, simply because these drugs have not been widely used. On the other hand, there are countries, particularly in Asia and parts of the former Soviet Union and South Africa, where either or both classes have already been lost to resistance. The

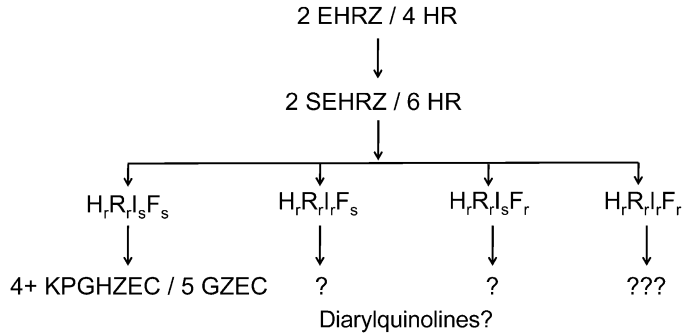


Figure 13.4 Recommended cascade of regimens.

recommendations and suggestions given here obviously do not apply to such settings (see Chapter 8).

A large number of countries can benefit now from the recommended approach while awaiting the outcome of a clinical trial. The regimen is being used in settings other than Bangladesh (it is being successfully implemented in Cameroon, Benin and some other francophone countries; A Trébucq, unpublished data), and the clinical challenge that has emerged is injectable drug-associated ototoxicity, not Gfx-associated dysglycaemia. A large proportion of patients have already received an aminoglycoside with a second-line regimen (not just the one proposed here), and are thus to receive additionally cumulative doses of an injectable drug with the third-line regimen. One important operational research challenge is to determine the minimum duration of injectable drug use to reduce the risk of irreversible ototoxicity. In this context, it is disturbing that official recommendations actually suggest a minimum of 8 months of injectable drug use.

A regimen containing drugs that cause a multitude of often complex adverse events must be centralised under the care of highly specialised clinicians. This most often entails treatment far from patients' homes. The inhumanity of this approach was amply demonstrated during the sanatorium era. To truly deserve the name 'national programme', TB services must be decentralised and brought close to patients' homes. Treatment regimens must thus be manageable by health-care workers at least at the intermediate level, and preferably at the peripheral level. Thus, the regimens chosen in the cascade should minimise management difficulties and not rely on complex laboratory and clinical examinations in the diagnosis and management of adverse drug events. The sequential regimens proposed here meet this criterion, and thus hold the promise that the treatment of MDR-TB can be brought nearer to the homes of patients who require it. Lastly, for patients who have received SLDs in the past, individualised regimens with SLDs and third-line drugs must be recommended (see Chapter 8).

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Tuberculosis infection control: minimal requirements given limited resources

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- Introduction
 - Basic concepts regarding the propagation of *M. tuberculosis*
 - Administrative control measures
 - Accurate and timely TB diagnosis
 - Separation/isolation of TB patients and persons suspected to have TB
 - Prompt start of anti-TB treatment
 - Health facility risk assessment
 - Development of a TB infection control plan
 - Staff, patient and visitor education
 - Environmental control measures
 - Ventilation
 - Ultraviolet germicidal irradiation
 - Architectural design of new health facilities renovated for DR-TB
 - Respiratory protection and personal protection measures
 - Monitoring and evaluation of infection control activities
 - Monitoring latent TB infection and TB disease among health-care workers
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Infection control (IC) consists of a package of measures focused on stopping the transmission of tuberculosis in hospitals or other congregate settings. There are three main types of measures: administrative, environmental and protective. Administrative measures are the most important: they are economic and preventive, covering a variety of public health activities such as accurate and timely TB diagnosis, isolation of TB patients or suspects, prompt initiation of anti-TB treatment and development of risk assessment and IC plans as well as staff and patient education. These measures usually yield great benefits in TB infection prevention at a much reduced cost, and can be implemented even in the most difficult scenarios. Environmental measures aim to reduce the concentration of infective particles in facilities for TB patients or suspects. Protective measures are used to reduce the likelihood of infection in settings where the other two types of mea-

asures cannot reduce infection risk. Usually considered the most important by health-care workers, protective measures are subject to several caveats that reduce their effectiveness in the field. Prevention of TB through IC should be prioritised, especially in health facilities where HIV-positive individuals, children or patients with other immunodeficiencies are present. Considering the suffering and cost associated with treating multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), preventing MDR-TB or XDR-TB cases (especially through administrative measures) turns IC into an extraordinarily cost-effective practice.

Introduction

TB IC consists of a combination of measures aimed at minimising the risk for transmission of TB bacilli within populations. Despite ample evidence of

the important role of transmission of TB, especially in hospitals, the relevance of these practices was not recognised until after the deadly outbreaks of XDR-TB in HIV populations in South Africa. IC is currently but one crucial component in the package of measures for preventing MDR-TB, and is included among those designed to reduce the burden of TB among HIV patients. Transmission of TB bacilli is an important problem in congested health facilities with poor IC measures and a major concern in settings with high TB prevalence. TB IC has become a key challenge in the era of MDR- and XDR-TB because these are serious conditions with limited treatment options. It was previously thought that resistant strains presented a much reduced capacity of transmission. However, many studies point to a similar risk of transmission in MDR-TB and even XDR-TB strains, especially in immunocompromised populations. Recent outbreaks of XDR-TB among HIV-infected patients with accompanying high death rates have highlighted the relevance of primary transmission of resistant strains and the importance of these purely non-clinical preventive measures. HIV-infected and other immunocompromised patients, such as individuals with diabetes mellitus (DM), seem to present a higher likelihood of becoming infected during contact with TB patients and are at greater risk of developing active TB disease after infection with *Mycobacterium tuberculosis*. The key activities for TB IC are administrative and environmental measures and respiratory protection. Below is the hierarchy of control measures and activities, by order of priority.

- 1 *Administrative controls* are management and work practices aimed at reducing the risk of exposure to TB for patients, visitors and health-care workers. These include adopting policies and plans for IC, changing procedural tasks at health facilities (e.g., screening patients for TB and triaging for fast-tracking or separation), screening and protecting health-care workers from TB and monitoring and evaluating TB IC interventions.
- 2 *Environmental controls* are aimed at reducing the concentration of infectious particles in the air space shared by patients and health-care workers. They notably target natural ventilation, fans, ultraviolet germicidal irradiation (UVGI) and the use of filters.
- 3 *Respiratory protection/personal protection* involves the use of personal protective equipment (PPE) to safeguard health-care workers working in high-risk areas from transmission of TB bacilli. It may include use of respirators that have the capacity to block entry of particles of the size of aerosolised *M. tuberculosis*.

Prevention of TB through IC should be prioritised, especially in health facilities and congregate settings (places where people are brought together,

for example, health services or incarceration facilities), for HIV-positive, DM and otherwise immunodeficient patients. We focus on TB IC within health-care facilities here, but many of the same measures are applicable to other congregate settings. Considering the suffering and cost associated with MDR-TB treatment, preventing just one new MDR-TB case turns these activities into extraordinarily cost-effective measures (especially administrative measures).

Basic concepts regarding the propagation of *Mycobacterium tuberculosis*

TB propagation is not solely a pathogenic issue, but is also influenced by other factors. Some basic knowledge about the mechanisms of infection is key to truly understanding how it can be controlled.

- *Virulence* is the capacity of the pathogen to cause disease from infection. This depends mainly on a pathogen's ability to escape the human immune system.
- *Transmissibility* is the capacity for an index case to infect other persons. It depends on the patient's behaviour and contact opportunities, disease presentations (a person with cavitory TB disease is more likely to transmit TB bacilli to another person than a person without cavitory TB) and environmental conditions.
- *Fitness* measures the number of secondary cases caused by an individual infected soon after disease introduction into a population with no pre-existing immunity to the disease in the absence of interventions to control the infection. Fitness merges the concepts of virulence and transmissibility, and especially reflects the infectiousness of a specific TB strain.

Based on laboratory experience, it was previously thought that MDR-TB strains, being a mutant sub-selection of bacillary population, had significantly reduced fitness compared with drug-susceptible strains. However, recent studies suggest that the fitness of MDR-TB strains is at least similar to susceptible or wild strains. In fact, similar fitness was found among susceptible and MDR-TB strains in settings where MDR-TB was common. At the same time, highly virulent strains like the Beijing strain are associated with MDR-TB in many areas. In addition, patients with MDR-TB in many parts of the world receive inappropriate treatment regimens that do not cure them but instead simply prolong their lives and thereby amplify the resistance pattern in the community.

When discussing TB prevention, it is helpful to understand the basics of the TB transmission cycle:

- 1 TB bacilli are spread through coughing. Individuals with the most frequent and strongest coughs have the highest capacity to infect others. Those who have smear-positive TB, especially with cavitory disease and who are not on effective anti-TB treatment, have an increased chance of spreading TB bacilli. To reduce the opportunity for transmission, patients should be offered a mask or handkerchief and taught to cover their mouths and noses when coughing. This is called 'cough hygiene', or 'cough etiquette', and it is one of the simplest, cheapest and most effective ways to limit droplet nuclei in the environment. Coughing patients should be quickly identified and separated from others. Rapid diagnosis, together with early and appropriate treatment, leads to a quick decrease in the bacillary burden and limits the patients' infectious capacity and thus the number of contacts that may become infected.
- 2 After being released into the air in tiny droplets, TB bacilli remain infectious for 2–8 hours depending on environmental conditions, such as ventilation and sunlight. In conditions with poor ventilation and insufficient sunlight, bacilli may remain in the air for 2–8 hours, or more. It is therefore necessary to create environmental conditions that are conducive to the removal or destruction of infectious particles. These conditions include improved ventilation, natural or ultraviolet light and filters.
- 3 Once in the environment, infectious particles and the potential host 'come together' through breathing. It is necessary to limit the opportunities for contact between infectious particles and potential hosts. Separation of coughing individuals from others is one way to achieve this. Health-care workers can also use personal protection with respirators in high-risk areas.
- 4 After TB bacilli and the potential host have had contact, depending upon the virulence of the strain and the potential host's immune system, either 1) the contact is effective, or 2) the contact is ineffective and infection is avoided. The risk of infection for each contact with TB bacilli depends mainly on host factors that include immunocompetence (mainly macrophage capacity) and nutritional status. Ideally, persons at risk, such as people living with HIV (PLH) and individuals with DM or other immunodeficiencies, should maintain adequate nutrition, blood glucose balance and immune responses thanks to early and effective anti-diabetic and antiretroviral treatment.
- 5 From the time of infection in an immunocompetent person, approximately 10% develop TB disease in their lifetime, with half of these developing TB disease within 2 years of infection. The immune system status plays an important role in keeping infection in a latent

state. However, a person with HIV infected with *M. tuberculosis* has a 10% per year risk of developing TB disease. TB preventive therapies can be used to prevent the development of active TB disease in persons who have been infected or have what is known as latent TB infection (LTBI). Whenever possible, it is important to optimise nutritional status and immune status and adequately manage other co-morbidities. In many cases, like those of recent converters, HIV-positive individuals and children may benefit from treatment for LTBI. Most current evidence on LTBI treatment is based on the use of isoniazid (H) or H+rifampicin. It should nonetheless be noted that these treatment modalities are unlikely to provide good results for persons infected with MDR-TB strains.

The IC measures discussed below play a fundamental role in prevention at different stages of the TB transmission cycle.

Administrative control measures

Administrative measures are the first priority in TB IC. They include the following.

Accurate and timely tuberculosis diagnosis

Identification of suspected TB patients should begin as soon as patients enter clinics or outpatient clinics in hospitals. Clerks registering patients should be trained to ask simple questions that identify TB suspects. These questions include whether the person has a cough of any duration. Patients with symptoms and signs of TB should immediately be referred to the nurse overseeing these patients in the clinic. They should also have access to a designated, well-ventilated waiting area. In high HIV burden countries and settings, the presence of fever, weight loss and night sweats should be queried in initial screening for TB. Nurses responsible for triaging may use a written questionnaire with more detailed questions to identify patients suspected of or confirmed to have TB and the tests or treatments they may have been given. They should ask patients with a cough to cover their mouths and noses with a handkerchief or tissue paper while coughing and take them to another part of the health facility to separate them from other patients.

The first step to take to reduce exposure to others from a potential TB source is to identify the potential TB patient with capacity to infect others. This is why diagnosing TB as early as possible avoids further risk to the community and results in better outcomes for patients. A fast-tracking system should be put into place to ensure that TB suspects in need of medical tests

or procedures are accompanied to other departments and not made to wait with others in waiting rooms. The receiving department should be informed in a timely manner to minimise delays. Whenever possible, tests or procedures that can be conducted in isolation rooms should be performed there to minimise the risk of transmission to other patients and staff.

TB suspects will need sputum for smear microscopy. Patients should be guided on how to produce the specimen and taken to a ventilated or open-air space to produce the sputum. The specimen should be taken to the laboratory for microscopy. A system should be put into place to ensure that results are promptly transmitted and processed. Patients with one or more positive sputum smear microscopy results should be started on appropriate anti-TB treatment without delay. Patients should be provided with a health education session on why this is necessary and how the treatment should be taken. Frequently, patients will mingle indoors with others during leisure activities (e.g., watching television). Ensure that they wear a mask during such activities while still smear-positive.

Separation/isolation of tuberculosis patients and persons suspected to have tuberculosis

Persons suspected of having TB should be separated/isolated whenever possible and a designated waiting area should be arranged for them, for example, in health-care facilities. This is one of the most effective ways to reduce the risk of infection and transmission of TB in these facilities. The role of undiagnosed patients in TB transmission, especially in emergency services, has been largely underestimated.

For patients diagnosed at the community level and not treated at the hospital, the same IC measures should be observed at home, especially when babies, children or elderly persons, those with DM or HIV-infected people live in the same household. Isolation of the patient in a well-ventilated room should be advised in addition to the use of masks or handkerchiefs whenever possible during the first 2 weeks of treatment.

Prompt start of anti-tuberculosis treatment

Starting appropriate anti-TB treatment quickly reduces infectiousness. Normally, when the smear is negative, the risk of transmission is considerably reduced. Early treatment is one of the most effective ways to reduce the risk of infection in others. It is currently thought that transmissibility is reduced considerably in less than 15 days from the start of an effective treatment, even when the smear is still positive.

TB patients should nonetheless cover their mouths and noses with a surgical mask or handkerchief when visiting health and other congregate settings for a period of 2 weeks if no drug-resistant TB is suspected. Practically

speaking, problems arise when primary MDR-TB patients are receiving first-line anti-TB medications, because transmission risk is not reduced. In such cases, smears and culture will remain positive. Molecular-based technology for the diagnosis of TB and resistance may eventually reduce the time between patient presentation and appropriate treatment initiation.

Health facility risk assessment

A risk assessment should be performed in each TB facility and especially in those managing MDR- or XDR-TB patients. Assessment should include measurement of TB epidemiological indicators (district and health centre) to determine the level of risk. Actions and procedures affecting risk of infection should also be timed (e.g., time needed to perform and deliver results from sputum and time patients spend in waiting areas) when evaluating areas of major risk, particularly diagnostic areas (for sputum collection, sputum induction, bronchoscopy, chest X-ray, etc.). A sketch should be made of the facility to analyse how the air, TB patients and their samples flow to help identify the risk areas where IC needs to be improved.

Development of a tuberculosis infection control plan

It is recommended that health facilities have an infection control committee and appoint a person responsible for IC, referred to as the IC focal point or person. The latter could be an experienced nurse, and should have the authority to directly implement or at least influence the uptake of the IC plan. Based on an intra-hospital risk transmission evaluation (described above), the committee should develop an action plan that makes responsibility for IC a reality. In each facility, current practices should be evaluated prior to the creation of an IC plan to identify those that need to be changed. A proficient plan will include a realistic package of specific IC activities necessary for each particular setting, indicating when the activities are to be performed and by whom. Every plan should include the following basics:

- Evaluation of the manner in which suspected or confirmed infectious TB cases are identified and isolated from other patients, health facility staff and visitors
- Triage methods for TB suspects/cases to ensure expedited care
- Methods for TB diagnosis, either on-site or through referral
- Methods to minimise employee exposure to TB
- Methods to train and educate staff regarding TB symptoms/signs, and TB IC
- Environmental controls that reduce the likelihood of TB exposure (and their maintenance)
- Methods to protect employees from TB during high-risk procedures

- Methods to screen employees for TB and rules about screening frequency
- Methods for follow-up of employees exposed to TB
- Methods of monitoring TB IC interventions (include indicators of process and impact of activities).

The IC plan should be written down and each health-care worker should know and understand it. A staff member should be specifically assigned to each of the above actions and charged with follow-up. These staff members' names should be noted next to each action/set of actions in the TB IC plan.

Staff, patient and visitor education

Patients, staff and visitors should understand the risks involved before entering a facility with a high risk of TB and especially MDR- or XDR-TB. Both verbal and written information should be made available to visitors at every visit. Posters depicting basic TB IC measures should be displayed in waiting areas and wards. Administrative IC measures should also be followed in emergency services, medical and other wards where PLH and patients with DM may be admitted.

Environmental control measures

Environmental measures are aimed at reducing the number of infectious particles in the environment where patients or others may be located. The basic measures to achieve this include ventilation (natural or mechanical), full UVGI radiation (whether natural or artificial) and the use of filters. Note that environmental measures will not be useful unless fundamental administrative measures are also followed.

Ventilation

Ventilation, whether natural or mechanical, allows fresh air to enter a room, thereby diluting the concentration of airborne infectious particles. Ventilation thus reduces the likelihood that a person in a room will breathe in air containing infectious droplet nuclei. In ventilated areas, fresh air mixes with the air already in the room. The more effective the mixing of the air, the better the dilution of airborne pollutants and the greater the reduction in risk of airborne pathogen transmission.

Natural ventilation

Natural ventilation can be ensured by keeping doors and windows open. Because the doors to consultation rooms in health facilities are usually closed for privacy, windows should be open when possible. To ensure adequate natural ventilation, the total surface area of windows opened to let air in or

out should represent the equivalent of 20% of the floor area. Health facility managers should assess the adequacy of natural ventilation. Renovations to improve natural ventilation should be considered if resources allow.

If natural ventilation is not adequate, propeller fans can be used to increase ventilation. Propeller fans mix the air in a room, diluting infectious particles by spreading them throughout the room. This dilution effect should be combined with a mechanism that continuously allows new air to enter the room and old air to leave it. Replacement of room air with fresh air can be accomplished by keeping windows or doors open. The overall effect is fewer infectious particles in the room, and a much reduced risk of TB transmission. A room with an open window and fan provides a much safer environment for both health-care workers and patients. Propeller fans used to encourage air movement in a room must be carefully positioned to maximise benefits. A smoke test can be used to determine the direction of air movement, using visible smoke as a monitoring tool to observe air flow. This can be done, for example, by burning a stick of incense in an indoor setting. The smoke will move in the same direction as both the air and any potentially infectious particles. Clinic staff should be trained to perform and interpret smoke tests.

Mechanical ventilation and air filters

Fans and other devices can be used to enhance ventilation in settings where natural ventilation is inadequate. Fans should facilitate rapid movement of contaminated air to the outside and the entrance of fresh air into the facility. Staff and patients that need to be protected from TB should be placed in the area of the room where air enters. Patients who are coughing and likely to spread TB should be placed in the area near where the air is exhausted by natural ventilation, airstreams or fans. High-technology and negative-pressure systems are expensive and require regular maintenance. Hence in developing countries, advanced ventilation systems are only indicated in special settings such as national reference laboratories. Air filters can be either fixed or mobile devices that can clean the air in areas of limited size. HEPA (high-efficiency particulate air) filters meet the main international quality standards and are recommended in TB settings. Nonetheless, their use in low- and middle-income countries poses similar problems to ultraviolet germicidal irradiation and high-tech mechanical ventilation as they tend to be expensive and require regular and costly maintenance by specialised technicians.

Ultraviolet germicidal irradiation

UVGI comes from natural sunlight. There are also special UV lamps that utilise UV radiation to inactivate *M. tuberculosis*-containing droplet nuclei in the air. Good natural lighting of rooms that are visited by patients suspected or confirmed to have TB is desirable. UVGI devices are special lamps

that emit this specific wavelength of radiation, and may be used in a return or exhaust air duct to kill TB germs so that the re-circulated air is cleaned of infectious organisms. The lamps must be installed about 7 feet off the floor. Room fans or a ventilation system are recommended to mix the disinfected air in the upper portion of the room with the contaminated air below. Guidelines on the use of UVGI should be strictly followed when installing UVGI equipment, as this type of radiation may cause temporary harm to the eyes and skin. Facility staff should also receive adequate education about the benefits and risks of UVGI equipment and maintenance. They should strictly adhere to maintenance requirements to minimise dangers and ensure that the equipment is working properly at all times. Although upper-air UVGI helps to dilute the overall room concentration of TB germs, it is of little benefit to health-care workers in close proximity with patients, especially in high-ceilinged rooms. Though they can be effective and useful in low- and middle-income countries, use of these devices is limited by their high cost and complicated maintenance. In many of the countries observed, maintenance has been poor (expired lamps, inappropriate allocation, dirty lamps, etc.), leading to ineffective germicidal capacity and a false sense of security among the staff.

Architectural design of new health facilities renovated for drug-resistant tuberculosis

To date, the best architectural design for DR-TB wards is still the classical sanatorium model with high roofs, large windows and fewer than four patients per room. This design enables rather extensive ventilation and bacilli inactivation using natural and no-extra-cost measures. Not infrequently, in new MDR-TB wards with recent funding, UV lamps can be found in rooms with small windows and low ceilings. The use of UV or negative-pressure devices that are not properly maintained gives health workers a false sense of security. In many instances, old sanatorium-style wards provide a more secure environment for IC.

Respiratory protection and personal protection measures

Personal protective equipment is used in situations where administrative and environmental control measures do not suffice to prevent transmission of TB bacilli to staff. Staff working in health facilities with a low risk of TB transmission do not need PPE because administrative and environmental controls are sufficient for protection. Health-care workers should not wear surgical masks because they do not protect from inhalation of aerosolised droplet nuclei.

The appropriate PPE for preventing TB transmission to health-care workers is a respirator capable of filtering particles of 3 microns (similar in

size to *M. tuberculosis*) with at least 95% efficiency. The most commonly used respirators are classified as N95. There are many different types and sizes of respirators available. It is important to properly fit respirators to health-care workers, testing the face-seal capacity (known as a 'fit test'). Various sizes and models of respirator have been developed to assure a proper seal to each individual's face. A correctly fitted respirator should show less than 10% air leakage. Sadly, in the field, there are few MDR-TB workers who have had a proper fit test, and usually there is only one size of respirator available at a facility, if any.

Respirators are often bent, crushed or simply do not fit properly, and this reduces their effectiveness. Working with a respirator can be very uncomfortable, especially if it becomes wet after several hours of use. When such situations occur, health-care workers tend to stop using them.

Overall, respiratory protection is often perceived by staff as the most important IC measure, but there are typically important limitations to its use (noted above), as well as a lack of appropriate accompanying administrative and environmental control measures. The result is limited benefits from all such measures. For example, in one country visited by the authors, all staff used respirators when entering MDR-TB wards, but these wards were connected to other wards and the medical students' lecture room by two doors usually left wide open. In addition, patients freely moved about the hospital without wearing masks. Hence, infectious areas were not restricted to the TB wards where clinicians used respirators.

Monitoring and evaluation of infection control activities

The TB IC plan serves as the basis for monitoring and evaluating TB IC interventions. Implementation of the IC plan should be monitored on a daily basis to ensure that all activities are being carried out. Each activity within the IC plan should have a staff member assigned to monitor implementation. Planned activity implementation should be evaluated and a reassessment of the level of risk of the health facility should be conducted to determine if the activities are appropriate or if there is a need to revise the plan to further reduce the risk of TB transmission. The effectiveness of the IC plan should be evaluated annually under the responsibility of a designated staff member.

Monitoring of latent tuberculosis infection and tuberculosis disease among health-care workers

It is important to monitor the incidence of latent TB infection and active TB disease among health professionals and other staff who work in health facilities. Latent TB infection can be detected using a tuberculin skin test

(TST) or PPD (Mantoux test) or interferon-gamma release assays if the country has sufficient resources. Comparing the number of persons with positive reactions over several years gives an overview of nosocomial TB infection. However, there are limitations to the accuracy of this measurement because staff working in high TB burden countries tend to have positive TST/PPD test results. PPD-negative health-care workers should be especially cautious when working in MDR-TB wards due to the risk it involves.

All health-care workers should be screened for TB symptoms at the time of recruitment and at least annually. In high-burden settings, all health-care workers should be educated about TB symptoms and encouraged to come forward for evaluation if they experience any of them. Health-care workers that have symptoms of TB should be examined without delay. Sputum microscopy examination should be carried out, followed by chest X-ray, molecular diagnostic testing (if available) and other tests, as necessary. Health-care workers diagnosed with TB disease should be started on TB treatment according to national guidelines and supported in treatment adherence.

Another useful precautionary measure is the calculation of the TB rate among health-care workers and comparison with national TB or MDR-TB rates. If the rate in the hospital is higher than the national average, it usually means that working in the facility is a risk factor for TB. This can be easily calculated by multiplying the number of patients by 100 000 and dividing by the total number of health-care workers. For example, in a country with a TB rate of less than 80 cases per 100 000 population, a local hospital had two staff members infected with TB in a year (one susceptible TB and one MDR) out of a staff of 86. Although two cases per year does not look like a high number, if calculated as a rate, the hospital had a TB case rate of 2,325 per 10^5 , which was 29 times the national rate. The MDR-TB rate was 1,163 cases per 10^5 , or more than 100 times the country's rate.

Regarding concomitant disease risks, knowing their HIV and DM status allows health-care workers 1) to request transfers to working areas with decreased risk and 2) to access intermittent preventive treatment with isoniazid if found to be HIV-positive after active TB is ruled out. HIV-positive health-care workers should be supported through access to antiretroviral therapy. In addition, clinicians caring for patients with TB-DM should ensure that patients' glucose levels are well controlled.

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Treatment delivery and adherence: organising ambulatory directly observed treatment and social support

Edith Alarcón

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To achieve cure in a drug-resistant tuberculosis (DR-TB) patient, it is very important to guarantee that he/she takes all of the prescribed drugs. Treatment must be administered by a trained person (preferably a health-care worker) who will assure that the patient takes all doses of the prescribed drug. This is recommended to prevent development or amplification of resistance to the drugs. Guaranteeing the correct administration of treatment is fundamental. Incorrectly administered treatment may become a risk factor for treatment failure and the appearance of DR-TB or amplification of the initial pattern of resistance. In order to achieve this, the commitment of both the patient and the person administering treatment is very important so that the therapy will have the hoped-for result: 'the patient's cure'. Administration of second-line drugs (SLDs) may result in more side effects, and it is quite important for the persons administering treatment to be trained to recognise them and provide continuous information to patients and their relatives and/or caregivers. This chapter will review the importance of ensuring adherence to treatment, associated risk factors,

treatment modalities and strategies recommended to help prevent irregularity in the taking of SLDs prescribed for DR-TB.

Introduction

Most TB cases have *Mycobacterium tuberculosis* strains that are sensitive to anti-TB drugs, but DR-TB represents an emerging threat to global TB control. Directly observed treatment (DOT) is an excellent means of preventing

acquired resistance (caused by prior incomplete or improper treatment). Development of resistance to anti-TB drugs is associated with incorrect therapy, which may be due to various causes such as lack of adherence to treatment, medical error, inadequate supply of drugs, malabsorption of drugs and/or organisational failure in the patient's administration of treatment.

To achieve cure in a TB patient, two equally important interventions are required. The first is to design an appropriate treatment plan for the patient, following all of the premises discussed in previous chapters. The second is to take the necessary steps to guarantee that the patient takes the prescribed drug as scheduled. TB is a disease requiring prolonged treatment that must be spread over several months, even after the patient becomes asymptomatic. It is important to remember that treatment (with an appropriately designed therapeutic plan) is not synonymous with cure. When a patient is first diagnosed with TB and thus has a very high probability of having an *M. tuberculosis* strain sensitive to all drugs, the two premises discussed are relatively simple to fulfil because highly effective treatment plans can be used. It is merely necessary to guarantee adherence with well tolerated drugs over a period of 6 months. Despite this seeming simplicity of treatment, problems with adherence to treatment are the main barrier to achievement of TB control. The situation is even more problematic in patients with DR-TB because treatment plans are more complex to design, usually entail far more toxic associations and must be administered over a longer duration. Therefore, such therapy plans are not only less efficient, but ensuring adherence is also much more complicated because additional strategies must be identified to guarantee that the treatment is followed. Here we review strategies to help ensure compliance with both drug-sensitive and DR-TB treatment.

What is directly observed treatment and why is it important?

The treatment plans proposed in these Guidelines will cure most recently diagnosed TB cases without promoting resistance to drugs. Although the situation is more complicated when the patient suffers from DR-TB, the plans proposed herein can also cure a significant number of these patients. However, as previously stated, in order to achieve cure, it is of utmost importance to ensure that the patient takes all of the drugs according to medical instructions. Treatment must be administered by a trained person (preferably a health-care worker) who will observe the patient taking all doses of the prescribed drugs. This is recommended to prevent development or amplification of resistance to the drugs.

TB patients may have many other concerns that they consider more important than their own disease and that may affect their ability to complete

treatment. It is therefore important to treat patients with respect and make them feel that they can discuss any problems that arise. The health-care worker must be able to respond to problems as they occur to minimise chances for treatment interruption. If the prescribed treatment is not followed due to adverse effects or any other reasons, treatment failure, DR-TB or amplification of an initial pattern of resistance will likely ensue. The commitment of both the patient and the individual administering treatment is very important to achieve cure. The hope is that with proper health personnel guidance and education, the DR-TB patient will understand and commit to adhering to the treatment over the necessary time period (18–24 months) to regain his or her health and protect others around him/her from infection with TB.

Behavioural science studies show that the patient population can be segmented according to the degree of disposition towards following health recommendations, so we can expect to find patients who accept treatment and follow instructions and others who are unwilling to take daily, long-term treatments. Treatments are often prescribed for those who are not prepared to follow them. The health staff must be able to assess patients' willingness to follow instructions, advise them regarding the instructions and monitor patients' progress at each contact.

What are the modalities of directly observed treatment?

To achieve adherence to DR-TB treatment, it is very important for the patient to be cared for by a trained person and to be treated with respect and kindness. It is also important to agree on hours of care that are flexible and meet the patient's needs. SLDs produce more side effects, so it is essential for the person administering the treatment to be trained to recognise adverse reactions and to provide continuous information to the patient and his or her relatives or caregivers. Depending on the patient's needs and physical condition, the following are recommended.

Ambulatory at the health service

The patient will go to the health establishment closest to his or her home. This is recommended for most drug-sensitive TB and DR-TB cases. If the patient can identify a (previously trained) support person, treatment may be administered at the clinic or medical centre where that person works.

Ambulatory in the patient's home

The health-care worker or person responsible for observing treatment (community agent) may provide DOT in the patient's home if there are limitations that prevent transport to the nearest health facility.

If the medical decision is made to split the DR-TB treatment into two daily doses and the patient cannot go to the health facility twice a day or the service is closed in the afternoon, it is important to train a community agent to administer the second daily dose. This measure makes treatment adherence more likely and reduces the cost of transport to the health facility twice a day. It also improves treatment acceptance because twice-daily dosing can reduce the risk of adverse effects.

For patients who cannot go to the health facility due to mobility problems, or if children or elderly persons have no one to accompany them, the health staff or a well-trained community agent may administer the drugs at home. To achieve adherence to treatment, it is important to guarantee that the person who administers treatment is responsible, respects confidentiality and is accepted by the patient. It is not recommended that a close relative be the treatment observer because, due to closeness to the patient, the relative may be manipulated into modifying the treatment, which would be harmful to the patient.

Hospitalisation

Hospitalisation is reserved for cases in which the patient is quite ill or has complications from DR-TB treatment or another concurrent illness (renal insufficiency, diabetes, etc.). Hospitalisation far from a patient's family can cause other psychological and social problems that may cause family problems. In these health facilities, personnel have to take special care and make infection control the priority, meaning administrative, environmental and respiratory protection measures must be in place to reduce the risk of transmission to health personnel, other patients and hospital visitors.

What knowledge must the directly observed treatment support person have?

The treatment support person for the patient with TB or DR-TB must be prepared to support him/her at all times and to discuss and respond to patient concerns. This support person (health-care worker, community agent, volunteer) will see the patient daily for 18–24 months and become very close to him/her. The support person must also be trained to transmit the following knowledge to the patient:

- How TB is transmitted. For contagion to occur, the healthy person must be in frequent or prolonged contact with someone affected with DR-TB or be in an unventilated, enclosed environment with that person. Contagion can thus take place in a health facility waiting room with no air circulation or if the person sleeps in the same room with someone who has TB or DR-TB.

- What DR-TB consists of.
- The most common side effects from second-line anti-TB drugs.
- When/how often the patient must go to the health service.
- When sputum samples must be collected for follow-up smears and *M. tuberculosis* cultures.
- When the patient must go to the health-care provider's office for evaluation. Patients with DR-TB should have a medical appointment monthly during the intensive phase, every 2–3 months in the continuation phase and upon the occurrence of any adverse reaction or complication during treatment.

The importance of infection control at the health service and in the DR-TB patient's home must be emphasised to reduce the risk of transmission to others.

What factors affect adherence to treatment?

There is a persistent tendency to focus on medical factors affecting therapy adherence, although studies have shown that factors relating to the patient's health or socioeconomic conditions or the health teams and systems themselves also have an impact. These factors must be recognised and addressed.

- *Socioeconomic factors*: Patient's poverty, education level or unemployment; lack of effective social support networks; unstable living conditions; distance between the patient's home and the treatment centre; cost of transport to the health centre; high cost of drugs for adverse reactions (when not covered by the health system); cultural and popular beliefs about the illness and treatment; family dysfunction and age (children, teenagers and the elderly who are dependent on a caregiver at home).
- *Health team-/health system-related factors*: These problems are generally due to a lack of knowledge about adherence and effective interventions:
 - Disorganised health services; suboptimal relationship between the health provider and the patient; health-care workers who are not properly trained and/or are overworked, have no proper supervision or are not supported in their tasks; inability to identify potential non-adherent patients; and limited hours of care at health service centres.
 - System with little ability to provide follow-up in case of no-shows; inability to establish community support; and the patient's inability to take care of him- or herself.

- Inadequate treatment observation by health personnel, due to national programme norms that are unclear. For example, treatment may be prescribed daily including Saturdays and Sundays, when the health services offer care from Monday to Friday, so the staff sends treatment for those 2 days home with the patient to be self-administered; or
- Health personnel who perform multiple jobs and have insufficient time for DOT may send drugs home with patients.
- Relationship between the patient and health staff (doctor, nurse) in which the patient feels like staff are doing him or her ‘a favour’.
- Lack of experience; inadequate link to patient support system; lack of flexibility in hours of care.
- Health personnel beliefs (e.g., stigma of TB, fear of being infected, impression of being a low-level worker).
- *Patient-related factors*: Patients with erroneous knowledge about TB and DR-TB transmission, disease process, perceptions and expectations; altered mental states caused by substance abuse, depression and/or psychological stress; asymptomatic patients who feel well after treatment alleviates symptoms and therefore think it is not necessary to continue treatment and stigma; fear and shame.
- *Illness-related factors*: These include severity of symptoms; severity of the disease and availability of effective treatments; degree of disability and the ability/inability to work; speed of symptom improvement: as symptoms abate, the patient has a greater tendency to cease treatment or to take drugs irregularly; and concurrent disorders: TB-HIV (human immunodeficiency virus), TB-DM (diabetes mellitus), etc.
- *Treatment-related factors*: Complex and prolonged treatment, failure of earlier treatments; adverse effects, drug interactions and availability/lack of medical and psychological support for treatment and lack of affordability of drugs for the treatment of adverse reactions, inability to work due to effects of treatment.

What interventions can improve adherence?

Socioeconomic

- Inquire as to family and employment situation: help patients seek solutions and eliminate possible obstacles to treatment.
- Include family and friends (with patient’s prior consent) in treatment support.
- Establish adherence support groups with the participation of patients who have been cured through the programme.

- Develop ties to local community organisations in case support is needed for necessities such as food (popular eateries), where poor people are supplied with food for free.
- During home visits, assess living conditions, food availability and transport options.

Within the health team/health system

- Train health staff so quality of care and the approach to treatment adherence by health-care providers improves. Devote adequate time to the patient. Establish trust.
- Explain treatment plan (at the beginning of intensive phase and continuation phase), verify that the patient understands and is committed to following the plan. Stress the consequences of non-adherence. Offer warmth and attention to inspire patient trust.
- Monitor adherence through review of the treatment card and strengthen communication measures when the patient does not come to the centre for scheduled appointments.
- Strengthen the message to the health staff about the importance of treatment adherence.
- Serve as educator and information source, support staff and ensure continuous monitoring.
- Treatment adherence requires a multi-disciplinary focus and the co-ordinated actions of health professionals, researchers, health planners and policy makers.

With the patient

- Assure that health workers discuss with patients their expectations about their future life, beliefs about a disease that is commonly stigmatised, predispositions to follow medical orders and motivation to complete treatment.

Illness-related

- Confirm that the patient is familiar with the diagnosis of TB and assess the level of comprehension and attitude towards illness, considering the treatment regimen, illness severity and prognosis.
- Inquire into previous treatment, risky behaviours and pre-existing social problems.

Treatment-related

- Design and execute individualised intervention strategies to improve treatment adherence.

- Alert the patient to possible adverse drug reactions.
- Supply information about TB treatment and the importance of regimen completion.
- Adapt treatment to the needs of patients at risk for non-adherence, include verbal or written agreements to return for treatment appointments.
- Facilitate information exchange during treatment, allow scheduling flexibility.
- Therapeutic relationship: set joint goals, help with reminders, consider use of reminder letters or calls (or home visits within 24–48 hours for patients who do not keep treatment appointments).
- Maintain constant and intensive staff supervision.

Organisation of supervised treatment

When the DR-TB diagnosis is made, administration of drugs and patient follow-up must be organised in accordance with the treatment norms of the particular country. Treatment plans must be flexible and individualised for specific patient circumstances, following these important principles and actions:

- Treatment plans must have at least four anti-TB drugs that are new or have a high probability of being sensitive to the *M. tuberculosis* strain being treated. When some anti-TB drugs may not be sensitive to the *M. tuberculosis* strain in a specific patient's case or are very weak, more than four drugs may be justified.
- Obtain an accurate history of anti-TB drugs previously administered to the patient and examine the results of drug susceptibility testing.
- Use drugs and doses appropriate for the patient's weight and tolerance.
- Use an injectable during the intensive phase of treatment.
- Administer DOT daily throughout the treatment and record each treatment administered.
- Obtain written informed consent (or verbal consent if patient cannot read and/or write) before starting treatment, including the patient's promise to follow the treatment plan.

The responsibilities of the person administering treatment include establishing stable and ongoing communication with patients and giving them encouragement to prevent abandonment of treatment. This must be continued until cure is achieved. DR-TB treatment services must be evaluated and health staff trained, bearing the following recommendations in mind:

- Select an appropriate environment for treatment administration that has ample lighting and proper natural ventilation (preferably used only for treatment administration).
- Check that treatment is actually administered by health centre nursing staff and verify that medicines have been swallowed.
- Develop an individualised treatment plan for each patient with the patient's name on each individual box (preferably). If there are no second-line drugs available locally, these should be requested according to the country's health policy.
- Use treatment cards to track attendance at appointments and administration of drugs.
- Treatment cards should include: patient name, initial bacteriology, TB type, prescribed treatment plan, recordkeeping for appointment attendance, verification of drug administration including doses, smear and culture results, weight, records of home visits, concurrent illnesses, adverse reactions (if any) and assessment of patient contacts.
- Calculate the dose to administer based on patient weight and age, according to national norms.
- Weigh patient monthly as an indicator of progress.
- When administering drugs, the following must be remembered:
 - Correct drug.
 - Correct dose according to treatment phase.
 - Do not split doses, unless absolutely necessary.
 - Observe the taking of drugs.
 - Patient oversight and follow-up should include timely response to adverse reactions (at each appointment, ask patient about signs/symptoms of possible adverse reactions).
 - Do not give drugs to be taken at home (during any phase of treatment).

Procedures to ensure the preservation of drugs

- Supervise and educate technical and assistant nursing staff regarding proper storage and preservation of drugs.
- Verify drug expiration dates.
- Follow manufacturer instructions for preserving drugs (e.g., protect from sunlight and humidity, prevent exposure to excessive heat, keep refrigerated).
- Correctly handle drugs according to packaging (blister packs, fixed combinations and vials).
- Ensure a suitable and safe place to store drugs in active use.
- Keep drugs well secured.

Factors that favour adherence to treatment

- Availability of drugs at no cost to patient, including those for adverse effects.
- Optimised relationship between staff and patients.
- Good quality of care.
- Easy access to health services for treatment.
- Convenience of health service scheduled hours.
- Short wait time for patient care at appointments.
- Quiet environment and privacy fostering trust and an encouraging atmosphere.

Infection control in the drug-resistant tuberculosis patient's home

TB is transmitted from person to person through the air. The factors that influence TB transmission in the home are:

- Infectiousness, which is measured by smear results, culture results, cavitation status and cough frequency.
- Whether the patient takes steps to contain contagion, for instance by wearing masks or covering the mouth when coughing.
- Whether the patient receives appropriate treatment and whether it is given under DOT. If these steps are taken, it is likely that infectiousness will be notably reduced after 2–3 weeks of initiating treatment.
- Number of people with whom the patient shares the home and bedroom.
- Whether the home has windows and whether they are left open for ventilation.

DR-TB is transmitted the same way as drug-sensitive TB, so it is very important that a home visit be made even before treatment initiation to assess living conditions, adequacy of ventilation, home-based support, number of family/home members and the persons and number of persons sharing the bedroom with the patient. The patient should be encouraged to sleep in a separate room, but if this is not possible, social or family support networks should be enlisted to support him. Improve ventilation conditions in the home and guide and educate family members with steps to reduce transmission through infection control measures. Advise and teach the patient the importance of using masks or face coverings to reduce contagion, especially in enclosed environments or when using public transport.

Infection rates are similar among the contacts of DR-TB and drug-sensitive TB patients. However, because DR-TB patients are at higher risk of

unsatisfactory response to treatment and SLDs, they tend to be contagious for a longer period of time and thus may infect a higher number of contacts.

Strategies to improve adherence

Use of incentives

Incentives should be used to encourage TB patients to adhere to treatment and improve the patient/health staff relationship. Possible incentives include:

- Support groups
- Award ceremonies upon satisfactory completion of treatment
- Reimbursement of travel expenses
- Food support
- Home visits
- Telephone calls
- Meetings with patients and their families
- Greetings on birthdays and anniversaries.

Malnutrition is a serious problem in many countries, and food is considered a necessary facilitator for treatment success rather than an incentive. Giving incentives entails a responsibility, as much for the patient as for the health staff: both must keep their promises. It is important to remember that when health personnel promise but do not deliver an incentive, their relationship with the patient and credibility in the community may be adversely affected. To use incentives effectively, health staff must know the patient and recognise the difference between their own perceptions and the real needs of the patient.

Community intervention

Provide organisation, participation and education regarding healthy lifestyles to TB patients, their families and the community. Develop strategies for advocacy, communication and social mobility.

Health personnel may identify cured patients who have the skill and disposition to support others. Such support may include the following:

- Promote the formation of mutual aid support groups and productive employment for people affected by TB and DR-TB.
- Promote mutual support among current and former patients.
- Strengthen the abilities, experiences and resources of basic social organisations to address the TB problem in their community.
- Advise basic organisations on aspects of TB control with a social approach.
- Train and supervise support staff.
- Share experiences about adverse effects.

Indicators used to assess treatment adherence

MDR-TB treatment normally takes 2 years or more. The representative of the national tuberculosis programme (NTP) needs to be aware of patient progress/condition when evaluating treatment outcomes 2+ years after treatment initiation. This is particularly important for DR-TB treatment programmes. The following indicators may be of help in assessing treatment adherence:

- Conversion of smear and sputum culture from positive to negative: conversion measurement is recommended at least in the first 6 months of DR-TB treatment.
- Reduction of symptoms.
- Clinical improvement.
- Weight gain/loss.
- Daily attendance at the health service, confirmed by review of treatment cards.
- Rate/number of no-shows for treatment appointments. When possible, health staff should visit the patient with DR-TB following a no-show to prevent discontinuation of DR-TB treatment.
- Reduction of desertion rates, which can be measured each time the DR-TB cohort is assessed (usually 30 months after the last patient of the year begins treatment).
- Study of user satisfaction through surveys on knowledge, attitudes and practices relating to TB treatment.
- Health provider satisfaction level assessed via surveys regarding knowledge, attitudes and practices by type of health provider.

In conclusion, adherence to DR-TB treatment is highly important, and all steps to facilitate adherence should be welcomed in all NTPs. The underlying reasons for country-level success in TB treatment are related to medical, psychological and socioeconomic factors, which in turn affect adherence.

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Monitoring and evaluation of drug-resistant tuberculosis management

Einar Heldal

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 - How are data tabulated, assessed and used to facilitate and improve management of MDR-TB in the future?
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 - Percentage of MDR-TB suspects that show resistance to FLDs and MDR-TB
 - Percentage of MDR-TB cases that have resistance to SLDs
 - Number of MDR-TB cases that are registered
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 - Delays between identification as confirmed MDR-TB patient and start of MDR-TB treatment
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Good recordkeeping, regular reporting and critical assessment of data should be given high priority, as these are the bases for improvement of drug-resistant tuberculosis (DR-TB) management and guide policy development. We describe here indicators used to assess the DR component of TB programmes, including the coverage of drug susceptibility testing (DST) of multidrug-resistant TB (MDR-TB) suspects, the percentage of MDR-TB suspects confirmed to have MDR-TB, the percentage of MDR-TB cases with resistance to fluoroquinolones (FQs) and second-line injectable drugs (2LIs), the number of MDR-TB cases registered by category, the percentage of MDR-TB cases that start MDR-TB treatment, MDR-TB treatment results and delays in MDR-TB treatment start. Definitions include categories of MDR-TB patients and treatment results. Health staff records MDR-TB suspects in request and reporting forms for culture and DST, while MDR-TB patients are entered in MDR-TB treatment cards and MDR-TB registers. Performance is reported through quarterly reports of completeness of rapid test, culture and DST in groups of MDR-TB suspects, quarterly reports of MDR-TB case finding and treatment start and quarterly reports of interim and final results of treatment in confirmed MDR-TB cases who started treatment 12–15 months earlier. The national tuberculosis programme (NTP) tabulates quarterly reports over time

and by area to assess each of the indicators, facilitating critical assessment so low-performance areas can be targeted. The number of newly registered MDR-TB cases should decrease over time, resulting in a lower level of incurable/untreated cases (extensively drug-resistant TB (XDR-TB)), so that infectious MDR-TB cases in the community continue to decline.

Introduction and objectives

Health services must record all diagnosed and treated TB patients to ensure proper management for each individual case, but also so the information can be reported, tabulated and analysed for use in assessments of the implementation of diagnosis and treatment procedures. Management of DR-TB is relatively new, and to date there are no clinical trials documenting optimal treatment regimens while diagnostic algorithms are being developed and revised. Good quality information is urgently needed to critically assess implementation, improve performance and guide policies. The objectives of this chapter are to describe how health-care providers should manage MDR-TB suspects (i.e., completing request forms for culture analysis) and individual MDR-TB patients (MDR-TB treatment cards), how laboratories use registers to record culture and DST results, how the NTP monitors the management of MDR-TB patients (MDR-TB suspect register, MDR-TB register, quarterly reports on case finding and treatment outcomes) and how the NTP tabulates, analyses and uses data. This chapter focuses on MDR-TB, but DST of MDR-TB suspects will also identify some poly-resistant strains. These cases can be quantified from the laboratory register (for culture and DST) and from the MDR suspect register. Some may also be included in the MDR-TB register if they require similar management to cases with MDR-TB, such as treatment start using second-line drugs (SLDs). In most settings, there will be few such cases, mainly patients with rifampicin (R) resistance detected by rapid test while additional DST may show that the strain is sensitive to isoniazid (H).

Management of MDR-TB is an extension of basic TB management, using similar recordkeeping for each patient and periodic reports of case finding and treatment. Additional information must also be included, however, such as DST results, SLD treatment and treatment duration (typically 9–12 months but prolonged to 24 months in some patients). In smaller countries, there may be only one laboratory performing DST (though more can likely conduct rapid tests), one site to start MDR-TB treatment and one MDR-TB register, so data will not be reported but only used by the NTP for its own quarterly assessment. In large federal states, each state/province may function similarly to a country. Other countries may have more than one DST laboratory, more than one MDR-TB treatment start site and one MDR-TB register for each site. Reports are in these cases submitted for each site, or data are amalgamated in one central MDR-TB register. In most countries, districts have only a handful of MDR-TB cases and perhaps no MDR-TB register while patients are managed with MDR-TB treatment cards. Quarterly reports of MDR-TB case finding and treatment outcome will not be meaningful at the district level in such scenarios. This chapter is based upon the International Union Against Tuberculosis and Lung Disease (The Union) publications *Management of Tuberculosis: A Guide to the Essentials of Good*

Practice (the 'Orange Guide', 2010) and *Priorities for Tuberculosis Bacteriology Services in Low-Income Countries* (the 'Red Book', 2007), the World Health Organization (WHO) *Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis* (2008 update) and indicators from *Multidrug-Resistant Tuberculosis (MDR-TB) Indicators* (WHO 2010).

Indicators

Similar to basic TB programmes, the objective of MDR-TB management is to reduce TB transmission through early case identification and by ensuring effective treatment without creating additional resistance. In practice, this means defining persons suspected of MDR-TB, performing DST to confirm MDR-TB, starting timely MDR-TB treatment and ensuring treatment completion. The goal is to improve the MDR-TB situation, documented by a decline in the number of newly registered MDR-TB cases, while maintaining a very low level of incurable/untreated cases (mainly XDR-TB) so that the number of infectious MDR-TB cases in the community keeps declining. The main indicators to monitor the DR component of the TB programme are therefore as follows:

- 'Coverage' of drug resistance testing in MDR-TB suspects following results of DST, which may consist of three steps: 1) rapid test for R resistance, 2) culture (for DR testing of SLDs), and 3) DST.
- Percentage of patients in groups defined as MDR-TB suspects confirmed as patients with MDR-TB.
- Percentage of patients with MDR-TB whose strains are resistant to FQs and 2LIs (including XDR-TB).
- Number of cases with MDR-TB registered by category: 1) no previous TB treatment, 2) treated with first-line drugs (FLDs) only, 3) treated with both FLDs and SLDs, 4) confirmed MDR cases alive but not on adequate treatment and not included in the first three categories.
- Percentage of confirmed MDR-TB cases who start MDR-TB treatment.
- Treatment results in confirmed MDR-TB cases: percentage cured, completed, failed, lost to follow-up, died or transferred out of district.
- Delay between MDR-TB diagnosis and MDR-TB treatment start in confirmed MDR-TB cases.

Definitions

An **MDR-TB case** can refer to a TB patient with *confirmed MDR-TB* if resistance to R and H is documented, or with *unconfirmed MDR-TB* if the doctor decides to start MDR-TB treatment without MDR-TB confirmation and the

MDR-TB diagnosis is not later discarded. An **MDR-TB suspect** is a TB patient where NTP guidelines indicate that a DST should be taken. Possible **sites of disease** are pulmonary cases, with tuberculosis of the lungs, and extra-pulmonary cases, including those with pleural and miliary tuberculosis (the specific site should be recorded). **XDR-TB** is a subgroup of MDR-TB with additional resistance to an FQ and at least one injectable SLD such as kanamycin (Km), amikacin (Am) or capreomycin (Cm). XDR-TB cases are always confirmed and can appear in all the categories below. It is important to assign each patient to the right category of MDR-TB to be able to accurately follow trends in MDR-TB and ensure adequate treatment until results of DST for SLDs are available. The category is defined by the treatment history and *assessed at the time of sputum sample collection, which is ultimately used to confirm MDR-TB*. There are four categories of MDR-TB:

- 1 Patients who never received previous TB treatment for as much as 1 month.
- 2 Patients who were treated only with FLDs, further divided into subgroups according to results of previous treatment:
 - A A *relapse* is a patient who, having previously been treated, was declared cured or completed treatment prior to once again becoming sputum smear-positive.
 - B *Treatment after failure of the first treatment* is a patient who, while on treatment, is smear-positive at 5 months or later during the course of treatment, and who starts retreatment.
 - C *Treatment after failure of retreatment* is a patient who, while on retreatment with FLDs, is smear-positive at 5 months or later during the course of treatment.
 - D *Late converters* are patients with positive smear after 3–4 months of FLD regimens.
 - E A patient recorded as *treatment after default* is one who was treated for 1 month or longer and who returns to the health service sputum-positive after having interrupted treatment for 2 or more months and starts retreatment.
 - F A patient is recorded as *transferred out* if he/she was originally registered as a case in another TB register but transferred to the current facility to continue care.
 - G All other patients not previously registered with MDR-TB are categorized as *other*, which includes smear-negative or extra-pulmonary cases who have been previously treated and so-called ‘chronic’ cases who have failed retreatment in the past.
- 3 Patients who received MDR-TB treatment previously: these patients should be subdivided according to results of previous MDR-TB treatment (relapse, after default, after failure, other).

- 4 Confirmed MDR-TB patients not receiving MDR-TB treatment at the end of the year and not included in the previous categories. This group is included when generating the *Quarterly Report of MDR-TB Case Finding and Treatment Start* (Appendix, Form 5). Patients may end up in this group because SLDs are not available, if they have failed MDR-TB treatment and are considered incurable with current drugs or if they refuse treatment. While patients in categories 1, 2 and 3 are counted over a quarter or year, representing 'incident cases', patients in this category are counted at a specific time, usually at the end of the year (contributing to 'prevalent' cases).

Results of MDR-TB treatment for each individual patient should be recorded as described below. The first of these events to occur is recorded as the treatment outcome.

- *Cured* refers to a patient who has completed MDR-TB treatment according to programme protocol and has a negative culture at the last month of treatment and at least one previous occasion.
- *Treatment completed* refers to a patient who completed treatment but in whom culture examination results are not sufficiently complete to classify the patient as cured. (This includes patients for whom the final smear examination was not performed.)
- *Failure* should be declared when a change of regimen is required (defined as two or more drugs being replaced) or treatment termination is decided upon for any of the following reasons:
 - Lack of bacteriological response accompanying lack of clinical improvement at 6 months of treatment for patients not previously treated with SLDs and at 12 months for patients previously treated with SLDs or patients with XDR-TB. Lack of bacteriological response is defined as lack of culture conversion by month 6, or month 12 at the latest, and/or no decrease in smear positivity grade.
 - Bacteriologic reversion, with concomitant clinical deterioration after initial response, occurring after at least 6 months of treatment for patients not previously treated with SLDs or 12 months for patients previously treated with SLDs. Bacteriological reversion is defined as two consecutive positive smears or two consecutive positive cultures after initial conversion. An isolated positive smear or culture without clinical deterioration after initial bacteriological response is insufficient evidence to declare failure.
 - Adverse drug events. Replacement of a single drug due to adverse drug events is not classified as treatment failure.
- *Died* is recorded when a patient dies for any reason after diagnosis and before completing treatment.

- *Defaulted* is recorded for any patient who has failed to adhere to the treatment regimen for more than two consecutive months after the date of the last attendance for treatment.
- *Transfer out* indicates any patient for whom treatment results are unknown and who was transferred to another basic management unit to continue treatment.

What records are necessary for multidrug-resistant tuberculosis patient management?

Records of multidrug-resistant tuberculosis suspects

All TB patients defined as MDR-TB suspects by national guidelines should have sputum collected for rapid DST for R at a minimum. The health worker should complete the *Request and Reporting Form for TB Culture and Drug Susceptibility Test* (Appendix, Form 1) and ensure that sputum is sent to the designated laboratory. If DST is requested, it is important to specify which registration group the patient belongs to at the time the sputum is collected. This information is needed to monitor the coverage of DST in groups at risk for MDR-TB.

When the sample is received in the laboratory, staff enters the information in the *Tuberculosis Laboratory Register for Culture and Drug Susceptibility Testing*. Results are entered (rapid test for type, R resistance, culture, DST) on the request form when ready and also sent to the requesting unit and entered in the laboratory register (Figure 16.1). Rapid DST results should be communicated by phone as soon as they become available. The NTP central unit (in some settings there may be a designated intermediate level) should also enter the information in a basic *MDR-TB suspect register*, which is a list of all MDR-TB suspects identified in the district for whom drug resistance tests have been performed with registration number, date and category of patient when sputum was collected. The MDR suspect register should include DST specimen referral/results information and preferably unique patient and referred specimen identifiers. The intermediate level should send reports to the central level or send a periodically updated file via computer (using a uniform format). The MDR-TB suspect register is often based on the laboratory register for culture and DST with the addition of MDR-TB suspects from district quarterly reports for cases where samples were not received in the laboratory. This information is the basis for assessment of coverage of culture and DST.

Records of multidrug-resistant tuberculosis patients

When the patient starts treatment for MDR-TB, the health-care worker fills in the *TB patient card*. This card should be the same as the one used for TB

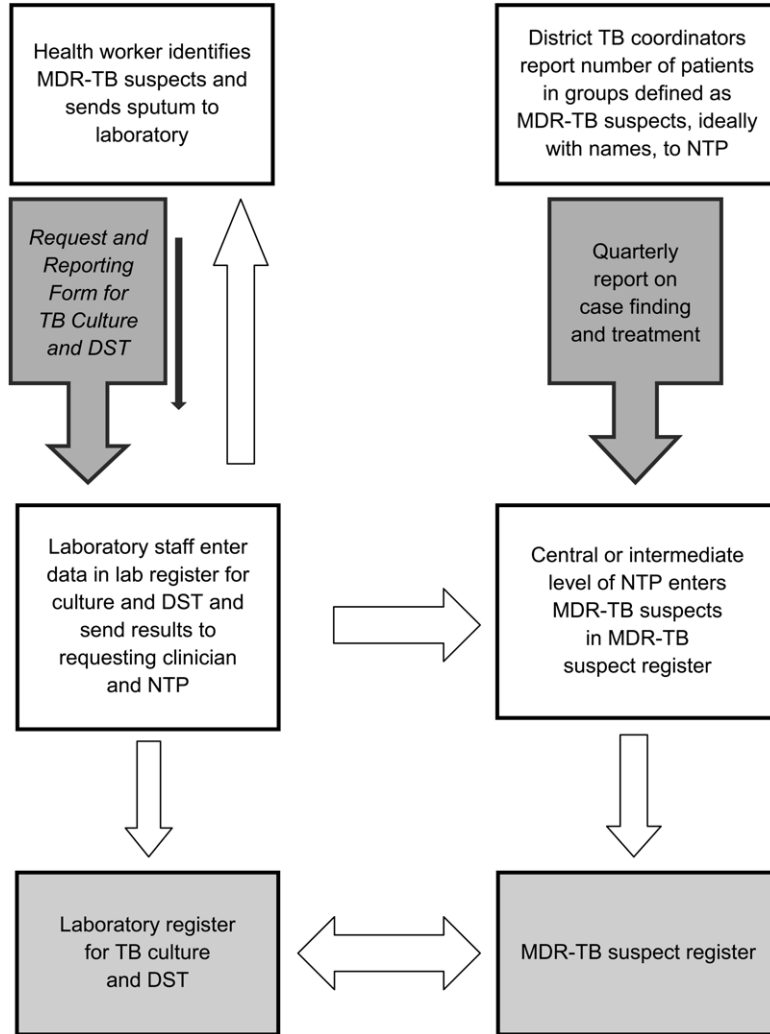


Figure 16.1 MDR-TB suspects tested (left column) and MDR-TB suspects reported in the routine recording and reporting system (right column).

patients with drug-susceptible disease but also includes information about MDR-TB treatment. It contains key information about diagnosis and treatment of TB. The patient keeps this card. The health-care worker also fills in the *MDR-TB Treatment Card* (Appendix, Form 2), which is kept in the health facility where the patient receives treatment. This card includes the same information as the TB patient card plus more detailed information including category of patient, previous TB treatment, smear and culture results during treatment, changes in drug regimen, recordkeeping for daily administration of drugs and treatment outcome. When a sputum examination

result (smear and culture) is communicated to the health service facility, it should be recorded immediately on the MDR-TB treatment card.

The health-care worker should enter all confirmed MDR-TB cases in the *MDR-TB Register* (Appendix, Form 3), including those who do not start treatment because they die or are lost to follow-up before treatment start or because there are no SLDs available. The register must also include unconfirmed MDR-TB cases who start MDR-TB treatment. It is important for the central unit of the NTP to maintain regular (weekly if possible) communication with the laboratory regarding confirmations of MDR-TB to ensure that the central MDR-TB register is complete and up-to-date.

In most countries, a national/central MDR-TB register is kept in the reference hospital(s) where most MDR-TB patients start their treatment and stay until smear is negative. Treatment is typically continued at the patient's local district. If the district has a fair number of MDR-TB patients, it is advisable to maintain a district MDR-TB register. Patients should be recorded in numerical order by the date when they become known to the health-care worker responsible for the register. Numbering commences with number 1 (one) at the beginning of each calendar year, regardless of when the patient was diagnosed or commenced treatment. Drawing a line after the last patient registered in a given quarter, or starting registration for a new quarter on a new page of the register, facilitates the counting of patients at reporting time. Information on HIV testing, cotrimoxazole preventive therapy and antiretroviral therapy should be included in the MDR-TB treatment card and MDR-TB register.

One line in the MDR-TB register is equivalent to one treatment episode of a patient, although confirmed MDR-TB patients who do not start treatment should be included. If the patient defaults from MDR-TB treatment but comes back and a new MDR-TB treatment is started, the patient should be registered again in the 'treatment after default of MDR-TB treatment' category. If the patient comes back after default and the clinician decides to continue the same treatment, there is no need to re-register the patient. Thus the same line can be used, but the treatment outcome will remain 'default'. If a patient fails MDR-TB treatment and starts a new MDR-TB treatment, the treatment result should be 'failure' and the patient re-registered in the category 'treatment after failure of MDR-TB treatment' (Figure 16.2).

If a patient starts MDR-TB treatment based on confirmation of R (and possibly also H) resistance, and the results of DST for SLDs (taken at the same time as the sample showing MDR-TB or, more commonly, when the results of MDR-TB tests become available) arrive 3–4 months later showing XDR-TB, the regimen will often be modified, changing two or more SLDs. The MDR-TB treatment outcome will then be changed to 'Failure/changed to XDR-TB treatment' and the patient reregistered as 'Treatment after failure of MDR-TB treatment', and ticked off as XDR-TB in the column 'Type of

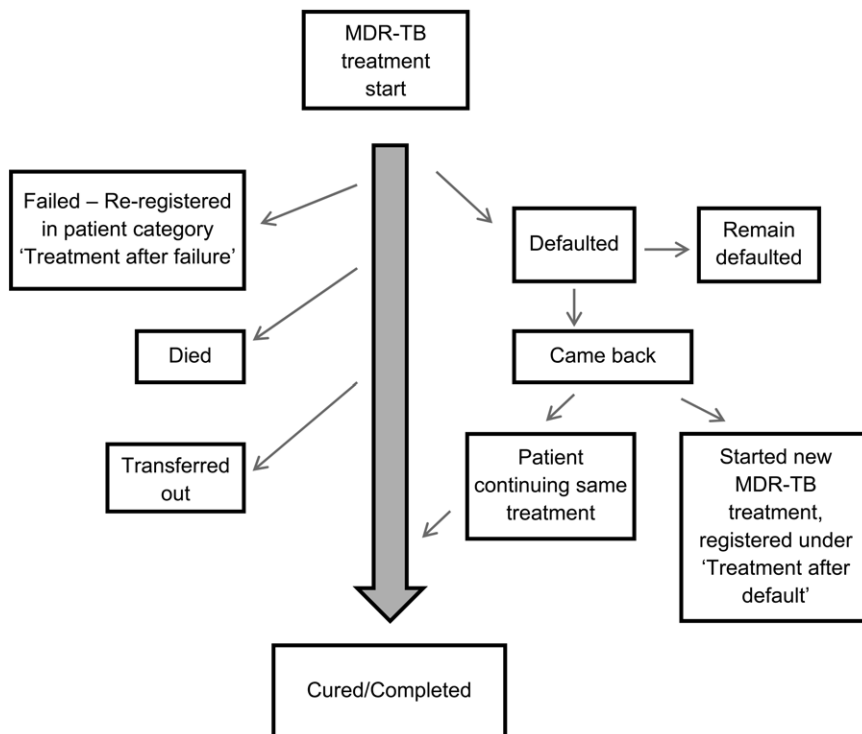


Figure 16.2 Results of MDR-TB treatment.

resistance' in the MDR-TB register. The date of XDR-TB registration will be the date as of which the patient is entered as an XDR-TB case. In some cases where the result of XDR tests arrives after 3–4 months, the treatment will not be changed, and the patient will therefore not be registered again. The date of XDR-TB registration will then be the date of DST results showing XDR-TB (from the MDR-TB treatment card). The finding of XDR-TB should be made clearly visible in the MDR register to facilitate counting during quarterly assessment. MDR-TB patients may also be found to have XDR-TB in samples taken during follow-up of treatment. If the treatment is changed with two or more SLDs, the patient should be registered again as 'Treatment after failure of MDR-TB treatment'. If treatment is not changed, the same line will be used, but the presence of XDR-TB should be made clearly visible.

How are results reported?

Quarterly Report of Coverage of DST in Risk Groups for MDR-TB

This form (Appendix, Form 4) is usually filled in (or generated by computer) by the central NTP unit (in some settings at the intermediate level) because

it requires results of laboratory tests. It provides information about the total number of TB patients in risk groups for MDR-TB from the routine quarterly district reports of case finding: relapses, treated after default and treated after failure. The quarterly report from the district should also contain a list with the names of MDR-TB suspects for whom sputum was sent for culture and DST, specifying date of district TB registration and category of MDR suspect. The quarterly report should include also names of patients in other risk groups such as 'chronics' (basically, failures of retreatment from previous years), and 'late converters' (smear-positive at 3–4 months of treatment) if the NTP have included these groups as MDR-TB suspects. It should also be noted whether sputum was sent for testing. This information should also be entered in the district TB register. Comparing the names in the quarterly reports from the districts (often in a MDR-TB suspect register) with the laboratory register for culture and DST will provide data on how many of the MDR-TB suspects actually had sputum received for culture, rapid test and DST, and how many had results regarding resistance to R, H and SLDs. If the district TB register contains information about which patients had sputum sent and the result of the tests, this information should be entered in the quarterly reports from the districts and also be used to fill in Form 4.

The central NTP unit compares the names of the individuals for whom sputum is sent to the laboratory (according to district quarterly reports) from the 'MDR-TB suspect register' to the laboratory register for culture and DST to assess how many of them had results recorded with positive cultures, results of DST and confirmations of MDR-TB. This information is entered in Form 4 to assess how representative the MDR-TB suspects tested are and to facilitate interpretation of DST results. This includes assessment of the extent to which the groups with the highest risk for MDR-TB are tested. Such analyses are dependent upon the reliability of district quarterly reports.

Quarterly Report of MDR-TB Case Finding and Treatment Start

This report (Appendix, Form 5) is based on the MDR-TB register. Block I consists of four groups. Groups I–III include all MDR-TB patients registered during the previous quarter. Group I are new patients and Group II are retreatment cases who have received only FLDs. Group III contains patients who were previously registered as having MDR-TB but are registered again because they have relapsed, failed or defaulted and returned to MDR-TB treatment. Group IV contains confirmed MDR-TB patients not under treatment and who are not included in Groups I–III. All MDR-TB cases should be classified according to type and whether MDR-TB is confirmed or unconfirmed. All patients registered with XDR-TB during the quarter should be entered in the right column. These patients are not necessarily among the MDR-TB cases listed to the left, as there may be delays in results of DST for SLDs.

Block II contains all patients who started MDR-TB treatment during the quarter (by date of MDR-TB treatment start), and will therefore usually be somewhat different from the patients in Block I. Because the MDR-TB register lists patients by date of registration, it may be challenging to identify patients who started treatment during the quarter due to various reasons for treatment delay that may be spread over several quarters of MDR-TB registration. If the MDR-TB register is computerised, a list should be generated by date of treatment start to facilitate tabulation.

Quarterly Report of Interim and Final Result of MDR-TB Treatment in Confirmed MDR-TB Cases Who Started Treatment 12–15 Months Earlier

This report (Appendix, Form 6) is also based on the MDR-TB register. Its purpose is to provide as much updated information as possible regarding treatment results, especially rates of failure, deaths and defaults that may require quick policy intervention for improvement. The most recent group of patients having completed short treatment (9–12 months) comprises patients who started treatment during the quarter 12–15 months prior. For instance, if the assessment takes place April 1, 2012, the first quarter of 2011 can be assessed. Again, it is easier to identify patients if the MDR-TB register is computerised and sorted by date of treatment start. For each patient who started MDR-TB treatment during this quarter, check first whether treatment results are already recorded and enter the results in the form. If there is not yet a treatment result, the patient should still be on treatment. Look for smear and culture results at 12 months (negative, positive, no result) and enter this information. Enter data separately for patients who received the short treatment (all should have finished treatment) and for patients on prolonged treatment who will for the most part still be on treatment. For patients on short treatment, the result of culture at 12 months may not yet be available, so outcome will not be 'cured' but rather 'completed'. This outcome can be corrected when data are tabulated again at a later date.

How are data tabulated, assessed and used to facilitate and improve management of multidrug-resistant tuberculosis in the future?

Case finding and treatment outcome should be assessed quarterly, just as for TB cases with drug-sensitive *Mycobacterium tuberculosis* strains. In most countries, the number of MDR-TB cases is modest, and such assessments only take place at the central/national level. However, all units that have a fair number of MDR-TB patients and an MDR-TB register should conduct the same reporting and analysis. The MDR-TB register should be updated, entering results of smear and culture tests during follow-up and treatment

results, before the quarterly assessment is made. The focus of data analysis is the extent to which MDR-TB management objectives are achieved. These objectives are 'to reduce TB transmission, through early identification of MDR-TB cases and ensuring effective treatment without creating additional drug resistance.' The quarterly assessment should be done to show differences between districts and provinces during the previous quarter, identifying areas of low performance where corrective intervention should be targeted, and changes over time (trends) including the last years and quarters for comparison. This is usually accomplished by entering quarterly data from *Coverage of DST in Risk Groups for MDR-TB* (Appendix, Form 4), *MDR-TB Case Finding and Treatment Start* (Appendix, Form 5) and *Interim and Final Result of MDR-TB Treatment* (Appendix, Form 6) into tables. Districts and provinces are listed in rows to facilitate their comparison, with key variables listed in columns. In order to assess time trends, the main variables are entered as rows and the period (years and quarters) in columns. The sequence here utilises the previously listed indicators.

Percentage of multidrug-resistant tuberculosis suspects that have drug susceptibility test results for rifampicin and isoniazid

Data from the *Quarterly Report of Coverage of DST in Risk Groups for MDR-TB* (Appendix, Form 4) are tabulated to calculate the percentage of MDR-TB suspects tested in the various groups (Figure 16.3). The percentage tested is calculated as the total number of individuals with results of DST to R and H divided by the total number of MDR-TB suspects reported the previous

MDR-TB suspect group	2010	2011	2012-1q	2012-2q	2012-3q	2012-4q
After failure of retreatment						
After failure of first treatment						
After default						
Relapse						
'Chronic'/backlog						
New (contacts of MDR-TB cases)						
Late converter (smear+ at 3–4 months)						
Total						

Figure 16.3 Table for recording percentage of patients in groups defined as MDR-TB suspects with a DST result for rifampicin and isoniazid.

quarter, multiplied by 100. Data for the table should be calculated on the national and province and/or district level. Taking one MDR-TB suspect group at a time, provinces/districts can then be entered as rows, making it easy to identify provinces/districts with low performance.

The NTP should define targets, usually 100% of failures of retreatment, first treatment and 'chronic'/backlog cases; relapses in many countries will have a much lower percentage of MDR-TB and lower coverage may be more acceptable if not all can be tested. The table shown in Figure 16.3 is also used to make logical decisions regarding expansion plans and to define how coverage in each group should be realistically increased over time. Several countries have problems ensuring that smear microscopy examination is conducted in all pulmonary TB cases. Because MDR-TB suspects are usually defined based on smear microscopy, this weakness limits the detection/documentation of MDR-TB cases. Low performance should be further assessed by identifying where the problem lies: 1) sputum not sent for culture, 2) no culture result or 3) no DST result (only results of rapid test for R). Common challenges include long delays in the transport of samples from the facility to the laboratory, low yield of cultures because of transport delays and slow reporting back to the field sites.

Percentage of tested multidrug-resistant tuberculosis suspects that have multidrug-resistant tuberculosis

The table shown in Figure 16.3 can also be used to assemble data from the right section of the *Quarterly Report of Coverage of DST in Risk Groups for MDR-TB* (Appendix, Form 4) to show the percentage of MDR-TB suspects confirmed with MDR-TB. The percentage with MDR-TB is calculated by dividing the number of patients with confirmed MDR-TB by the number of patients with DST results for R and H (or only R if rapid test used), multiplied by 100. Analysis must also consider previous tables to assess the extent to which patients are selected for testing if the coverage is low, and therefore if the data are representative. If not all are tested, often those with the most serious disease may be selected, resulting in higher proportions of MDR-TB.

Comparing data for each group of patients by province and district should help identify areas with higher percentages of MDR-TB, which should then be investigated as possible 'hot spots'. Hot spots can be identified both through the percentage of MDR-TB suspects among all TB cases, the percentage of MDR-TB suspects confirmed with MDR-TB and the absolute number of MDR-TB cases. The table shown in Figure 16.3 is also used to assess whether the most relevant risk groups for MDR-TB are targeted for testing by looking at the size of the target group and the percentage with

confirmed MDR-TB. For instance, if the percentage of MDR-TB is low (below 15%), many of those with a positive rapid test for R may be false-positive.

A similar table can also be created to show the percentage of MDR-TB cases with XDR-TB, dividing the number of XDR-TB cases (among the MDR-TB cases) by the number of MDR-TB cases with these SLD results, multiplied by 100.

Percentage of multidrug-resistant tuberculosis suspects that show resistance to first-line drugs and multidrug-resistant tuberculosis (calculated annually)

The table shown in Figure 16.4 is developed from the MDR-TB suspect register by date of registration as TB cases. It shows the same data as the previous table (MDR %; Figure 16.3) but contains information on DST of more drugs. It is usually assembled once per year. NTPs should track the level of resistance to key drugs in different patient groups to establish trends and assess whether recommended regimens (prescribed before results of DST are available) are adequate. This table is similar to the WHO's standard table for drug resistance surveys. The lower the percentage of patients with DST results, the lower the representativeness of the statistics.

This table (Figure 16.4) can also be used to make separate assessments of each of the three groups: new, previously treated with FLDs and previously treated with SLDs. The number of poly-resistant cases can also be included in the table.

	2009		2010		2011		2012	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
All registered TB cases (sm+)								
All with rapid R/H result (% of all registered)								
All with culture (% of all registered)								
All with DST results (% of all registered)								
All R-resistant (% of all with DST results)								
All H-resistant (% of all with DST results)								
All E-resistant (% of all with DST results)								
All S-resistant (% of all with DST results)								
All R- and H-resistant (MDR-TB) (% of all with DST results)								

Figure 16.4 Table for recording DST patterns (national data, full year; data from MDR-TB suspect register; includes both new and previously treated with FLDs and previously treated with SLDs).

	2009		2010		2011		2012	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
All MDR-TB cases								
MDR-TB cases with DST results for SLDs								
Resistance to ethambutol								
Resistance to streptomycin								
Resistance to ofloxacin								
Resistance to kanamycin								
Resistance to amikacin								
Resistance to capreomycin								
Resistance to all available injectables								
Resistance to ofloxacin and any injectable (XDR-TB)								
Resistance to ofloxacin and all injectables								

Figure 16.5 Table for recording DST patterns (national data, full year; data taken from MDR-TB suspect register).

Percentage of multidrug-resistant tuberculosis cases that have resistance to second-line drugs

The table shown in Figure 16.5 is also developed from the MDR-TB suspect register by date of registration as TB cases. In addition to all data in the previous tables, it contains information on DST for confirmed MDR-TB cases. It should be assembled once per year. For MDR-TB patients, it is important to know the level of resistance to FQs and injectables, especially because there is a long delay in getting DST results for these drugs (until rapid tests for SLD resistance become routinely available). This information has implications as to whether the 9–12 month regimen recommended by The Union can be used or if additional drugs may be needed. Again, the lower the percentage of patients in the groups with DST results, the lower the representativeness. New cases are usually limited to a few close contacts of confirmed MDR-TB cases, and additional surveys are needed to provide representative data.

This table (Figure 16.5) can also be divided into three groups of patients: new, previously treated with FLDs and previously treated with SLDs.

Number of multidrug-resistant tuberculosis cases that are registered

The table shown in Figure 16.6 is assembled from the *Quarterly Report of MDR-TB Case Finding and Treatment Start* (Appendix, Form 5). Registered

Patient group	2010	2011	2012-1q	2012-2q	2012-3q	2012-4q
Group I: First-time TB						
Group II: Previously treated with FLDs						
Relapse						
After default						
Failure of first treatment						
Failure of retreatment						
Late converter (smear+ at 3–4 months)						
Transfer in						
Other						
Group III: New registration of patients previously registered as treated with SLD						
Group IV: Confirmed MDR-TB patients alive but not on treatment (and not included in Groups I–III)						

Figure 16.6 Table for recording number of patients registered with confirmed MDR-TB/XDR-TB in the MDR-TB register by quarter (by date of MDR-TB registration).

MDR-TB cases are tabulated and entered by category: Group I, new TB cases; Group II, previously treated only with FLDs; or Group III, previously registered with MDR-TB but registered again due to relapse, failure or default with MDR-TB treatment. Group IV contains confirmed MDR-TB patients who, at the time of assessment, are alive with confirmed MDR-TB but not on treatment and not included in Groups I–III.

Tabulation by district and province (for the last quarter, with patient categories listed in columns) shows the number of registered MDR-TB cases, but also needs to take into consideration the coverage of DST in MDR-TB risk groups to identify areas with a higher proportion or absolute number of MDR-TB cases. The number of MDR-TB cases often increases rapidly as diagnostic and treatment facilities are expanded, while true trends can only be assessed once a high proportion of MDR-TB suspects undergo DST. The number of ‘other’ (including ‘chronic’) cases usually declines quickly as they are tested and adequately treated, while the number of MDR-TB cases among new and retreatment cases will be more stable, depending on how the NTP works to reduce the number of retreatment cases. An increase over time in the group of confirmed MDR-TB not on treatment is a very serious

warning sign that the situation is deteriorating, with an increasing number of sources of infection in the community.

Recording how many of those who started treatment for confirmed multidrug-resistant tuberculosis were cured, completed, failed, lost to follow-up, died or transferred out

The table shown in Figure 16.7 is based on the MDR-TB register and includes tabulated data from the *Quarterly Report of Interim and Final Results of MDR-TB Treatment in Confirmed MDR-TB Cases Who Started Treatment 12–15 Months Earlier* (Appendix, Form 6). Its purpose is to provide updated results of treatment that may require quick intervention for improvement as soon as possible, especially in rates of failure, deaths and defaults. Assessment includes cohort analysis, which means that patients are divided into groups according to date of treatment start, grouped according to 3-month periods or years. Assessment is tabulated every 3 months for the status of all patients grouped by quarter of treatment start. This assessment is of status at a specific number of months after treatment start (i.e., 3, 6, 9, 12, 15, etc.). Patients should be assessed again 3 months later and new data tabulated. As it typically takes 2–3 months to receive results for culture tests, an extra quarter is added to allow for receipt of culture results.

In the top row of column 1 in the table (Figure 16.7), enter the first quarter that MDR-TB treatment was provided and then list successive quarters down the rows until the most recent completed quarter. The patients in the last row have started treatment 0–3 months prior. This cohort cannot be assessed yet (apart from the number of patients who started) because the last patient in the cohort just started, so status is entered at '0' months (column 2). This is also the case for the previous quarter (treatment started 3–6 months earlier) because culture results are not yet available. For patients who started 6–9 months prior, assessment of status at 3 months should be available. For patients who started 9–12 months prior, status at 6 months can be assessed. For patients who started 12–15 months prior, assessment of status at 9 months is available. For patients who started 15–18 months prior, status can be assessed at 12 months, which is the typical treatment duration for most patients, so this will likely be the final result for most patients. This data would thus be included in Form 6. For instance, if assessment is completed on April 1, 2012, treatment start 12–15 months earlier would be the first quarter (January–March) of 2011. Adding an additional 3-month delay for culture results, a 12-month assessment can be conducted for the fourth quarter (October–December) of 2010.

However, those who started treatment earlier should also be included in the form in case any patients underwent prolonged treatment (and therefore still do not have a final outcome) and to facilitate assessment of

changes over time: those who started 18–21 months earlier are assessed at 15 months, those who started 21–24 months earlier at 18 months, those who started 24–27 months earlier at 21 months and those who started 27–30 months earlier at 24 months. If all four quarters in a year have finished treatment, data can be combined into one row for the whole year.

Each of the confirmed MDR-TB patients with a date of MDR-TB treatment start should then be ticked off in the form. The date of treatment start determines for which quarter, and therefore with which row, the patient should be assessed. If the patient already has a treatment result, it should be entered in the form. The absence of treatment result means that the patient is still receiving treatment. Look for smear and culture results (negative, positive, no result) at the last quarterly follow-up, as calculated above.

Interim outcomes before 12 months are especially useful if performance is not acceptable (usually high rates of failure, death or default). In such cases, changes in interventions may be needed to improve outcomes, and it is likely that the NTP will want to document changes as soon as possible. Outcomes after 12 months are needed to adjust results from ‘completed’ to ‘cured’, allowing time for culture results to arrive. Figure 16.8 shows assessment examples for different quarters. The MDR-TB register contains patients entered by date of registration, usually soon after diagnosis with MDR-TB. The dates of treatment start may not follow the same sequence because delays can vary. It may therefore be challenging to complete this table including all patients in the register, because they may be recorded under different quarters of treatment start. One of the advantages of computerised systems is that the sequence of patients can be altered so they can be sorted

Date of MDR-TB treatment start	Time since last patient in the quarter started MDR-TB treatment	Status assessed after number of months (including 3-month delay for culture result)
4th quarter (October, November, December) 2010	15 months	12 months = final
1st quarter (January, February, March) 2011	12 months	9 months
2nd quarter (April, May, June) 2011	9 months	6 months
3rd quarter (July, August, September) 2011	6 months	3 months
4th quarter (October, November, December) 2011	3 months	0 months
1st quarter (January, February, March) 2012	0 months	0 months

Figure 16.8 Sample table showing patients listed by quarter during which they started MDR-TB treatment, months since the last patient in the quarter started treatment and assessed status after a specific number of months (example of assessment April 1, 2012).

by treatment start, facilitating completion of the table (or generating the table automatically). This form is updated quarterly, but for quarters where only a few patients are still on treatment, their names (or unique identifiers) may be noted on the form with only these patients being followed up the next quarter.

The percentage of cases who fail, die and default should be calculated for each quarter/year and added to the right section of the table. For cohorts where all patients should have completed treatment, the success rate should be calculated. Reasons for high failure rates include inadequate regimens, low-quality drugs and treatment without direct observation. Causes for high death rates include late treatment start, HIV infection and concomitant disease. High default rates can be due to long hospitalisations, especially if far away from home, long distances for daily directly observed treatment (DOT) and unsatisfactory management of adverse reactions. Reasons for high transfer out rates include inadequate coordination with other districts/provinces. Separate versions of the table shown in Figure 16.8 can be created for new cases previously treated with FLDs and cases previously treated with SLDs.

Delays between identification as confirmed multidrug-resistant tuberculosis patient and start of multidrug-resistant tuberculosis treatment

The time lag between identification as MDR-TB suspects and the start of MDR-TB treatment in confirmed MDR-TB cases is obtained from the MDR-TB register, and the time to treatment start is calculated for each quarter (Figure 16.9). NTPs should define the acceptable length of delay (within a range) and the proportion of cases defined as acceptable should be entered. Reasons for not starting treatment (yet) include that the patient died or disappeared before treatment start, that drugs were not available, that the resistance pattern was considered untreatable, that the patient refused treatment and that hospital beds were not available.

A similar table could be made to assess delay from identification as MDR-TB suspect until confirmation as MDR-TB patient. Possible reasons for unacceptable delay would include sputum not collected timely for DST, delayed transport of sputum to laboratory, unacceptably slow results from laboratory and backlog in recording results.

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Management of second-line medicines for tuberculosis treatment

Cécile Macé, Christophe Perrin

-
- Introduction
 - Selection of medicines to treat DR-TB patients
 - Quantification
 - Procurement of DR-TB medicines
 - Quality assurance of DR-TB medicines purchased
 - Prices of DR-TB medicines
 - Importation of DR-TB medicines
 - Storage and distribution in-country
 - Rational use
-

This chapter provides guidance on the procurement and management of second-line anti-tuberculosis (anti-TB) or drug-resistant tuberculosis (DR-TB) medicines with the objective of ensuring continuous availability for treatment of patients with DR-TB. The purpose of drug management is to guarantee the availability of the quality-assured drugs necessary for achievement of medical treatment goals. Adequate management of medicines is subject to international and national regulations and requires continuous adaptation to patient needs (e.g., changes in epidemiological profiles and individual drug resistances) as well as to the specific constraints of the DR-TB pharmaceuticals market. Guidance is given to countries on selection, quantification and procurement including quality assurance, pricing information, importation procedures, storage, distribution and rational use of DR-TB medicines.

Introduction

As with any other medicines, the management cycle of DR-TB drugs includes the selection of medicines, quantification of need, management of procurement processes including quality assurance of medicines purchased, storage and distribution to treatment centres and rational drug use. Today's worldwide market for DR-TB medicines is complex due to limited availability and the high cost of quality-assured sources, long delivery delays from manufacturers and sometimes insufficient production capacity. These factors must be taken into consideration by national tuberculosis programmes (NTPs) when planning interventions and particularly their needs for DR-TB medicines.

Selection of medicines to treat drug-resistant tuberculosis patients

The list of medicines to treat DR-TB patients in a country should be defined based on the national evidence-based treatment guidelines when such guidelines exist, failing which they can be selected according to international

recommendations. In countries using standardised regimens, the list of medicines is easily defined. In contexts where individualised regimens are used, the list of medicines will be more exhaustive but should be as standardised as possible.

Medicines currently used to treat DR-TB are classified into five groups (Table 9.1):

- Group 1: First-line oral anti-tuberculosis medicines: isoniazid, rifampicin, ethambutol, pyrazinamide
- Group 2: Fluoroquinolones: ofloxacin, levofloxacin, moxifloxacin
- Group 3: Injectable anti-tuberculosis medicines: streptomycin, kanamycin, amikacin, capreomycin
- Group 4: Less effective second-line anti-tuberculosis medicines: ethionamide/prothionamide, cycloserine/terizidone, P-aminosalicylic acid (acid or salt)
- Group 5: Less effective medicines or medicines for which clinical data are sparse: clofazimine, amoxicillin with clavulanate, linezolid, imipenem, clarithromycin, high-dose isoniazid, thiacetazone

Once the list of medicines to be used has been defined, it is very important to include them in the National Essential Medicines List (NEML). This is vital to standardising DR-TB treatment at the country level, facilitating the import of medicines into the country (essential medicines are exempted from taxes or have lower import taxes in many countries) and encouraging manufacturers to register and market their products in specific countries. The World Health Organization (WHO) EMLs for adults and children could be used by NTPs as an example to support the introduction of these products in their NEMLs.

Quantification

Quantification of need for DR-TB medicines is a difficult exercise, particularly when individualised regimens are used. The best way to quantify medicine needs for DR-TB treatment is the morbidity-based approach. This means using the recommended regimens (considering the dose recommended for each medicine) and the number of patients to be treated with each regimen for a certain period of time. Such quantification exercises should take into account:

- Shelf life of medicines purchased (to define the periodicity of orders, i.e., the length of time between two consecutive orders)
- Lead time from the supplier (i.e., the time period between placement of an order and receipt of the products ordered)

- Estimated size of buffer stock needed to deal with unforeseen situations (delivery delay or unexpected increase in consumption due to an increase in disease rate) and avoid stock-out situations
- Level of stock available (or inventory) when the quantification process is complete

Given that the shelf life of some DR-TB medicines is 24 months and that they are often delivered with 75%–80% remaining shelf life (around 18 months), it is highly recommended that the necessary medicines be ordered for 12 months at a time but supplied in two partial deliveries at 6-month intervals. This will enable fresh products to be delivered each time, while guaranteeing procurement for at least 12 months. Buffer stock levels at national and peripheral levels should also take this into account to avoid losing products due to expiry.

Procurement of drug-resistant tuberculosis medicines

NTPs currently have two options to procure medicines for DR-TB treatment: 1) buy directly from manufacturers/wholesalers (on their own or with support from national procurement centres) using their own procurement procedures, or 2) buy through the Global Drug Facility (GDF) of the Stop TB Partnership. For countries preferring to buy on their own, procurement offices should be aware that purchasing small quantities directly from manufacturers in the current market context may be a significant challenge considering that the availability of quality-assured products is limited and that production capacity for some products does not match current demand.

The advantages of buying through the GDF include: 1) access to quality-assured medicines complying with international norms and standards; 2) benefits of long-term agreements signed by the GDF, with prices set through a tender process based on annual estimated pooled volumes; 3) access to a stockpile for emergency orders at the GDF procurement agent level. Potential difficulties of utilising the GDF include the requirement to prepay in full before the GDF confirms orders and potential delivery delays because the small number of approved sources requires substantial advance planning.

Quality assurance of drug-resistant tuberculosis medicines purchased

DR-TB treatment medicines are critical to ensure adequate medical care. It is therefore of utmost importance to ensure the use of quality medicines. At country level, this is normally the responsibility of national pharmaceutical regulatory authorities charged with guaranteeing the quality, efficacy

and safety of products produced, sold and/or distributed in the country. Unfortunately, according to a WHO survey, less than 1/3 of developing countries have an effective national regulatory system for medicines. These authorities often have limited capacity and resources (e.g., low-income countries). Purchasers in these countries must thus reinforce their procurement systems to guarantee the quality of the products supplied under their auspices and to avoid buying sub-standard medicines.

A number of initiatives and documents currently exist to help TB treatment purchasers identify quality-assured medicines:

- The list of WHO prequalified medicines, which is updated regularly and can be found at <http://apps.who.int/prequal/>
- The list of medicines approved for procurement with The Global Fund grants (products approved by stringent regulatory authorities, pre-qualified by the WHO or temporarily approved for procurement based on a risk/benefit analysis performed by an Expert Review Panel (ERP; available at http://www.theglobalfund.org/en/procurement/quality/pharmaceutical/#A_B)
- The list of products approved for GDF procurement based on an assessment conducted by the ERP on behalf of the GDF and The Global Fund (available at <http://www.stoptb.org>)

Products not mentioned in any of these documents should be carefully assessed according to WHO standards. These medicines may have been rejected after assessment through one of these quality assurance systems or may still need to be assessed.

Prices of drug-resistant tuberculosis medicines

Some information is also available in the public domain regarding prices of DR-TB medicines. This information could be useful for countries to ensure that the prices they obtain through their national procurement system are acceptable. Countries may on occasion be tempted to allow products at lower cost, but they should always ensure price comparison among products of similar level in terms of quality assurance. Price information on quality-assured sources can be found in:

- The GDF Product Catalogue (http://www.stoptb.org/gdf/drugsupply/drugs_available.asp)
- 'DR-TB Drugs under the Microscope', a document published jointly by Médecins Sans Frontières and The International Union Against Tuberculosis and Lung Disease (The Union; available at http://www.msfaccess.org/sites/default/files/MSF_assets/TB/Docs/TB_report_UndertheMicro_ENG_2011.pdf).

Importation of drug-resistant tuberculosis medicines

In most countries, importation of drugs requires that the products be registered in the country where they are imported. Registration is the responsibility of the manufacturer/supplier. However, in many countries, for public health interest, it is possible to get a special import authorisation by national pharmaceutical regulatory authorities. It is advisable to get these authorisations before medicines are shipped to the country to avoid delays in customs clearance. If this is not done, there is a high risk of delay at the customs level with inappropriate storage conditions possibly impacting the quality of the products. When registration is required to import DR-TB medicines, the regulatory authority should consider the possibility of fast-tracking the registration of products already approved by stringent regulatory authorities or prequalified by the WHO.

Storage and distribution in-country

To preserve the quality of medicines received in-country, all of them should be stored in dry, well-ventilated premises that offer protection from direct sunlight and dust. Temperatures should normally be maintained between 15°C and 25°C. Though manufacturers may indicate on secondary packaging and the leaflet that some medicines require specific storage conditions to retain quality, safety and efficacy throughout shelf life (see PASER® guide to 'Good Storage Practices'). A distribution system should also be in place to ensure continuous availability of drugs at site level. Distribution should be based on quarterly reports provided by the peripheral level, specifying the regimens used, the number of patients already under treatment, the number of patients expected to be enrolled in the next quarter and the available stock at the time of the report. Transport arrangements should be secured to ensure that quality of products is guaranteed along the distribution channel.

Rational use

DR-TB products should be used with caution and under close patient monitoring by clinicians, considering the toxicity of some of these products. Measures should be put in place to avoid misuse of these products, thereby avoiding loss of susceptibility to the DR-TB medicines and production of strains that will be extremely difficult to cure with currently available medicines. Use of fluoroquinolones, for example, should be limited to the treatment of DR-TB. Information on medicines and their side effects should be made available to clinicians who treat patients with DR-TB, along with training in appropriate regimen prescriptions that include these medicines.

Drug information sheets are available from the WHO. Medicines to deal with side effects should also be made available in-country as DR-TB medicines become available.

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Appendices

- Form 1 Request and Reporting Form for TB Culture and Drug Susceptibility Test
- Form 2 MDR-TB Treatment Card
- Form 3 MDR-TB Register
- Form 4 Quarterly Report of Coverage of DST in Risk Groups for MDR-TB
- Form 5 Quarterly Report of MDR-TB Case Finding and Treatment Start
- Form 6 Quarterly Report of Interim and Final Results of MDR-TB Treatment in Confirmed MDR-TB Cases Who Started Treatment 12–15 Months Earlier

Request and Reporting Form for TB Culture and Drug Susceptibility Test

Patient identification (ID)

TB register no.: _____ TB register date: ____/____/20____ MDR register no.: _____
 Surname and first name of patient: _____ Age (yrs): ____ Sex: ____
 Ward / Department: _____ Address: _____
 *HIV-status: Pos / Neg / Unknown _____

TB disease type and treatment history

Site: Pulmonary Category: New Return after default
 Extrapulmonary (specify): _____ Relapse Late converter
 Failure "Chronic" case
 Last previous treatment: First Retreatment Other
 First MDR-treatment (second-line drugs)
 Other _____
 MDR contact: Yes No Unknown
 Currently on treatment: No / Yes Type: First / Retreatment / First MDR-treatment / Other
 Since date: ____/____/20____

Origin of request

Region ID: _____ District ID: _____ Local laboratory ID: _____
 Date specimen was collected: ____/____/20____ Specimen ID no.: _____
 Local laboratory: Smear result: 1st ____ 2nd ____ specimen
 Microscopy technique used: Ziehl-Neelsen Direct smear
 Fluorescence Concentrated smear

Request for testing at the reference laboratory

Reason: Diagnosis Specimen: Sputum Other (specify): _____
 Follow-up at ____ months during treatment Sputum in preservative, type _____
 Requested tests: Microscopy (type _____) Culture DST (first / second line) Rapid test
 Person requesting examination: Name: _____ Position: _____
 * Information that can be disclosed optionally ID = identification number or code

Reference laboratory results

Date received in Reference Laboratory ____/____/20____ Laboratory specimen ID: _____
 Microscopic examination: previously reported on date ____/____/20____

ID #	Neg	1-9	1+	2+	3+	
						<input type="checkbox"/> Hot Ziehl-Neelsen <input type="checkbox"/> Cold staining <input type="checkbox"/> Fluorescence <input type="checkbox"/> Direct smear <input type="checkbox"/> Concentrated smear

Culture result: previously reported on date ____/____/20____ Will follow

ID #	Contami-nated	Neg	Non-TB mycobacteria (species)	Mycobacterium tuberculosis complex			
				1-9 colonies actual count	10-100 col 1+	>100-200 col 2+	>200 col 3+

Results of *M. tuberculosis* drug susceptibility testing: Will follow
 Phenotypic Genotypic Method _____

ID #	S = susceptible; R = resistant; C = contaminated; ND = not done							
	INH	Rifampicin	Ethambutol	Streptomycin	Pyrazinamide	Ofloxacin	Kanamycin	
µg/ml								
Result								

Date: ____/____/20____ Signature: _____

MDR-TB Treatment Card (page 1 of 4)

Name: _____
 District TB registration number: _____ County/district: _____
 Date of district TB registration: _____ Treatment unit: _____
 Address: _____

Date of MDR registration: _____
 MDR-TB Registration Number: _____
 Disease site: pulmonary / extrapulmonary
 If extrapulmonary, specify site: _____

Telephone: _____ Age: _____ Sex: M / F
 Name, address and phone number of treatment supporter: _____

At MDR treatment start: Confirmed or Suspected: C / S

Used 2nd-line drugs previously more than one month? Yes / No
 If yes, specify: _____

Previous TB treatment episodes

Start date (year if unknown)	Regimen	Outcome

Category of patient	Tick off one
I. New	
II. Previous FLD treatment	
Relapse	
After default	
After failure	
Late converter	
Transfer in	
"Chronic" case	
Other**	
Specify: _____	
II. Previous MDR-TB treatment***	

HIV test	HIV information	
	Date	Result* (P,N,I,R,A)
ART start		
CPT start		

Follow-up tests during treatment – To be adapted according to regimen

	M0	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M21	M33
Date														
Audiogramme														
Weight														
Creatinine														
Potassium														
TSH														
SGPT														
SGOT														
Blood glucose														
Pregnancy (P/N/A)														
Chest X-ray (Yes/No)														

*HIV result: P = positive; N = negative; I = indeterminate; ND = not done. ** Other = all other not treated with 2nd-line drugs before. *** These patients should be subdivided according to results of the previous MDR-treatment (MDR-R, MDR-D, MDR-F, MDR-T, MDR-O).

MDR-TB Treatment Card (page 4 of 4)

Comments:

Treatment outcome	Tick off	Date
Cured		
Completed		
Failed		
Died		
Lost to follow up		
Transfer out*		
*Add which BMU transferred to:		

Review panel meetings – dates and decisions

Date	Decision	Next Date

Quarterly Report of Coverage of DST in Risk Groups for MDR-TB

Name of Area: _____ Patients registered in quarter _____ of (year) _____	Area tuberculosis coordinator: _____ Signature: _____ Date: _____
---	--

MDR-TB suspect group*	Total MDR suspects reported during the quarter**	Total MDR suspects with DST performed	Rifampicin sensitive	Resistant to rifampicin			Confirmed MDR-TB cases										
				Isoniazid sensitivity		Total MDR	Fluoro-quinolone		2nd-line injectable drug			Confirmed XDR-TB					
				R	S		NA	R	S	R	S						
After failure																	
After default																	
Relapse																	
Other***																	

* The three retreatment groups should each be further subdivided according to the previous treatment: first treatment or retreatment.
 ** This information comes mainly from the Quarterly reports, except for the "chronics", the New, and the Late converters for which other sources of information must be found.
 *** "Other" should be specified, including "chronics", (patients who have failed retreatment in the past and who are not included in the other groups above), new cases (usually MDR contacts) and "late converters" (smear positive at 3-4 months).
 R = resistant; S = sensitive; NA = not available.

Quarterly Report on MDR-TB Case Finding and Treatment Start

Name of Area: _____ Patients registered in quarter _____ of (year) _____	Area tuberculosis coordinator: _____ Signature: _____ Date: _____
--	---

Block I: Number of patients registered with MDR-TB/XDR-TB in the MDR-TB register during the quarter (by date of MDR-TB registration)

Category of patient		Rifampicin resistant (INH unknown or sensitive)	Confirmed MDR	Confirmed XDR
I. New (first time TB)				
II. Previously treated with FLDs	After failure*			
	After default*			
	Relapse*			
	Other**			
III. New registration of patients previously registered as treated with SLD***				
IV. Confirmed MDR-TB patients alive but not on treatment (and not included above)				

*The three retreatment groups should each be further subdivided according to the previous treatment: first treatment or retreatment.

**"Other" should be specified, including "chronics" (patients who have failed retreatment in the past and who are not included in the other groups above) and "late converters" (smear positive at 3–4 months).

***May be subdivided by result of the previous MDR-treatment (MDR-R, MDR-D, MDR-F, MDR-T, MDR-O).

Block II: Number of MDR-TB patients who started MDR-TB treatment during the quarter (by date of MDR-TB treatment start)

	New case	Previously treated with 1st-line drugs	Previously treated with 2nd-line drugs	Total
Confirmed cases				
Suspected cases				
Total				

If relevant, add Block III with the same table for confirmed XDR-TB patients starting XDR-TB treatment.

About The Union

Founded in 1920, the International Union Against Tuberculosis and Lung Disease (The Union) is dedicated to bringing innovation, solutions and support to address health challenges in low- and middle-income populations. With nearly 15,000 members and subscribers from 150 countries, The Union has its headquarters in Paris and offices serving the Africa, Asia Pacific, Europe, Latin America, Middle East, North America and South-East Asia regions. Its scientific departments focus on tuberculosis, HIV, lung health and non-communicable diseases, tobacco control and operational research. Each department engages in research, provides technical assistance and offers training and other capacity-building activities leading to health solutions for the poor.

For more information, please visit www.theunion.org

