



**SAAARC Regional Training Manual for
Programmatic Management of Drug Resistant
(DR) Tuberculosis
2017**

SAARC Tuberculosis & HIV/AIDS Centre (STAC)

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PREFACE

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

It has been acknowledged that good treatment is a pre-requisite to the prevention of emergence of resistance. National TB Control Programmes (NTCPs) in Member States recognize that implementation of a good quality DOTS programme is the first priority for TB control in the country. Prevention of emergence of MDR-TB in the community is more imperative rather than its treatment. Provision of DR-TB management is a supplementary service under the expanded framework of the DOTS package. Therefore, in every DOTS implementing unit of the country, DOTS would be prioritized above DR-TB programme with a view that effective DOTS programme reduces the emergence of MDR-TB.

Considering the growing concern over MDR-TB, specific measures now need to be taken within the National Tuberculosis Control Programmes (NTCPs) to address the MDR-TB problem through appropriate management of patients and strategies to prevent the propagation and dissemination of MDR-TB. This SAARC Regional Training Manual for Programmatic Management of Drug Resistant Tuberculosis has been developed based on the latest WHO recommended guidelines and has included all the evidence based text from the latest documents, e.g. WHO Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis, 2014; WHO Guidelines for the programmatic management of drug-resistant tuberculosis 2011 update; WHO TB Report 2014 etc. I hope this manual facilitates Programmatic Management of Drug Resistant Tuberculosis activities under the NTCPs, so that patients with DR/MDR-TB are both correctly identified and properly managed.

Human resource development is essential to implement, sustain and scale up TB Control activities. For the development of human resources training is vital. Training is one of the fundamental components of National Tuberculosis Control Programmes & becomes more important when DOTS is being implemented. For the development of human resources in the region STAC has been organizing different trainings since 1994 and trained ample number of professionals and health workers working for prevention and control of tuberculosis in the Member States. At this stage when DOTS is being implemented in full swing in each Member State with full population coverage, attention is to be given towards programmatic management of MDR-TB cases.

I hope the training this manual will be beneficial for SAARC Member States for strengthening human resource working for prevention and control of DR/MDR-TB.



Dr. R. P. Bichha
Director, STAC

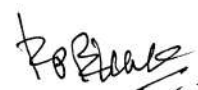
ACKNOWLEDGEMENTS

It is my pleasure to introduce “**SAARC Regional Training Manual on Programmatic Management of Drug Resistant TB (PMDT)**” in a revised form as a tool to facilitate SAARC Regional Training of Trainers on Management of Drug Resistant TB in SAARC region.

This manual is prepared based on the Guidelines developed by Second Workshop to Develop Regional Guidelines for Treatment of MDR-TB & Third Meeting of Lab Directors from Reference Laboratories in SAARC Region held in Bhutan in 2007. The technical support and information were also browsed from “Guidelines for the programmatic management of drug-resistance tuberculosis EMERGENCY UPDATE 2008, MDR & XDR-TB, global report on surveillance and response 2014” Management of MDR-TB: A field guide-a companion document to Guidelines for the programmatic management of drug-resistant tuberculosis 2011, developed by WHO, and National DOTS-PLUS Guidelines developed by member countries of SAARC, WHO Guidelines for the programmatic management of drug-resistant tuberculosis 2011 update and WHO Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis,2014. The contributions of these organizations & all individuals are sincerely acknowledged.

I would also like to appreciate the support provided by National TB Programme Managers from SAARC Member Countries and the efforts rendered by the experts of STAC to produce this manual.

Lastly, I will be grateful for your valuable suggestions, feedback and comments that might be helpful to improve this present manual in future.



Dr. R P Bichha
Director, STAC

ABBREVIATIONS

AFB	Acid Fast bacilli
AIDS	Acquired Immune Deficiency Syndrome
ATT	Anti-TB Treatment
CAT	Category
C/S	Culture Sensitivity
DOTS	Directly Observed Treatment Short Course
DOT	Directly Observed Treatment
DRS	Drug Resistance Surveillance
DR	Drug Resistance
DST	Drug Susceptibility Testing
EP	Extra -Pulmonary
GFATM	Global Fund to fight AIDS, TB & Malaria
GLC	Green Light Committee
HIV	Human Immuno Deficiency Virus
IUATLD	International Union Against TB and Lung Diseases
IRL	Intermediate (often regional) Laboratory
MDR	Multi- Drug Resistance
MTB	Mycobacterium Tuberculosis
NRL	National reference Laboratory
NTRL	National TB Reference Laboratory
NTP	National TB Programme
PAS	Para Aminio Sali Salic Acid
PPM	Public Private Mix
QA	Quality Assurance
RNTCP	Revised National TB Control Programme
STAC	SAARC TB and HIV/AIDS Centre
SAARC	South Asian Association for Regional Cooperation
S S	Sputum Smear
TB	Tuberculosis
WHO	World Health Organization
XDR	Extensively Drug Resistance

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Course Description

This course has been designed to be conducted over five days. It is composed of lectures, in class readings, exercises, case discussions, field visits, which together are intended to provide diverse and compelling learning experiences for participants. Each session generally includes power point presentations, followed by discussion.

COURSE OBJECTIVES:

-) To update global/regional MDR/XDR TB and principles of MDR TB control Programme
-) To discuss evidence based management of MDR/XDR TB
-) To update recent advances in rapid diagnosis of Drug Resistance Tuberculosis
-) Introduce programmatic Management of MDR- XDR TB in resource limited settings
-) Describe current global and regional epidemiology of TB, DR and XDR-TB
-) Describe the *M. tuberculosis* and new developments in laboratory aspects.
-) Foresee the strengths and weakness of diagnostic approach to DR-TB

Methodology

Following will be the basic methodology;

- Plenary sessions & reading of manual
- Power Point presentations
- Discussions & exercises
- Sharing of experiences and best practices

The training will be facilitated with the help of regional and local resource persons and other technical people trained on "*Programmatic and Clinical Management of MDR- & XDR-TB Patients*".

Participants:

The participants are General Physician and In-charge of the MDR, XDR TB treatment Centres working in SAARC Member States and additional participants from National TB Control Programme from host country.

Expected Outcome:

-) Participants will be acquainted with the problems of MDR- XDR TB and its consequences in the region
-) Participants will be trained for "Management of MDR- XDR TB Patients" and its implementation and evaluation.
-) Participants will attain the role of Trainer for Training of health staff

SESSION –I

Information on Multiple-Drug Resistance Tuberculosis (MDR-TB)

This session describes the General information on MDR-TB in the region, the causes and preventive measures through the effective implementation of National TB Control Programmes.

The participants will learn:

- **Background information on MDR-TB**
- **Causes of Drug Resistant Tuberculosis**
- **Magnitude of the MDR-TB problem**
- **MDR-TB problem in SAARC Region**
- **Frame work for Effective Control of Drug Resistant TB**

SESSION -I

GENERAL INFORMATION ON MDR-TB

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

As with other infectious diseases, from staphylococcal infection to malaria, pathogens have almost invariably developed resistance to the drugs. Tuberculosis is no exception: strains resistant to streptomycin, first anti-tuberculosis drug were identified within months of the start of use, in the mid 1940s, of this. Indeed, the emergence of drug resistance was the primary reason that therapy for TB evolved to include treatment with more than one drug for up to 18 to 24 months – the standard of care for over two decades. The advent of rifampicin in the early 1970s permitted a drastic reduction in the duration of therapy to six months while the efficacy of treatment improved. But those familiar with drug resistance in general would have predicted the emergence of resistance to what are now termed as “first-line” drugs, and by the mid-1990s, most countries participating in a global survey of anti-TB drug resistance, registered cases of MDR-TB. The worse was yet to come: in 2006, extensively drug-resistant TB (XDR-TB) emerged. This rapidly changing terrain required health officials and providers to respond with novel and effective responses.

MDR-TB is defined as TB caused by *Mycobacterium tuberculosis* resistant in vitro to the effects of isoniazid and rifampicin, with or without resistance to any other drugs. Resistance is defined by specific laboratory criteria. XDR-TB is defined as resistance to Rifampicin and Isoniazid as well as to any one of the fluoroquinolones and to at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin).

This training manual offers updated information of TB control programmes to medical workers in countries faced with MDR-TB and other drug-resistant forms of TB. Taking account of important developments and recent evidence, this manual aims to disseminate consistent, up-to-date recommendations for the diagnosis and management of MDR-TB in a variety of geographical, political, economic and social settings. In addition, this manual provides standards for registering, monitoring and reporting the treatment outcomes of patients with DR-TB. This uniform information management system will allow systematic, consistent data collection and analysis, which will play an important role in shaping future policies and recommendations. The manual can be adapted to suit diverse local circumstances as they are structured around a flexible framework, combining a consistent core of principles and requirements with various alternatives that can be tailored to the specific local country situation.

BACKGROUND INFORMATION ON DRUG-RESISTANCE TB

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

In 2006, MDR-TB strains with additional resistance to second-line drugs were described as extensively drug-resistant TB (XDR-TB) strains, further compromising treatment options available to patients infected with these strains. Since then, clinicians in some settings have reported patients infected with strains in which virtually all treatment options have been exhausted. In 2009, the 62nd World Health Assembly urged WHO Member States to provide universal access to care for drug-resistant TB patients. In that resolution, it was acknowledged that national TB programme managers, clinicians, nurses, all care providers and affected people themselves need guidance on how best to bring together different elements of health systems and services needed to effectively address the MDR-TB challenge.

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

Definitions of drug resistance

DR-TB is **confirmed** through laboratory tests that show that the infecting isolates of *Mycobacterium tuberculosis* grow in vitro in the presence of one or more anti-tuberculosis drugs.

For the purposes of monitoring, drug-resistant cases are classified in categories based on DST in

clinical isolates confirmed to be *M. tuberculosis* (note, the categories are NOT mutually exclusive):

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

Global Magnitude of MDR-TB:

) Globally, 3.5% of new and 20.5% of previously treated TB cases was estimated to have MDR-TB in 2013. This translates into an estimated 480 000 people having developed MDR-TB in 2013. On average, an estimated 9.0% of patients with MDR-TB had extensively drug resistant TB (XDR-TB).

) If all notified TB patients (6.1 million, new and previously treated) had been tested for drug resistance in 2013, an estimated 300 000 cases of MDR-TB would have been detected, more than half of these in three countries alone: India, China and the Russian Federation. In 2013, 136 000 of the estimated 300 000 MDR-TB patients who could have been detected were diagnosed and notified. This was equivalent to almost one in two (45%), and up from one in six in 2009.

-) Progress in the detection of drug-resistant TB has been facilitated by the use of new rapid diagnostics. A total of 97 000 patients were started on MDR-TB treatment in 2013, a three-fold increase compared with 2009. However, 39 000 patients (plus an unknown number detected in previous years) were on waiting lists, and the gap between diagnosis and treatment widened between 2012 and 2013 in several countries.
-) The most recent treatment outcome data are for patients started on MDR-TB treatment in 2011. Globally the success rate was 48%. Five of the 27 high MDR-TB burden countries achieved a treatment success rate of 70%: Ethiopia, Kazakhstan, Myanmar, Pakistan and Viet Nam. Health system weaknesses, lack of effective regimens and other treatment challenges are responsible for unacceptably low cure rates, and the MDR-TB response is seriously hampered by insufficient funding. These barriers must be urgently addressed.
-) Five priority actions – from prevention to cure – are needed to address the MDR-TB epidemic. These are: 1) high-quality treatment of drug-susceptible TB to prevent MDR-TB; 2) expansion of rapid testing and detection of MDR-TB cases; 3) immediate access to quality care; 4) infection control; and 5) increased political commitment, including adequate funding for current interventions as well as research to develop new diagnostics, drugs and treatment regimens.

SAARC Regional Magnitude of MDR-TB:

The MDR TB cases in the region ranges from less than one to four percent among new TB cases and it ranges from less than one to almost 30 percent among the retreatment TB cases. In 2013 Pakistan had 4.3% of new tuberculosis cases with MDR-TB, which is the highest in the SAARC region. However, in India there were 20,000 new MDR-TB cases among notified pulmonary TB cases. In case of retreatment Bangladesh has 29% of new tuberculosis cases with MDR-TB, which is the highest in the SAARC region. However, in India there were 41,000 MDR-TB cases among retreatment TB cases.

	New		Retreatment	
	% of TB cases with MDR-TB	MDR-TB cases among notified TB cases	% of TB cases with MDR-TB	MDR-TB cases among notified TB cases
Afghanistan	3.7	820	20	460
Bangladesh	1.4	2100	29	2600
Bhutan	2.3	4	16	31
India	2.2	20000	15	41000
Maldives	2.2	2	16	0
Nepal	2.2	520	15	590
Pakistan	4.3	9900	19	3100
Sri lanka	0.2	13	0.58	2
Regional		33359		47783

Recent developments and the Stop TB Strategy:

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

1. Pursuing high-quality DOTS expansion:
 - a. Political commitment with increased and sustained financing
 - b. Case detection through quality-assured bacteriology
 - c. Standardized treatment with supervision and patient support
 - d. Effective drug supply and management system
 - e. Monitoring and evaluation system and impact measurement
2. Addressing TB/HIV, MDR-TB and other challenges by implementing collaborative TB/HIV activities, preventing and controlling MDR-TB, and addressing prisoners, refugees and other high-risk groups and situations.
3. Contributing to health system strengthening by collaborating with other health-care programmes and general services, e.g. by mobilizing the necessary human and financial resources for implementation and impact evaluation, and by sharing and applying achievements of TB control.
4. Involving all care providers, including public, non-governmental and private providers, by scaling up public-private mix (PPM) approaches to ensure adherence to international standards of TB care, with a focus on providers for the poorest and the most vulnerable groups.
5. Engaging people with TB and communities by scaling up community TB care and creating demand through context-specific advocacy, communication and social mobilization.
6. Enabling and promoting research to improve programme performance and to develop new drugs, diagnostics and vaccines.

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

WHO has come out with the End TB Strategy for Tuberculosis prevention, care and control post 2015. The targets for tuberculosis prevention, care and control after 2015 are given below:

VISION -A world free of tuberculosis – zero deaths, disease and suffering due to tuberculosis

GOAL End the global tuberculosis epidemic

INDICATORS	MILESTONES		TARGETS	
	2020	2025	SDG 2030*	END TB 2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100000)	50% (<55/100000)	80% (<20/100000)	90% (<10/100000)
TB-affected families facing catastrophic costs due to TB (%)	Zero	Zero	Zero	Zero

*SDG- Sustainable Development Goals

Prevention of MDR-TB

It is well known that resistance levels are higher in areas with a poorly performing DOTS programme. Use of inadequate regimens and inappropriate Directly Observed Treatment (DOT) leads to increase in resistance levels in the community. It has been acknowledged that good and quality treatment is a pre-requisite to the prevention of emergence of resistance. National Tuberculosis Control Programme recognizes that implementation of a good quality DOTS programme is the first priority for TB control and to prevent the emergence of MDR-TB in the country. Prevention of emergence of MDR-TB in the community is more imperative rather than its treatment. Management of MDR-TB patients will be supplementary service under the expanded framework of the DOTS package. Therefore, in every DOTS implementing unit of the country, DOTS would be prioritized above DR-TB programme with the view that DOTS reduces the emergence of MDR-TB, and therefore, over time the need for DR-TB programme

Historical Perspective:

In 1997, WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) reported for the first time standardized information on drug resistance from surveys or surveillance systems conducted since 1994 in some 35 countries. This information confirmed what many had feared: drug resistance was widespread and MDR-TB was at a critically high level in some parts of the world, especially in some countries of the former Soviet Union. Stimulated by this new evidence, many realized that the time had come to address MDR-TB in a more proactive way than previously. WHO, in particular, decided to explore what could be done together with some key partners, such as the Harvard Medical School, the Centers for Disease Control and Prevention (CDC) and Médecins Sans Frontières (MSF). At two historic meetings – in Cambridge, Massachusetts, in April 1998, during which the term “DOTS-Plus” was coined, and in Geneva, Switzerland, in January 1999 – experts agreed on the need to face MDR-TB programmatically, i.e. no longer solely through individual practitioner’s efforts but through wider DOTS-Plus pilot projects implemented by, or in collaboration with, National TB control programmes. For this purpose, a formal WHO working group, named “DOTS-Plus for MDR-TB”, was established in March 1999 to assist countries and support efforts to assess the feasibility of DR-TB programme and to produce sound policy recommendations. This working group was later adopted by the Stop TB Partnership in 2001 as its very first “implementation” working group. While formulating draft guidelines for the management of MDR-TB, the new working group soon encountered an insurmountable obstacle: the price of most second-line anti-tuberculosis drugs recommended for use in the treatment of MDR-TB was unaffordable to countries in need. New frontiers in drug procurement would need to be explored and negotiations with producers embarked upon in order to make these drugs affordable to the poorest countries. The era of a renewed, human rights-based approach to medicine and public health had just begun, and the advent of the principle of access to care for all favorably influenced those discussions. It was decided that a coalition of partners strongly motivated to make MDR-TB treatment affordable would be more effective than any individual group in the negotiations with the pharmaceutical industry. The Green Light Committee (GLC) was thus born in June 2000: hosted by WHO as a partnership among five categories of participants (governments of resource-limited countries, academic institutions, civil society organizations, bilateral donors and WHO), it successfully negotiated prices of drugs with producers; solicited creation of, and adopted, sound policies for proper management of drug-resistant TB; established strict criteria to review proposals for DOTS-Plus projects; assisted countries in developing such proposals and ensured their proper implementation; and finally, provided access to quality-

assured second-line drugs at concessionary prices to those projects considered technically and scientifically sound and not at risk of producing additional drug resistance. In brief, the GLC rapidly became a model of good practice which, by providing access to previously unaffordable drugs, ensured that their use was as safe and rational as possible to prevent the emergence of “super”-resistant strains of *Mycobacterium tuberculosis*. In 2002, the GLC was adopted by the newly established Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) as its mechanism for screening proposals for DOTS- Plus financing. This was another historic milestone, and the GFATM is today the leading financial mechanism supporting the management of MDR-TB in resource-constrained settings. The Scientific Panel of the WHO Working Group on DOTS-Plus for MDR- TB produced its first set of guidelines – Guidelines for establishing DOTS-Plus pilot projects for the management of multidrug-resistant tuberculosis – in 2000, following discussions that began at a meeting in Madrid in September 1999. That document was based on the little evidence available at the time, gathered mostly from small-scale projects carried out in previous years and without established standards. Much more evidence has become available in subsequent years. First, the cost-effectiveness of DOTS-Plus has been shown in different settings, including Peru. Second, reasonably high cure rates have been achieved in country-wide programmes to treat MDR-TB, for instance in Latvia. Third, growing favorable evidence of feasibility and cost-effectiveness has accrued from a number of DOTS-Plus projects in several settings around the world. By September 2005, 35 GLC-approved projects had been implemented in some 29 countries around the world, providing treatment to more than 10 000 cases of MDR-TB in resource-limited settings. This new evidence mandated a revision of the previous guidelines in order to make available an updated set of recommendations. The new guidelines address this need and provide guidance on current best practice in the management of drug-resistant TB, especially MDR-TB, that should be adopted worldwide. The challenge is huge. Most of these patients would have no access to proper care and treatment without the existence of the GLC, the DOTS-Plus Working Group and funds made available through the powerful financial mechanisms existing today, such as the GFATM, the World Bank and some bilateral donors. The new guidelines were also needed in the context of the new Stop TB Strategy, launched in 2005 by WHO and the Stop TB Partnership. This strategy built on, to enhance the DOTS, explicitly identify the management of MDR-TB as a priority. The strategy recognizes the need to provide care to all patients affected by TB, whether the disease is caused by drug- susceptible or drug-resistant bacilli, and the need to avoid jeopardizing TB control efforts where drug-resistant TB is highly prevalent. Therefore, the management of MDR-TB now needs to be integrated into comprehensive national TB control plans in order to comply with the new Stop TB Strategy. Advocacy, built on a solid rationale and the proper demonstration of feasibility under different programmatic circumstances, is crucial to ensure that the integrated programmes will be fully adopted by all national TB control programmes. In conclusion, the new guidelines represent the best current knowledge in the management of drug-resistant TB and MDR-TB and offer ample options for tailoring diagnosis and care to different epidemiological and programmatic conditions worldwide. The recommendations, compiled by leading experts, should be followed without hesitation by all national TB control programmes and their partners as the most solid programmatic standards. At the same time, it is imperative to stress that the five elements of the DOTS strategy remain the cornerstone of TB control and the most effective tool for preventing the onset and dissemination of drug resistance. Without the essential elements of TB control fully in place, management of MDR-TB will undoubtedly fail in the long term. The new guidelines focus on care for MDR-TB patients, in the hope and expectation that, in future, the occurrence of massive numbers of cases can be prevented through sound TB control practices through Programmatic Management of drug Resistant Tuberculosis.

Introduction of XDR-TB:

In October 2006, the WHO Stop TB and HIV departments organized a meeting of the Global Task Force on XDR-TB at WHO headquarters in Geneva, Switzerland, in response to the XDR-TB emergency. During this meeting, eight recommendations were put forward to the international TB community, outlining key areas of response, beginning with strengthening of basic TB and HIV/AIDS control and proper management of MDR-TB.

The eight recommendations are:

- Strengthening basic activities to control TB and HIV/AIDS, as detailed in the Stop TB Strategy and the Global Plan, to avoid additional emergence of MDR-TB and XDR-TB;
- Scaling-up the programmatic management of MDR-TB and XDR-TB to reach the targets set forth in the Global Plan;
- Strengthening laboratory services for adequate and timely diagnosis of MDR-TB and XDR-TB;
- Expanding surveillance of MDR-TB and XDR-TB to better understand the magnitude and trends of drug resistance and the links with HIV
- Fostering sound infection-control measures to avoid MDR-TB and XDR-TB - transmission to protect patients, health workers, others working in congregate settings and the broader community, especially in high HIV prevalence settings;
- Strengthening advocacy, communication and social mobilization for sustained political commitment and a patient-centered approach to treatment
- Pursuing resource mobilization at global, regional and country levels to ensure that necessary resources are available
- Promoting research and development into new diagnostics, drugs, vaccines, and operational research on MDR-TB management to shorten the length of treatment

Causes of drug-resistant tuberculosis

Drug-resistant TB has microbial, clinical, and programmatic causes. From a microbiological perspective, the resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. An inadequate or poorly administered treatment regimen allows drug-resistant mutants to become the dominant strain in a patient infected with TB. Table 1.1 summarizes the common causes of inadequate treatment. However, it should be stressed that MDR-TB is a man-made phenomenon—inadequate treatment, low quality drugs and poor adherence lead to the development of MDR-TB.

Table 1.1 Causes of inadequate anti-tuberculosis treatment

HEALTH-CARE PROVIDERS: INADEQUATE TREATMENT	DRUGS: INADEQUATE SUPPLY/QUALITY	PATIENTS: INADEQUATE DRUG INTAKE
Inappropriate guidelines	Poor quality medicines	Poor adherence (or poor DOT)
Noncompliance with Guidelines Absence of guidelines Poor Training Financial Disincentives	Unavailability of certain drugs (stock-outs or delivery disruptions) Poor storage conditions	
No monitoring of Treatment	Wrong dose or combination	Lack of information Lack of Money(no treatment available free of charge) Lack of means to adhere to treatment (transportation, food, etc.)
Poorly organized or funded TB control Programmes Poor patient education Poor management of adverse drug reactions Poor treatment support	Poor regulation of medicines	Adverse effects Social barriers Malabsorption Substance abuse/dependency Disorder Adverse effects Social barriers HIV Diabetes mellitus Under nutrition Psychiatric condition

Genetic mutations that confer resistance to anti-TB drugs are naturally occurring but very rare. Pulmonary cavities contain about 10^7 – 10^9 bacilli; thus, they are likely to contain a small number of bacilli resistant to each of the anti-TB drugs but unlikely to contain bacilli resistant to two drugs simultaneously.

Drug	Mutations per one bacterium/generation
Isoniazid	2.56×10^{-8}
Rifampicin	2.25×10^{-10}
Ethambutol	1.0×10^{-7}
Pyrazinamide	2.95×10^{-8}

According to the table above, the probability that a bacillus would spontaneously mutate to be resistant to both isoniazid and rifampicin would be $2.56 \times 10^{-8} \times 2.25 \times 10^{-10} = 5.76 \times 10^{-18}$. Treatment with both isoniazid and rifampicin together is likely to kill all TB bacilli, including drug-resistant mutants. This is why combination therapy is so important for TB. The same is not true of monotherapy, however. In the first culture, there are naturally occurring organisms that are resistant to isoniazid, rifampicin, and streptomycin. With streptomycin treatment (which was the first TB treatment regimen), most of the susceptible

organisms will be killed, including those that are resistant to isoniazid or rifampicin but susceptible to streptomycin. It is only the streptomycin-resistant organisms that will multiply and eventually dominate.

The best way to prevent drug resistance is to treat TB with combinations of drugs. Conversely, the fastest way to create drug resistance is to treat with inadequate treatment regimens. Since drug susceptibility testing (DST) is not widely available in many settings, most patients who are infected with a drug-resistant strain will be treated with a standardized regimen of first-line anti-TB drugs such as 2SHREZ/1HREZ/5HRE. These patients often develop additional drug resistance, a phenomenon called “amplification of resistance.”

MDR-TB patients who are treated with standardized regimens of first-line anti-TB drugs often display the “fall and rise” phenomenon. After the start of treatment, the bacillary content of the sputum decreased markedly until it was close to the borderline of demonstrability by direct microscopy 10^4 and 10^5 . (To find about 10 acid-fast bacilli in about 100 oil-immersion fields, the number of bacilli per milli-litre of sputum must be around 50000, i.e. between 10^4 and 10^5 .) Thereafter, if the bacillary content dropped further: the sputum become negative by smear microscopy and positive only by culture – the “fall”. After a certain time, the bacillary content increases again, the sputum again becomes positive by direct smear – the “rise”. What occur, in fact, is the “fall” of the susceptible bacilli and the “rise” of the resistant mutants of the strain.

More common causes for MDR-TB in SAARC region are considered to be lack of good compliance from patients, inadequate counseling from health care providers and inadequate monitoring of the treatment care.

Addressing the sources of MDR-TB

- The framework approach described in this manual, including the integration of DOTS and DOTS-Plus, can help identify and curtail possible sources of drug-resistant TB. The factors that may be contributing to the development of new cases of MDR-TB should be reviewed. Well administered first-line treatment for susceptible cases is the best method to prevent the development of resistance in such cases. Timely identification of MDR-TB cases and adequately administered Category IV regimens are essential to stop primary transmission. DOTS/ DR-TB programme integration works synergistically to shut down all the potential sources of TB transmission

Frame work for Effective Control of MDR-TB

The framework for the management of Multi-drug resistant TB

The framework is organized around the same five components of the DOTS strategy, as the underlying principles are the same. The core components are comprehensive, ensuring that all essential elements are included, and are:

1. Sustained political commitment

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

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

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

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

For faster diagnosis of the resistant bacilli, Genexpert is the new molecular technology which detects bacilli and presence or absence of resistance to Rifampicin within two hours of setting up the test (described below).

GeneXpert Test | TB Diagnosis & Resistance Testing

The GeneXpert MTB/RIF test is a new molecular test for TB which diagnoses TB by detecting the presence of TB bacteria, as well as testing for resistance to the drug Rifampicin.

New TB tests such as the GeneXpert MTB/RIF test

New TB tests are needed because of the difficulties associated with the tests that are currently used both to diagnose TB as well as to detect drug resistance.

Traditionally TB has been diagnosed by looking for evidence of TB either through the use of the chest X-ray, through sputum smear microscopy, or through the culturing of bacteria. Each of these TB tests has their disadvantages, one of the most significant issue for culture is the time it takes and for sputum is the issue of accuracy.

How does the GeneXpert MTB/RIF test work?

The test is a molecular test which detects the DNA in TB bacteria. It uses a sputum sample and can give a result in less than 2 hours. It can also detect the genetic mutations associated with resistance to the drug Rifampicin.

Advantages

The main advantages of the test are, for diagnosis, reliability when compared to sputum microscopy and the speed of getting the result when compared with culture. For diagnosis of TB, although sputum microscopy is both quick and cheap, it is often unreliable. It is particularly unreliable when people are HIV positive. Although culture gives a definitive diagnosis, to get the result it usually takes weeks rather than the hours of the Xpert test. <http://www.tbfacts.org/xpert-tb-test.html>

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

An appropriate treatment strategy consists of a rational method for designing the optimal treatment regimen, a patient-centered approach for delivering this regimen with direct observation, and a plan for monitoring and managing adverse drug reactions. Designing an optimal regimen requires professional expertise to consider several factors together, including:

- Representative data on drug resistance surveillance (DRS) of well-defined local groups of TB patients, distinguishing new cases and different types of re-treatment cases;
- History of drug use in the country and in the individual;
- Specific array of available second-line drugs;
- Availability of DrugSusceptibilityTest (DST) to first- and selected second-line drugs;
- Reliable options for delivering directly observed therapy (DOT) for up to two years;
- Addressing patients co-infected with HIV;
- Proper infection control policies implemented.
- Treatment of pediatric drug resistant cases

A standardized regimen for certain groups of patients may be more appropriate than an individualized regimen in some countries, while in others the converse may be best. The choice between hospitalization and ambulatory treatment depends on several factors in addition to the severity of the disease. Such factors include the availability of hospital beds with adequate infection control measures to prevent nosocomial transmission; the availability of trained personnel at hospitals and clinics to administer treatment and manage adverse drug reactions; the availability of a social support network to facilitate adherence to ambulatory treatment; and the presence of other clinical or social conditions in patients.

4. Uninterrupted supply of quality-assured anti-tuberculosis drugs

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

WHO, a WHO prequalification programme or that meets WHO Good Manufacturing Practice (GMP) standards. The Global Fund Quality Assurance Policy on Pharmaceuticals needs to be followed by the countries receiving Global Fund grants.

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

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

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

1. Magnitude and distribution of drug-resistant TB
2. Prevailing drug-resistance patterns
3. Options for case-finding
4. Existing infrastructure of the health-care system
5. Available laboratory capacity
6. Resources available for DOT over a prolonged period
7. Availability of financial resources
8. Quality standards of the laboratory network
9. Availability of human resources
10. Training needs
11. Existing legal framework for drug management of second-line drugs
12. Needs for external technical assistance (e.g. WHO, etc.)

Diagnostic Category IV includes patients with:

- **Confirmed MDR-TB.**

- **Suspected MDR-TB.** This requires that the relevant health authority (such as a review panel) recommends that the patient should receive Category IV treatment. Patients may be entered in the Category IV register and started on Category IV treatment before MDR-TB is confirmed only if representative DST surveys or other epidemiologic data indicate a very high probability of MDR-TB.

- **Poly-resistant TB.** Some cases of poly-resistant TB will require Category IV treatments. These patients require prolonged treatment (18 months or more) with first-line drugs combined with two or more second-line drugs and should be entered into the Category IV register. (Most programmes choose to keep cases of mono- and poly-resistance that do not require second-line drugs or require only one second-line drug, in the District TB Register).

SESSION –II

Structures and Responsibilities

This session describes the Structures and Responsibilities of different levels for Prgrammatic Management of Drug Resistant TB .

The participants will learn:

-) Provincial level, Tertiary Center and local level structures and responsibilities
-) Provision to be made under NTP

Session-II

STRUCTURE AND RESPONSIBILITIES

2.1 Chapter Objectives

This chapter describes the structure and responsibilities for PMDT at the provincial level/regional Institute/ Hospital and District level for management of Drug Resistant TB.

2.2 Provincial/ Regional level structure and responsibilities

While a national expert technical working group would have developed national level policies, technical and operational guidelines, the provincial level is where the majority of activities, implementation and monitoring occur. **Provincial PMDT Committees** may be responsible for developing plan of action for implementation, expansion, maintenance, supervision, monitoring and quality enhancement of PMDT services in the respective province.

2.3 DR-TB Institute/Hospital:

Treatment is decentralized, but the complicated clinical care requires a clinical expert resource centre. This may be called DR-TB Institute or any name given by the national programme. These DR-TB Institutes may be utilized to initiate treatment, follow-up case management, and manage complications. The national level needs to define the level/population for establishment of one DR-TB Institute and these sites are to be scaled up nationwide in a phased manner. The requirements to be fulfilled by an institute to be selected and the provisions under National programme to upgrade them to function as a designated DR-TB Institutes are enlisted below:

2.4 District level responsibilities :

- ❖ Perform sputum and other body fluid smear microscopy for diagnosis of tuberculosis
- ❖ Correctly record all patient details and results in the laboratory register
- ❖ Promptly send results of microscopy examinations to the corresponding DR Treatment Centre from where the specimens arrived
- ❖ Complete all recording reporting form necessary for evaluation of case finding activities of the Microscopy Centre
- ❖ Keep 100% of positive smears and 10% of negative smears for quality control
- ❖ Implement NTP smear microscopy Quality Control including lot quality control
- ❖ Arrange and dispatch specimens for culture and Drug Susceptibility Test (DST)

Requirements from Institute and Provisions which may be made from National Programme

A. Requirements from the Institute:

1. It should be preferably a Tertiary Care Hospital
2. Separate Ward for Male & Female should be available
3. All the PMDT services (beds, investigations and ancillary drugs for management of adverse drug reactions) to be provided to the patients
4. Relevant specialties like Pulmonologist, Physician, Psychiatrist, Dermatologist & Gynecologist etc. should be available or linkages for these services are established
5. DR-TB Centre Committee to be formed
6. National Training of DR-TB Centre committee (including Chairperson)

7. National Air Borne Infection Control Guidelines to be implemented in MDR TB ward.
8. Routine clinical laboratory investigation facilities to be made available for pre-treatment evaluation and monitoring
9. Ancillary drugs to be provided as per DR-TB Centre Committee`s advise
10. Management of adverse drug reactions (ADRs) as per PMDT Guidelines
11. Doctors and Nursing staff should be available from the institute
12. Records and Reports to be maintained for PMDT

B. Provisions to be made under National Programme:

1. Human Resources
2. Second Line Anti TB Drugs

The national programme needs to provide guidelines about the level where the DR-TB Institute needs to be established; the site may be established in a Medical College Hospital under the auspices of Department of Pulmonary Medicine or Department of Medicine (if the former department does not exist). The requirements from the institute listed above must be provided by the Medical College / Institutes including free laboratory investigations and ancillary drug supply as part of their commitment. The institute may be supported from the national level for provision of Air Borne Infection Control measures.

Private Hospitals and NGO Hospitals may also be considered to serve as DR-TB Institute at places where a government medical college is not available.

DR-TB Centre Committee may be established with an expert group of clinicians from the institute and local programme managers at every DR-TB Centre.

2.4 Coordination

As National Programme embarks on PMDT activities for the management of MDR-TB, coordination of activities at all level is critical. Co-ordination needs to include the contribution of all the key stakeholders, organizations and external partners, as considered below:

-) **National Programme, Ministry of Health,** The National Programme is the central coordinating body for all the activities. Commitment of the necessary resources, particularly towards a strong central management team, ensures that all aspects are in place from the procurement of second line anti-TB drugs to the appropriate implementation and monitoring of the PMDT service. As needed, partnerships with all relevant health care providers can be built. The national programme is supported by a National PMDT Committee, which may comprise of members from the national programme, the national level institutes medical colleges, other international partners with technical expertise and WHO. The terms of reference of National PMDT Committee should be well defined.
-) **Local Health System.** PMDT activities will be tailored to fit into the respective state/province and district levels infrastructure. The exact organizational structure of the PMDT services may vary between the different settings depending on how the local health care is provided. Transfer between hospitals to outpatient settings or between DOT centres requires great care, advance planning, good communication. Given the type of care required in the treatment of MDR-TB, a team of health workers including physicians, nurses, and social workers (wherever available) should be used.

) **Community Level.** Community involvement and communication with the community leaders can greatly facilitate implementation of PMDT, and may respond to needs that cannot be met by the medical services alone. Community education, involvement, and organization around TB issues can encourage a feeling of community ownership of TB programmes and reduce stigma. In some circumstances, communities can also help address the patient's interim needs including the provision of DOT, food and/or housing, vocational support etc.

2.5 Overview of model of care

Integration of PMDT services will require multiple care levels to work in coordination. No longer can the field level unit be totally self-sufficient as in basic DOTS. The care at the field level is supported by the laboratory and the DR-TB centre, coordinated by the district, and supported by State.

SESSION –III

National Planning and Universal Access

This session describes the aspects of Planning for effective implementation of Programmatic Management of Drug Resistant Tuberculosis.

The Participants will learn:

-) PMDT Vision
-) National Strategy for prevention and control of MDRTB

Session-III

NATIONAL PLANNING FOR UNIVERSAL ACCESS TO QUALITY DIAGNOSIS AND TREATMENT OF MDR TB.

3.1 Chapter Objectives

This chapter provides a brief overview of the PMDT Vision; the strategy for prevention and control of MDR TB; strategy to strengthen laboratory capacity and treatment services; the development of National PMDT scale up plan.

3.2 PMDT Vision

The National PMDT Vision needs to include prompt diagnosis and effective treatment of all TB patients with drug-resistant TB, through decentralized DST and PMDT treatment services integrated into National Programme. A phased approach needs to be developed, focusing first on those most likely to have drug-resistant TB. Realizing this vision will require more laboratory capacity, more second-line drugs, infrastructure and manpower.

Specific objectives may be formulated as:

-) By year (year to be inserted for planning purpose), complete nationwide geographical coverage of access to basic MDR TB diagnostic and treatment services;
-) By year (year to be inserted for planning purpose), expanded access to MDR-TB diagnosis and treatment for
 - all smear positive re-treatment TB cases and
 - new cases who have failed an initial first-line drug treatment
-) By year (year to be inserted for planning purpose), nationwide access to MDR-TB diagnosis and treatment for all smear positive TB (re-treatment or new) cases registered under National Programme before or early during their treatment*

The National Programme expects to treat so many nos. of MDR-TB and so many nos. of XDR-TB cases over the next 5 years. These numbers may be decided based on the estimated load of the patient, human and financial resources available for programmatic management of drug resistant TB.

3.3 National Strategy for Prevention and Control of MDR TB

The national response to MDR TB revolves around a strategy to prevent drug resistant TB and strategy to stop transmission of MDR TB. These are enumerated below:

Prevention of MDR TB

- Sustained high-quality DOTS implementation
- Promote rational use of anti-TB drugs
- Implement infection control measures

Stopping transmission of MDR TB

- Improve laboratory capacity for Rapid diagnosis of MDR-TB Initiation and rapid scale up of MDR-TB services
- Effective treatment of MDR-TB patients
- Evaluate the extent of second-line anti-TB drug resistance and management strategies

3.4 Improving laboratory capacity for rapid diagnosis of M/XDR TB

The national programme needs to develop a National Laboratory Scale up Plan, integrating contributions from national resources and donor resources, with the following set of activities:

-) Enhanced sputum processing capacity (staff, centrifuges, Bio-Safety Cabinets)
-) Nationwide availability of rapid diagnostic and DST facilities to meet MDR TB diagnosis and treatment requirements
-) Nationwide availability of sufficient culture capacity (solid + liquid) to meet part of follow-up culture requirements, given treatment scale-up plan
-) Engage with laboratories from other sectors like NGOs, Private Labs and Medical Colleges to meet demands beyond public sector service availability
-) Strengthened human resource capacity at select laboratories
 - o Microbiologist, Lab technician and Data Entry Operator at every province-level culture and DST laboratory

The national programme needs to review the capacity to examine nos. of MDR TB Suspects for diagnosis and prepare the annual plan accordingly. In addition, the national programme needs to develop and scale-up the availability of second-line anti-TB drug DST, necessary for diagnosis of XDR TB among those identified as MDR TB.

3.5 Initiation and rapid-scale-up of effective treatment services for MDR TB:

The scaling up of PMDT services is also based on a graded expansion of MDR TB suspects criteria (indication for testing) to enable the districts / provinces start slow, overcome the teething challenges in system adaptation for effective service delivery without compromising the quality of basic DOTS services and gradually scale up to move towards universal access. The national plans to gradually scale up treatment services to reach a stage whereby the country can develop the capacity to diagnose and treat the estimated incident drug resistant TB cases.

To that end, quality assured second line drugs are to be procured in adequate quantities by the programme and distributed to provinces. DR-TB Centres are to be scaled up across the country to meet the national requirement. Programme treatment infrastructures are provided additional human resource capacity for management and supervision including:

- o Pharmacist and Store Assistant at Provincial Drug Store
- o Sr. Medical Officer and SA at DR-TB Centres
- o Additional HR – Counselor at all DR-TB Centres to promote treatment adherence

Moreover, the following interventions may also be undertaken to enable system strengthening to effectively scale up treatment services of MDR TB:

-) Advocate rational use of anti-TB drugs (FQ in respiratory cases) with all professional associations and practitioners,
-) Procurement of rapid automated Cartridge-based Nucleic Acid Amplification Testing (CB-NAAT) for decentralized DST in districts, starting with difficult/inaccessible locations without sufficient laboratory capacity,
-) Procurement of second line anti-TB drugs for management of MDR TB cases scaled up gradually including drugs for management of Extensively Drug Resistant TB (XDR TB).

SESSION –IV

Laboratory Aspects

This session describes the General information on Laboratory Aspects for Programmatic Management of Drug Resistant TB.

The participants will learn:

-) Laboratory Requirements for Management of drug Resistant TB
-) Organization and Development of Laboratory Network
-) Functions and responsibilities of Different Levels
-) Limitations of Drug Sensitivity Testing
-) Newer Diagnostics and their role in Management of drug Resistant TB

LABORATORY ASPECTS

OBJECTIVES

This session describes laboratory services needed to diagnose all forms of drug-resistant TB.

General considerations

Optimal management of drug-resistant TB requires both mycobacterial and clinical laboratory services. Clinical laboratory services including basic haematology, biochemistry, serology and urine analysis which are required for the proper evaluation and monitoring of patients.

A comprehensive, routine system of internal quality control and external quality assurance is mandatory.

At a minimum, the Province level Intermediate Reference Laboratory or any other National Programme-certified Culture & DST laboratory should provide:

-) diagnostic culture on solid and/or liquid media,
-) confirmation of resistance to rifampicin by either molecular tests (CBNAAT-GeneXpert or Line probe assay) or other National Programme-approved technology;
-) confirmation of the species as *M. tuberculosis* or non- tuberculosis mycobacteria (NTM); and
-) testing for susceptibility to at least isoniazid and rifampicin by solid or liquid culture.

Central reference laboratories should establish formal links with a supranational TB reference laboratory to help ensure the quality of laboratory services and validation of DST results. This should be done before the start of the DR-TB control programme.

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

General definitions for the laboratory and DST

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

- **Phenotypic DST (conventional DST).**
Phenotypic testing determines if an isolate is resistant to an anti-TB drug by evaluating growth (or metabolic activity) in the presence of the drug
- **Genotypic DST (molecular DST).**
Genotypic testing detects mutations in the TB genome associated with specific drug resistance. (Note: genotypic testing is also used to identify *M. tuberculosis* by detecting the presence of TB-specific mycobacterial DNA).
- **Direct testing.**
Direct testing refers to testing directly from a clinical sample (most commonly a sputum specimen). In direct DST, processed clinical samples are directly inoculated onto media with and without drugs, or processed for molecular testing.
- **Indirect testing.**
Indirect testing refers to testing performed on cultured isolates of *M. tuberculosis*.

- **Critical drug concentration.**
This is the lowest concentration of a drug that inhibits growth of 95% of *M. tuberculosis* strains isolated from patients who have never been treated with/ exposed to that drug (i.e., presumably susceptible isolates), while at the same time not inhibiting growth of strains isolated from patients nonresponsive to therapy with that drug (i.e., presumably resistant to that drug). For some drugs, such as ethambutol, there is no optimal drug concentration that meets this definition. For such drugs, the concentration that shows the greatest difference between presumably susceptible and presumably resistant isolates is used in phenotypic DST. Typically, isolates of *M. tuberculosis* are tested against only the critical concentration of a drug.
- **Reproducibility.**
The ability of a test to be accurately reproduced or replicated, under independent conditions. Intra-operator reproducibility relates to the agreement of test results when a sample is tested multiple times independently by the same operator. Inter- operator reproducibility relates to the agreement of test results across different operators or laboratories.
- **Reliability and validity.**
The reliability and validity of a test depends on both the accuracy and reproducibility of the test. Accuracy is defined by comparing the test results with a gold standard and is usually expressed in terms of sensitivity and specificity, or in terms of positive and negative predictive values.
- **Validity.**
The validity of a test refers to whether a test is measuring what it is supposed to be measuring.
- **Cross resistance.**
Mutations that confer resistance to one anti-TB drug may also confer resistance to some or all of the members of the same drug family, and less commonly, to members of different drug families.
- **Minimum inhibitory drug concentration.**
The lowest concentration of drug that will inhibit growth of the *M. tuberculosis* isolate in vitro.

Organization and development of the laboratory network

The laboratory network has a structure based on a large number of Level I laboratories accessible to all TB suspects and patients, a moderate number of Level II laboratories located in mid-sized population centres and health facilities and a few (or even a single) Level III laboratories at the provincial or state or national level.

Each MDR-TB control programme must have a rapid, reliable means of collecting and transporting of specimens, cultures and information from the patient and physician to each level of the laboratory service and for returning the results.

There should be no financial barrier between the patient and the TB diagnostic services at any of these three levels. A country or region can control and prevent drug-resistant TB only if infectious patients are detected and cured without delay.

Ready access to microscopy for Acid-Fast Bacilli (AFB), culture and DST free of charge to the patient are essential elements of political commitment to control drug-resistant TB. DST

of at least isoniazid and rifampicin is needed in any programme for control of drug-resistant TB, DST of streptomycin and ethambutol is also desirable, although less essential.

Once DST of first-line drugs operates at a consistently high level of proficiency, laboratories serving populations and patients with significant previous exposure to second-line drugs, may consider extending their services to DST of second-line drugs.

Supranational TB Reference Laboratory (SRL) & its role in TB Control

SRL shall serve as partner of National or Regional reference laboratories of TB diagnostics in the Member States. SRL is the back-up for difficult diagnostic procedures (e.g. second line drug susceptibility testing), provide external quality assessment of the laboratory work and quality assurance for drug resistance surveys following WHO/IUATLD standards. Additionally, SRL provides following services to the partner laboratories:

A. Programmatic

1. Liaise with Global Laboratory Initiative (GLI) technical partners, National TB Reference Laboratories (NRLs) and National TB Programmes (NTPs) to facilitate implementation of WHO policy guidance on TB diagnostics and laboratory norms and standards.
2. Support the integration of quality TB diagnostic services within national laboratory policies and strategic plans incorporating cross cutting laboratory issues including quality management systems, supply management, specimen transport and referral and humanresource development.
3. Advocate for TB laboratory worker protection with use of current WHO TB bio-safety recommendations.
4. Support the implementation of an appropriate data management system.
5. Provide guidance on quality management systems for a process towards achieving laboratory accreditation to international standards.

B. Technical

1. Serve as the focal point for coordination of technical assistance to NRLs (or equivalent) to enable:
 1. Monitoring of the proficiency of drug susceptibility testing of *M. tuberculosis*
 2. Implementation of quality assured AFB microscopy (including external quality assessment) in laboratory networks
 3. Development of capacity and proficiency in performing conventional and new WHO endorsed technologies including:
 - a. Microscopy methods
 - b. Culture and identification methods
 - c. Drug susceptibility testing (phenotypic and molecular methods)
4. Development of laboratory components of drug resistance survey (DRS) protocols, data validation, and quality assurance as required
5. Susceptibility testing against first and/or second-line drugs (for both patient management and surveillance) until NRLs establishes capacity
6. On-site technical training or in-house training of laboratory staff as needed
7. Review of laboratory proposals in Global Fund applications
8. Operational research, as relevant, including the introduction of new laboratory tools

An indicative structure of laboratory infrastructure is given below:

Functions and responsibilities of the different levels of laboratory

Level I: The peripheral (often district) laboratory

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

Level II: The intermediate (often regional) laboratory (IRL)

- All the functions of Level I laboratory
- Fluorescence microscopy (optional)
- Digestion and decontamination of specimens
- Culture and identification of *M. tuberculosis*, DST for the +ve culture
- Training of Microscopists
- Support to and supervision of peripheral-level staff with respect to microscopy
- Preparation and distribution of reagents for microscopy in peripheral laboratories

Level III: The central (often national) reference laboratory (NRL)

- All the functions of Level I and II laboratories
- DST of *M. tuberculosis* isolates
- Identification of myco-bacteria other than *M. tuberculosis*
- Technical control of and repair services for laboratory equipment
- Updating and dissemination of laboratory manuals, including guidelines on diagnostic methods, on care and maintenance of equipment and on quality assurance
- Close collaboration with the central level of the national TB control programme
- Supervision of intermediate laboratories regarding bacteriological methods and their support (particularly training and supervision) to the peripheral laboratories
- Quality assurance of microscopy and culture performed at intermediate laboratories
- Training of intermediate-level laboratory staff
- Organization of anti-tuberculosis drug resistance surveillance
- Operational and applied research relating to the laboratory network, coordinated with the requirements and needs of national TB control programmes

The following are basic requirements for establishment of a Laboratory for Culture and DST:

Space in laboratory needed for:

-) Administration
-) Training and teaching (theoretical and practical)
-) A bench space or a table for incoming specimens (ideally near a window or latch). It should be located at a point far from the laboratory entrance-door, heavy pedestrian area (e.g. OPD) and free of airflow.
-) One well lit area for preparing and staining smears- While smears are being prepared the movement of persons working in that area should be limited to a strict minimum. Smears should not be prepared near open window.
-) One well lit area for microscopy reading.
-) One area for Culture
-) One area for DST
-) One area for recording and reporting
-) Store contaminated materials until they are destroyed or sterilized.
-) Store and supplies
 - o Microscopy (sputum containers, slides, reagents, disinfecting solutions, microscopes and their spare parts).
 - o Disposable and glassware for general laboratory works
 - o Chemicals
 - o Stock and technical parts for technical laboratory equipment
 - o Culture media preparation and distribution
 - Mycobacterium culture, identifications of the *M. tuberculosis* and non tuberculosis mycobacteria (*NTM*).
 - Molecular biological tests for prompt results and researches (depending on the resources available in the country)

Limitations of DST

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

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

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

In addition, laboratory technique, medium pH, incubation temperature and incubation time may also affect DST results. Cross-resistance and a lack of understanding of the molecular

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

Cross-resistance between the later- generation fluoroquinolones (ciprofloxacin and ofloxacin) is almost complete. Limited evidence suggests that the third-generation fluoroquinolones (notably moxifloxacin) do not have complete cross-resistance with the older generations and may have enhanced clinical benefit due to their low MICs, enhanced anti-mycobacterial activity, and improved biochemical structure providing metabolic stability and long half-life, theoretically reducing the selection of resistant mutants. While the clinical benefit of newer-generation fluoroquinolones has been validated in one small retrospective study, more clinical and laboratory research is needed to understand the extent of fluoroquinolone cross-resistance and its clinical relevance.

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

The clinician needs to understand the limitations of DST and interpret the results accordingly. DST provides an indication of the likelihood of a drug being effective. Drugs for which the DST results show susceptibility are more likely to be effective than drugs for which the DST shows resistance.

Choice of drugs used for DST

Each Level III laboratory must decide which drugs to test and how to test them according to the strategy for designing treatment regimens. This would also depend on the country scale up plan not only for expansion of laboratory services but also on the scale up plan for criteria of enrolment of patients and the decision on treatment of XDR-TB Patients. Reliable DST for at least isoniazid and rifampicin is a prerequisite for MDR-TB control programmes. Some programmes may choose to have these tests done at a distant laboratory until a local laboratory is able to conduct these tests.

DST for second-line drugs is not mandatory for programmes and is not recommended unless rigorous External Quality Assessment is in place, including proficiency testing by one of the supranational TB reference laboratories.

Infection control and Biosafety in the laboratory

The relative hazards of infective microorganisms handled in the laboratory are classified by WHO according to their risk of causing human disease, the potential for laboratory spread and whether effective treatment and prevention measures are available. Related bio-safety levels for laboratories have been defined, taking into account the pathogenic agent, the facilities available, and the equipment, practices and procedures required to ensure a safe laboratory working environment. *M. tuberculosis* is classified by WHO as a Risk Group 3 laboratory pathogen. Mycobacteriological culture and DST generate high-concentration aerosols requiring bio-safety level 3 containment precautions. Laboratory standards require the following essential measures to be in place and enforced:

- ➡ Appropriate and specific administrative controls (including good laboratory practice, standard operating procedures and accident management plans);
- ➡ Appropriate engineering controls functioning adequately as designed;

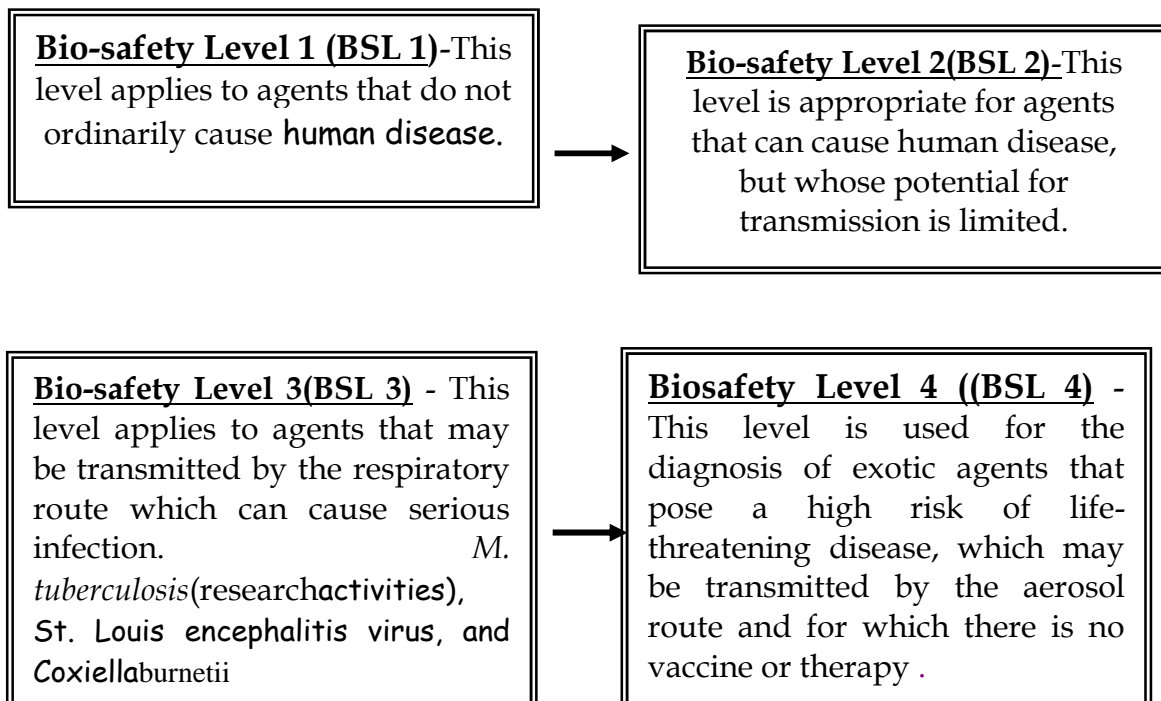
- Personal protective equipment appropriate for the tasks being performed;
- Proper waste management procedures;
- Proper procedures for general laboratory safety (including physical, electrical and chemical safety).

Biosafety level 3 containment requires the strengthening of laboratory operations and safety programmes, specifically those related to laboratory design, the use of specialized equipment to prevent or contain aerosols and health surveillance of laboratory staff. Published guidelines on bio-safety level 3 precautions should be rigorously followed and expert engineering consultation sought when establishing laboratory infrastructure for DST. Health and medical surveillance of laboratory personnel involved in mycobacteriological culture and DST are strongly recommended. Surveillance should include a detailed medical history, targeted baseline health assessment, monitoring of respiratory signs and symptoms, and a proactive plan for appropriate medical investigations when indicated.

Transmission of TB, including drug-resistant forms such as MDR-TB is a recognized risk for laboratory workers.

A well-maintained, properly functioning Class I or Class II biological safety cabinet (preferably class II) is an indispensable piece of laboratory equipment for the performance of culture and DST of specimens from MDR-TB patients. Masks designed to protect the wearer from tiny (1–5µm) airborne infectious droplets should always be used. e.g. N-95 respirators. Bio-safety level is a specific combination of work practices, safety equipment, and facilities which are designed to minimize the exposure of workers and the environment to infectious agents.

There are 4 standard Biosafety levels:



Newer Diagnostics:

Xpert MTB/RIF In 2010, WHO endorsed the Xpert MTB/RIF assay, a cartridge-based fully automated molecular diagnostic assay that uses real time PCR to identify *M. tuberculosis* complex DNA and the mutations associated with rifampicin resistance directly from sputum specimens, in less than two hours. The assay has similar sensitivity, specificity and accuracy as culture on solid media and has been recommended by WHO as the initial diagnostic test among persons at risk of MDR-TB. A policy update was issued at the end of 2013 and the key policy recommendations are given below. Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in adults and children suspected of having MDR-TB or HIV- associated TB.

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

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

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

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

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

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

Identification of *M. tuberculosis*: All mycobacterial isolates from solid or liquid cultures must be identified to allow differentiation of the *M. tuberculosis* complex from NTM. In countries with a high burden of TB, the vast majority of mycobacterial isolates will be *M. tuberculosis*. However, the prevalence of NTM varies among countries and can be more common in patients infected with HIV. There are a number of ways to identify *M. tuberculosis*: the tests can be phenotypic (the most common being the nitrate reduction and

niacin tests), immune-chromatographic, or genotypic (which analyses species-specific DNA sequences). Their full description is beyond the scope of this chapter and can be found in the literature.

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

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

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

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

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

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

Molecular LPA and the X-pert MTB/RIF are currently the only two molecular technologies endorsed by WHO for the genotypic detection of rifampicin resistance. In most settings,

particularly where fixed dose combination (FDC) first-line anti-TB drugs are used, resistance to rifampicin is strongly associated with resistance to isoniazid. Detection of rifampicin resistance therefore serves as a reliable (though not complete) proxy for MDR-TB. The advantages of rapid rifampicin testing include prompt screening of patients at risk of MDR-TB, earlier identification of patients on inappropriate first-line regimens, and allows for early interruption of MDR-TB transmission.

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

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

Laboratory safety requirements for persons who manipulate *Mycobacterium tuberculosis* complex species are enclosed at Annexure IV A.

4.6 Choice of Diagnostic Technology:

When the programme is scaling up the laboratory capacity of various Culture and DST laboratories at state level IRLs and other laboratories, the choice of technology to be used for diagnosis of MDR TB may determined as per recommendations of the National Laboratory Committee. For early diagnosis and prompt treatment of MDR-TB, **wherever available Molecular DST (e.g. Line Probe Assay (LPA)) is preferred diagnostic method** because of the rapid and highly-accurate rifampicin results, followed in preference by Liquid C-DST and then Solid C-DST.

MDR Diagnostic Technology	Choice
Molecular DST (e.g. LPA DST)	First
Liquid culture isolation and LPA DST	Second
Solid culture isolation and LPA DST	Third
Liquid culture isolation and Liquid DST	Fourth
Solid culture isolation and DST	Fifth

Similarly for follow up cultures, wherever available, Liquid Culture may be preferred over solid culture. However, this liquid cultures are required for at least the crucial months of follow-up (IP-3,4,5,6 and CP-18,21,24) and over and beyond this, it will be determined by the workload of individual laboratories.

Laboratories who have become functional should first achieve proficiency in culture recovery by solid or liquid culture. In parallel they can be trained for LPA technology and get proficiency tested for LPA. This will allow for expediting the process of laboratory support for initiating PMDT services, while the laboratory can continue efforts to get certified for DST in solid or liquid culture in the stipulated time required for such certification.

4.7 Specimen Collection

An often-overlooked problem is that of obtaining adequate good quality specimens at the peripheral laboratories. Unless specimens are collected with care and promptly transported to the laboratory under temperature control, diagnosis may be missed, and the patient could miss the chance to be detected and put on the correct treatment. A good sputum specimen may literally make the difference between life and death, and allow containment of the disease and prevent spread to others in the family and community.

The Laboratory technician needs to explain the process of collecting “a good quality sputum specimen” and avoid using vernacular terminologies that convey the meaning as saliva instead of sputum. In addition though the general guideline for collection of sputa is one spot and one morning, this does not preclude from collecting 2 spot specimens that need to be collected with a gap of at least one hour (60 minutes) if the patient is coming from a long distance or there is a likelihood that the patient may default to give a second specimen.

A good sputum specimen consists of recently discharged material from the bronchial tree, with minimum amounts of oral or nasopharyngeal material. Satisfactory quality implies the presence of mucoid or mucopurulent material. Ideally, a sputum specimen should have a volume of 3-5ml. The patient must be advised to collect the specimen in a sterile container (falcon tube) after thorough rinsing of the oral cavity with clean water.

Specimens should be transported to the laboratory as soon as possible after collection. If delay is unavoidable, the specimens should be refrigerated up to 1 week to inhibit the growth of unwanted micro-organisms.

4.8 Specimen transportation to culture-DST laboratories

Fresh sputum samples will need to be transported from the peripheral TB centre to the certified district DST laboratory in a cold chain within 72 hours. Ideally an agency (courier / speed post) with a pan district presence should be identified for this purpose. Two innovative models for specimen collection and transport using fresh samples in falcon tubes to be transported in cold chain using gel packs and their technical specifications have been developed by Gujarat (from peripheral DMCs) and Andhra Pradesh (from high burden DMCs at TUs/DTCs) of India. A sample of Technical Specification of these Transport Boxes for Sputum Samples transportation in Cold Chain are given at Annexure-4A.

All states and districts should establish sample transport system in cold chain irrespective of the time taken for transport considering the climatic conditions of the respective countries.

The following points are critical for the collection of fresh sputum samples at DMCs:

-)] The falcon tubes and the 3 layer packing materials like thermocol box, ice gel pack (pre-freezed at -20 degree for 48 hours), request for C-DST forms, polythene bags, tissue paper roll as absorbent, parafilm tapes, brown tape for packaging box, permanent marker pen, labels, bio-hazard sticker, scissors, spirit swab etc. should be supplied to the tuberculosis centre for collection of sputum.
-)] The falcon tubes should carry a label indicating the date of collection of the samples and the patient's details like name, date of sample collection, name of TB centre, Lab. No:- XYZ, specimen A or B
-)] The Lab technicians at TB centres should be trained to carefully pack the sputum samples in the cold box to avoid spillage of the samples.

- J The LT of TB centre issuing the falcon tubes to the patients should also give clear instructions to the patients on correct technique of collection of the sputum. Also the date of issue of the falcon tubes to the patient should be recorded.
- J The LT of the TB centre should ensure that the request for C-DST form is packed in a separate plastic zip pouch and placed in the cold box before sealing the lid of the box. Also, the bio-hazard symbol should be pasted on the external side of the cold box along with the label indicating the postal address of the certified C-DST Lab assigned.
- J The LT of the TB centre should promptly inform the sample transport agency like a courier / speed post service, speed post or a human carrier to collect and transport the samples

Sputum samples should be labeled with a “BIO-HAZARD” sticker in the containers used for transportation as per the national guidelines for Biomedical waste management of the respective countries. .

For every MDR TB suspect referred by the TB Centre, the date of referral and transport of sputa samples to the Culture & DST laboratory should be entered in the “Remarks” column of the respective Laboratory register and the TB Register in which the patient is registered for NTP DOTS treatment and in the Referral for Culture and DST Register held at the TB Centre. Alternatively the MDR-TB suspect referred to nearby the TB Centre selected for sample collection and transport for C-DST may be provided two falcon tubes by the concerned LT and instructed on collecting two samples (one early morning and one supervised spot). These samples will be taken by the patient / relative to the Centre selected for sample collection for C-DST from where these will be packed in cold boxes and transported to the certified laboratory for culture and DST. Once the sputum has been transported to the certified laboratory, the MDR suspect should return to continue their DOTS treatment.

Laboratory safety requirements for persons who manipulate *Mycobacterium tuberculosis* complex species and Technical Specification of Transport Box for Sputum Samples transportation in Cold Chain are given as Annexure-IV A and IV B respectively.

SESSION –V

Case-Finding Strategies

This session describes the Case finding and Case registration Strategies.

You will learn:

-) Case Registration, case finding strategy
-) Case finding strategy in HIV infected patients
-) Designing of Treatment Regimen for MDR-TB

Session-V

Case-Finding Strategies

This session describes the Programme strategy for case finding and diagnosis of patients with either suspected or confirmed MDR-TB.

Key recommendations (* indicates updated recommendation)

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

The management of drug resistant TB strategy strives to identify patients and initiate adequate treatment for drug-resistant cases in a timely manner. Timely identification and prompt initiation of treatment prevents the patient from spreading the disease to others, acquiring further resistance and progressing to a state of permanent lung damage.

It is strongly recommended that programmes have representative Drug resistance Surveillance (DRS) data for new patients, the different categories of re-treatment patients (failure after Category I, failure after re-treatment, default and relapse) and other high risk groups. Without this information, or when it is only partially available, designing an effective case-finding strategy is difficult and may be impossible. DRS data for the different groups also enable to determine the number of patients who should enter the programme to be calculated, which in turn greatly facilitates programme planning and drug procurement. Routine DST at the start of treatment may be indicated for all TB patients depending on available resources or only in specific groups of patients at increased risk for drug resistance. Programmes should instead examine DRS data from risk groups, together with their technical capacity and resources, to determine which groups of patients should get routine DST and/or inclusion into Category IV regimens.

Target Groups for drug susceptibility testing (DST):

RISK FACTORS FOR DRUG RESISTANT TB	COMMENTS
Failure of re-treatment regimen with first line anti-TB drugs (SHREZ)	Patients who are still sputum smear-positive at the end of a retreatment regimen have perhaps the highest MDR-TB rates in any group, often approaching 90%
Exposure to a known DR-TB case	Most studies have shown close contacts of MDR-TB patients to have very high rates of MDR-TB.
Failure of new TB regimens (HREZ)	Failures of Category I are patients who while on treatment are sputum smear-positive at month 5 or later during the course of treatment. Not all patients in whom a regimen fails have DR-TB, and the percentage may depend on a number of factors, including whether rifampicin was used in the continuation phase and whether DOT was used throughout treatment.

Failure of anti-tuberculosis treatment in the private sector	Anti-tuberculosis regimens from the private sector can vary greatly. A detailed history of drugs used is essential. If both isoniazid and rifampicin were used, the chances of MDR-TB may be high. Sometimes, second-line anti-tuberculosis drugs may have been used, and this is important information for designing the re-treatment regimen.
Patients who remain sputum smear-positive at month 2 or 3 of SCC	Many programmes may choose to do culture and DST on sputum smear-positive who remain sputum smear-positive at months 2 and 3. This group of patients is at risk for DR-TB, but rates can vary considerably.
Relapse and return after default without recent treatment failure	Evidence suggests that most relapse and return after default cases do not have DR-TB. However, certain histories may point more strongly to possible DR-TB; for example, erratic drug use or early relapses.
Exposure in institutions that have DR-TB out- breaks or a high DR-TB prevalence	Patients who frequently stay in homeless shelters, prisoners in many countries and health-care workers in clinics, laboratories and hospitals can have high rates of DR-TB.
Residence in areas with high DR-TB prevalence	DR-TB rates in many areas of the world can be high enough to justify routine DST testing in all new cases.
History of using anti-tuberculosis drugs of poor or unknown quality	The percentage of DR-TB caused by use of poor-quality drugs is unknown but considered significant. It is known that poor-quality drugs are prevalent in all countries. All drugs should comply with acceptable international quality assurance standards.
Treatment in programmes that operate poorly (especially recent and/or frequent drug stock-outs)	These are usually non-DOTS programmes with poor drug management and distribution systems.
Co-morbid conditions associated with malabsorption or rapid transit diarrhoea	Malabsorption may result in selective low serum drug levels and may occur in either HIV-non-infected or infected patients.
HIV in some settings	Data from the Global Project on Anti-TB Drug Resistance Surveillance (2) suggest an association between HIV and MDR-TB in some parts of the world, and numerous drug-resistant TB outbreaks have been documented in HIV- positive patients. Data are still limited and specific factors involved in this association may be country-specific. Even if HIV is not considered to be a risk factor for drug-resistant TB in a country, it is strongly recommended that all individuals with HIV-associated TB have DST to rule out drug-resistant TB and to avoid high rates of mortality due to unrecognized drug-resistant TB in these patients.

❖ **Strategies for programmes with minimal access to DST and limited resources**

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

The three groups who can be considered as high risk category for drugs resistant TB are discussed below.

• **Category II failures (chronic TB cases)**

Patients in whom Category II treatment has failed in good NTPs often have DR-TB. If the quality of DOT is poor or unknown (i.e. if regular ingestion of the medicines during Category II treatment is uncertain), patients may fail Category II treatment for reasons other than DR-TB.

• **Close contacts of DR-TB cases who develop active TB disease.**

Close contacts of DR-TB patients who develop active TB disease can be enrolled for treatment with Category IV regimens.

• **Category I failures.**

Since the prevalence of DR-TB in this group of patients may vary greatly the rate in this group must be documented before deciding whether enrolment in DR-TB control programmes can take place without DST. Programmes should conduct DRS surveys in this group to determine whether the routine use of Category II regimens provides an adequate re-treatment regimen for patients in whom Category I treatment failed.

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

- Any patient before the start of a retreatment regimen (those having failed a regimen, relapsed, or returned after loss to follow-up).
- All close contacts of drug-resistant TB patients who have been diagnosed with active TB.
- Patients not responding to first-line anti-TB treatment (remaining sputum smear-positive at month two or three).
- HIV-positive patients with active TB.
- Any TB patient coming from a group determined by the programme to have a significant risk for drug-resistant TB.

DST specimen collection

If DST is chosen as part of the case-finding strategy, it is recommended that two sputum specimens be obtained for culture and that DST be performed with the specimen that produces the best culture. DST does not routinely need to be carried out in duplicate. Procedures for collecting and managing specimens for culture and DST are described in Chapter II, which also addresses different techniques, limitations, quality assurance requirements and other issues of culture and DST. Previously treated patients may have had DST in the past but it may no longer reflect the resistance pattern of the strain they had at the time of enrolment in the DR-TB control programme.

An often-overlooked problem is that of obtaining good quality specimens at the peripheral laboratories. Unless specimens are collected with care and promptly transported to the laboratory under temperature control, diagnosis may be missed, and the patient could miss the chance to be detected and put on the correct treatment. A good sputum specimen may literally make the difference between life and death, and allow containment of the disease and prevent spread to others in the family and community.

The Laboratory technician needs to explain the process of collecting “a good quality sputum specimen” and avoid using vernacular terminologies that convey the meaning as saliva instead of sputum. In addition though the general guideline for collection of sputa is one spot and one morning, this does not preclude from collecting 2 spot specimens that need to be collected with a gap of at least one hour (60 minutes) if the patient is coming from a long distance or there is a likelihood that the patient may default to give a second specimen.

A good sputum specimen consists of recently discharged material from the bronchial tree, with minimum amounts of oral or nasopharyngeal material. Satisfactory quality implies the presence of mucoid or mucopurulent material. Ideally, a sputum specimen should have a volume of 3-5ml. The patient must be advised to collect the specimen in a sterile container (falcon tube) after thorough rinsing of the oral cavity with clean water.

Specimens should be transported to the laboratory as soon as possible after collection. If delay is unavoidable, the specimens should be refrigerated up to 1 week to inhibit the growth of unwanted micro-organisms.

Case-finding in pediatric patients

Pediatric cases require adjustments in diagnostic criteria and indications for treatment.

Younger children in particular may not be able to produce sputum specimens on demand.

Programmes should not exclude children from treatment solely because sputum specimens are not available; smear- and culture-negative children with active TB who are close contacts of patients with DR-TB can be started on Category IV regimens.

Case-finding in HIV-infected patients

Cases of HIV infection also require adjustment in diagnostic criteria and indications for treatment. The diagnosis of TB in HIV-infected people is more difficult and may be confused with other pulmonary or systemic infections.

People living with HIV are more likely to have smear-negative TB or extra-pulmonary TB. These and other WHO guidelines recommend the use of clinical algorithms that include the use of chest X-ray and culture to improve the ability to diagnose TB in smear-negative patients living with HIV. Because unrecognized MDR- and XDR-TB are associated with such high mortality in these patients, many programmes perform culture and DST testing for all patients living with HIV and with active TB. Programmes without facilities or resources to screen all patients living with HIV for DR-TB should put significant efforts into obtaining

them, especially if DR-TB rates are moderate or high. Some programmes may adopt a strategy of targeted DST for patients with increased risk of DR-TB or low CD4 count

Rapid diagnostic techniques for people living with HIV with active TB can be very useful to promptly identify those with DR-TB. If XDR-TB is prevalent, people living with HIV who have MDR-TB should be screened for XDR-TB with the use of liquid media or another validated rapid technique for DST of second-line injectable agents and a fluoroquinolone.

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

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

Use of rapid drug-resistance testing

Case-finding strategies can be greatly enhanced with rapid drug-resistance testing, which significantly improves the ability to identify earlier cases of DR-TB that can be isolated and started on treatment. Rifampicin is the most potent anti-tuberculosis drug of the first-line regimen, and rifampicin resistance most commonly occurs with concomitant isoniazid resistance. A positive rapid test for rifampicin resistance is a strong indicator that a patient may have MDR-TB, while a negative test makes a final diagnosis of MDR-TB highly unlikely.

Figure 3.1 is a suggested algorithm on the use of rapid drug-sensitivity testing for identification and initial management of patients suspected of TB who are at increased risk of DR-TB. It is based upon the important considerations outlined in this chapter regarding risk factors and case-finding strategies and is applicable to situations of both high and low HIV prevalence. The algorithm relies on determining the risk of drug resistance and involves HIV testing of all TB suspects, sputum smear microscopy and results from rapid sensitivity testing for at least rifampicin. It also includes the indications for the use of empirical treatment regimens for DR-TB while awaiting more complete DST results.

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

Not all DR-TB control programmes have the capacity to perform DST of second-line drugs. These guidelines recommend that all programmes develop the ability to do DST to isoniazid and rifampicin and, when proficient at those, to develop the ability to test the second-line injectable agents (kanamycin, amikacin and capreomycin) and a fluoroquinolone. This will enable programmes to perform case-finding for XDR-TB and to assure proper treatment.

The two strongest risk factors for XDR-TB are:

- (i) Failure of an anti-TB regimen that contains second-line drugs including an injectable agent and a fluoroquinolone.
- (ii) Close contact with an individual with documented XDR-TB or with an individual for whom treatment with a regimen including second-line drugs is failing or has failed.

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

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

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

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

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

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

Interpreting rifampicin resistance results from molecular testing

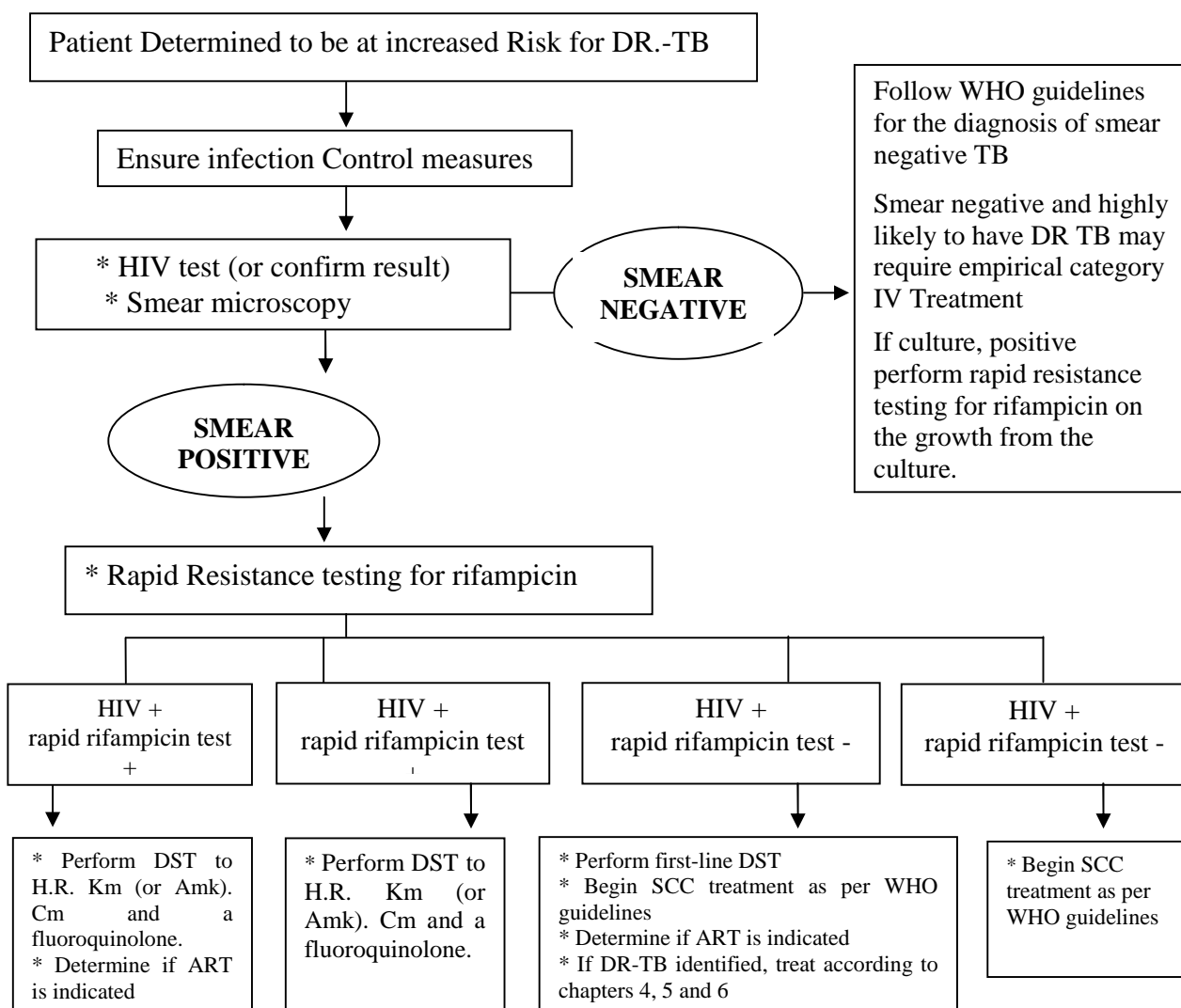
WHO-recommended molecular testing methods (Xpert MTB/RIF and line probe assays) have been found to have a high sensitivity and specificity for detection of rifampicin resistance. Molecular methods do not have perfect concordance with phenotypic culture-based DST and patient details such as treatment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

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

WHO-recommended molecular methods also have very high specificity for detection of rifampicin resistance. Nevertheless, any diagnostic test with a specificity of less than 100% when used in a population with a low prevalence of the condition can result in a lower positive predictive value, which means that a number of false-positive results are present among those diagnosed as having the condition. Increasing evidence, however, is showing that the occurrence of ostensibly false-positive rifampicin resistance detected by Xpert MTB/RIF compared to phenotypic culture-based DST methods may be linked to the detection by molecular methods of strains that are truly resistant to rifampicin, yet are not detected by culture-based DST. Such strains appear to have clinically-relevant mutations in the *rpoB* region conferring resistance to rifampicin, causing disease that is likely to fail first-line treatment. A recent study has shown that an epidemiologically-significant proportion (close to 10%) of rifampicin-resistant strains in first failure and relapsed patients are missed by phenotypic DST.

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


Figure 3.1 Algorithm for the use of rapid drug resistance Testing




- Improving the diagnosis and treatment of smear negative pulmonary and extra pulmonary tuberculosis among adults and adolescents: recommendation for HIV prevalent and resource constrained setting. Geneva. World Health Organization 2007 (WHO/HTM/TB/2007, 37; WHO/HIV/2007.01).
- Where rapid rifampicin testing is not available, the algorithm can be followed using liquid methods.
- Because of the high and quickly possibility of death with XDR-TB in HIV infected individuals., liquid media and other validated rapid techniques for DST of first and second line drugs (*H,R, Km (or Amk), Cm and a fluoroquinolone) are recommended for HIV infected individuals with risk factors for XDR-TB.
- Antiretroviral Therapy for HIV infection in Adults and adolescents 2006 revision WHO Geneva 2004
- Treatment of tuberculosis guidelines for national programmes, 3rd ed. Geneva. World Health organization 2003 (WHO/CDS/TB/2003.313).

SESSION –VI

Treatment Strategies



This session describes the aspects of Designing of treatment strategy for MDR TB, classes of Anti TB Drugs and Role of Drug Susceptibility Testing



TREATMENT STRATEGIES

Key recommendations

Designing of Treatment Strategy for MDR-TB

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

- Definition of terms used to describe treatment strategies:
- The following are definitions of terms often used to describe treatment strategies.
 - Standardized treatment: DRS data from representative patient populations are used to base regimen design in the absence of individual DST. All patients in a defined group or category receive the same regimen. Suspected MDR-TB should be confirmed by DST whenever possible.
 - Individualized treatment: Each regimen is designed based on the patient’s past history of TB treatment and individual DST results.
- TB programmes often use a combination of standardized and individualized approaches. However, in situations where DST is unavailable or limited to only one or two first-line drugs, programmes will most commonly use a purely standardized approach.
- “Empiric” refers to the initiation of treatment prior to determination of a firm diagnosis of drug-resistant TB. Empiric regimens can be used for both standardized and individualized treatment strategies. For example, an empiric XDR regimen refers to the use of a regimen designed to treat XDR-TB before the diagnosis of XDR-TB is made.

Essential assessments before designing a treatment strategy

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

only rarely and will likely be effective in DR-TB regimens, while others may have been used extensively and therefore, have a high probability of ineffectiveness in patients with resistant strains. It is recognized that some programmes may have to design strategies based on limited data, as treatment for many patients cannot wait until the full assessment information has been obtained. In these cases, the programme can still follow the basic principles put forth in this chapter on how to design an effective regimen and continue to collect the information.

Selecting treatment strategies:

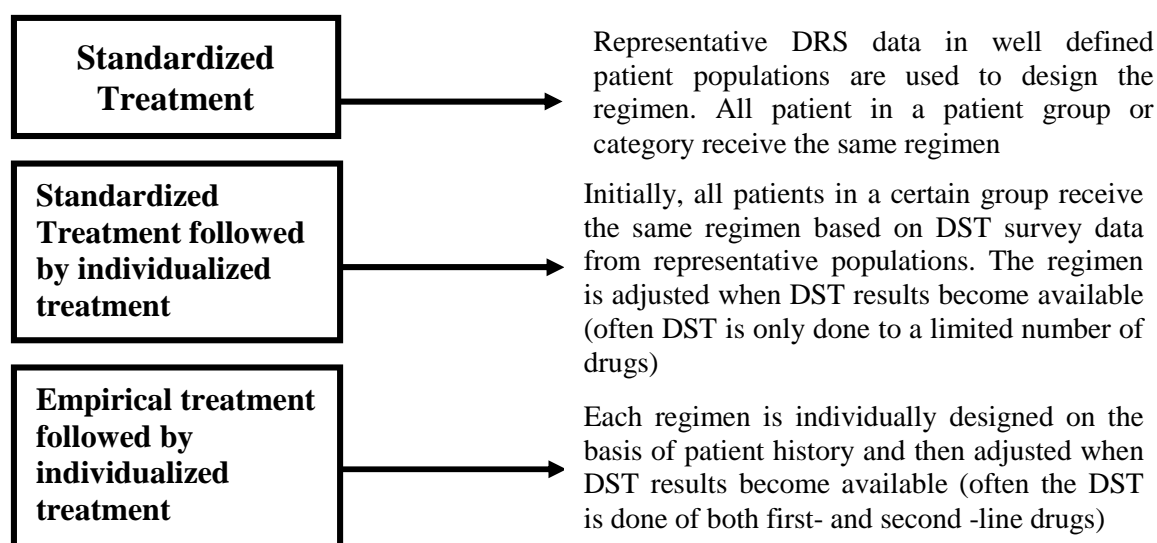
Advantages of individualized and standardized Treatment strategies

Standardized treatment regimen	Individualized treatment regimen
) Simple operational aspect of implementation	Avoids placing patients on toxic and expensive drugs to which the strain may be resistant
) Simple drug ordering	Identifies appropriate and specific regimen for each patient
) Easier training	
) Less likelihood of mismanagement	
) Less dependence on highly technical laboratory	

Treatment strategies involving standardized Category IV regimens offer several advantages. Standardized regimens are based on representative DRS from patient categories or groups. If DST is not available in the country, a Supranational TB reference laboratory can perform it to obtain representative patterns.

Standardized regimens may enable more patients to access care, while maintaining cure rates comparable to those obtained with individualized treatment strategies. Individualized treatment strategies require a high degree of laboratory capacity necessary to perform DST of second-line drugs. One advantage of individualized regimens is that they avoid placing patients on toxic and expensive drugs to which the strain is resistant. Individualized regimens have advantages in settings with high rates of resistance to second-line drugs where it may be difficult to find a standardized regimen that is appropriate for all patients. A strategy using a combination of standardized and individualized treatment will often be used. For example, a programme may choose to do DST of H, R, E and S only and place any patients with documented resistance on different standardized regimens based on the pattern of resistance found. Here, the programme is using individualized DST but then applying a set number of standardized regimens. This is the most frequently used strategy in settings where second-line drugs have not been widely used.

Figure 4.1 Common treatment Strategies for DR -TB



CLASSES OF ANTI-TUBERCULOSIS DRUGS

Group Name	Anti TB Agent	Abbreviation
Group -1 First Line Oral Agents	Isoniazid Rifampicin Ethambutol Pyrazinamide Rifabutin ^a Rifapentine ^a	H R E Z Rfb Rpt
Group-2 Injectable anti-TB drugs (injectable agents or parental agents)	Streptomycin ^b Kanamycin Amikacin Capreomycin	S Km Am Cm
Group 3- Fluoroquinolones ^d	Levofloxacin Moxifloxacin Gatifloxacin ^c	Lfx Mfx Gfx
Group 4- Oral bacteriostatic second-line anti-TB drugs	Ethionamide Prothionamide Cycloserine Terizodone ^e Para-Aminosalicylic acid Para-Aminosalicylate sodium	Eto Pto Cs Trd PAS PAS-Na
Group5- Anti-TB drugs with limited data on efficacy and/or long term safety in the treatment of drug- resistant TB (This group includes new anti-TB agents)	Bedaquiline Delaminid Linezolid Clofazimine Amoxycillin/clavulanate Imipenem/cilastatin ^f Meropenem ^f High-dose isoniazid Thiocetazone ^g Clarithromycin ^g	Bdq Dlm Lzd Cfz Amx/Clv Ipm/Cln Mpm High dose H T Clr

- a Rifabutin and Rifapentine have similar microbiological activity as rifampicin. Rifabutin is not on the WHO list of essential medicines, however it has been added here as it is used routinely in patients on protease inhibitors in many settings. Rifapentine is part of a latent TB infection and active TB treatment in some countries but to date is not part of any WHO endorsed treatment regimens.
- b There are high rates of streptomycin resistance in strains of MDR-TB; therefore, streptomycin is not considered a second-line anti-TB injectable agent.
- c Gatifloxacin can have “life threatening” side effects including serious diabetes (dysglycaemia). The drug has been removed from the formula of a number of countries. Safer alternatives are discussed below in the section of Group 5 drugs.
- d Ofloxacin is considered a weaker agent with less activity against TB than other fluoroquinolones and has been removed as a choice in Group 3 drugs (see section below on Group 3 – Fluoroquinolones for more information).
- e Terizidone has limited programme data and effectiveness data as compared to cycloserine.
- f Clavulanate (Clv) is recommended as an adjunctive agent to imipenem/cilastatin and meropenem.
- g Limited data on the role of thioacetazone and clarithromycin in MDR-TB treatment has resulted in many experts not including these drugs as options for Group 5.

Group 1

Group 1 drugs, the most potent and best tolerated, should be used if there is good laboratory evidence and clinical history to suggest that a drug from this group is effective. If a Group 1 drug was used in a previous regimen that failed, its efficacy should be questioned even if the DST result suggests susceptibility. For patients with strains resistant to low concentrations of isoniazid but susceptible to higher concentrations, the use of high-dose isoniazid may have some benefit (when isoniazid is used in this manner it is considered a Group 5 drug; see below). The newer-generation rifamycins, such as rifabutin, have very high cross-resistance to rifampicin.

Pyrazinamide is routinely added to MDR regimens unless there is a reasonable clinical contraindication for its use (hepatotoxicity or other serious adverse effect). DST to pyrazinamide is not reliable and for this reason it is considered an acceptable practice to use pyrazinamide in a regimen even when a laboratory result demonstrates resistance. Ethambutol is not routinely added to MDR regimens, however, it can be added if the criteria of it being a likely effective drug are met. Due to difficulties in testing, ethambutol is never considered a key drug in an MDR regimen, even if the strain is found susceptible.

Group 2

All patients should receive a second-line Group 2 injectable agent in the intensive phase of MDR-TB treatment unless resistance is documented or highly suspected. Either kanamycin, amikacin or capreomycin can be used as a first choice if all meet the criteria of “likely to be effective”. Given the high rates of streptomycin resistance in patients with MDR-TB (greater than 50% in some countries) and extensive use as a first-line agent in many countries, streptomycin is not often used in MDR regimens, even if DST shows susceptibility to it. Kanamycin and amikacin have lower costs than capreomycin, have less toxicity than streptomycin and have been used extensively for the treatment of drug-resistant TB throughout the world. Amikacin and kanamycin are very similar in structure, and they have a

high frequency of cross-resistance between them. Amikacin has a lower minimum inhibitory concentration and may be the most efficacious of the two, however, clinical comparison is lacking. Capreomycin may have cross-resistance with amikacin/kanamycin if the *rrs* gene mutation is present, but the clinical implications of this are not well understood. Limited evidence suggests that capreomycin has less ototoxicity than aminoglycosides. If an isolate is resistant to both streptomycin and kanamycin, or if DRS data show high rates of resistance to amikacin and kanamycin, then capreomycin is suggested as the injectable of choice. In cases where the strain is resistant to all the second-line injectable drugs (amikacin, kanamycin, and capreomycin), except streptomycin, streptomycin should be considered, as there is little cross-resistance between streptomycin and the other injectable agents.

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

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

Group 3

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

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

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

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

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

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

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

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

Group 4

Group 4: Oral bacteriostatic second-line anti-TB drugs. Both ethionamide and prothionamide are prodrugs that need activation by mycobacterial enzymes. There is no clear advantage of ethionamide over prothionamide; efficacy and side-effects also appear similar. Thus, the term “ethionamide/prothionamide” is used throughout this Handbook to indicate that either one can be used. Of the Group 4 drugs, ethionamide/prothionamide performed the best in the meta-analysis of MDR-TB treatment conducted to update the 2011 guidelines (1,4). However, it should be noted that *inhA* gene mutation in TB bacteria has been associated with cross-resistance with low-level isoniazid resistance and high-level ethionamide resistance (10). If the *inhA* gene mutation is present, ethionamide/prothionamide can still be included in an MDR regimen, but it should not be counted as a “likely effective second-line anti-TB drug”. Cycloserine and/or para-aminosalicylic acid (PAS) should be included in MDR regimens. Both PAS and cycloserine share no cross-resistance to other anti-TB drugs. Since the combination of ethionamide/prothionamide and PAS often causes a high incidence of gastrointestinal side-effects and hypothyroidism, these agents are usually used together only when three Group 4 agents are needed. Whether terizidone (containing two molecules of cycloserine) is equally efficacious as cycloserine was unknown at the time of this writing. The drugs in Group 4 may be started at a low dose and escalated over three to 10 days to reduce frequency or severity of side-effects (known as dose-ramping)

Group 5. Group 5 drugs are not recommended by WHO for routine use in MDR-TB treatment. Although all of them have demonstrated some activity at least in vitro or in animal models, the quality of the evidence of their efficacy and safety in humans for the treatment of drug-resistant TB varies. Most of these drugs are, with the exception of bedaquiline and delamanid, not registered for treatment of MDR-TB making their use as “off-label. In some cases the drugs are quite costly and require intravenous administration (imepenem and meropenem). However, they remain as options in cases where adequate regimens are impossible to design with medications from Groups 1–4. If a situation requires the use of Group 5 drugs, often experts will recommend using two to three drugs from the group given the limited knowledge of efficacy. The following is information that may help choose which Group 5 drugs to use when indicated (for full drug information see Part 3 – Individual Drug Prescribing Information).

- Bedaquiline – See Annex 4 for description of bedaquiline including its indications and safety monitoring requirements.
- Linezolid – Linezolid has shown good activity in vitro and

in animal studies. There are also a number of cases of off-label use in M/XDR-TB; it has recently been demonstrated to improve outcomes in XDR-TB (12,13) Of the Group 5 drugs it is considered one of the most effective against TB and is often a key drug in XDR treatment regimens (also see Section 5.15 and Box 5.4). It has numerous severe side-effects including: myelosuppression (anaemia, leucopenia, thrombocytopenia and pancytopenia), peripheral neuropathy and lactic acidosis. When serious adverse effects arise the drug often needs to be stopped (in some cases the adverse effect can be managed by decreasing the dose (usually from 600 mg daily to 300 mg daily). While 300 mg dosing is associated with fewer side-effects, it is not known if the lower dosing is as effective or if it will lead to a higher chance of resistance amplification, though some clinical experts have found that the lowering of the dosing due to anaemia quite often coincides with culture conversion, which increases the chance to keep the drug in the treatment regimen. • Clofazimine – A significant amount of experience with clofazimine in MDR-TB treatment exists (14–16), and it has been included in 9- to 12-month regimens and reported to have very good outcomes (17). However, the efficacy of clofazimine against TB remains unclear.

Group 6: Off-label use is the practice of prescribing a drug to treat a medical condition for which a stringent drug regulatory body has not approved the indication. It may also include using the drug in an age group not yet approved for or in a dosage or form of administration different from the original approval.

Clofazimine is often added to regimens for XDR-TB. In relation to adverse effects, skin pigmentation occurs in 75% to 100% of patients within a few weeks; reversal can take months to years after the treatment. • Amoxicillin/clavulanate – Generally, beta-lactam antibiotics are not regarded as very useful drugs against TB, but the addition of the beta-lactamase inhibitor makes them active in vitro against TB. There is limited evidence of in vivo bactericidal activity (18). While amoxicillin/clavulanate is probably a relatively weak anti-TB drug, it is often included within regimens because it is available, inexpensive and with few side-effects. • Imipenem/cilastin and meropenem. Imipenem and meropenem belong to the drug class “beta-lactam-carbapenem,” given only intravenously. Due to cost and difficulty in dosing, it is not commonly used in resource-constrained settings. A similar drug – Meropenem – is preferred for use in children and adults with central nervous system disease, as there is less association with seizure. Given that imipenem is rapidly degraded by renal proximal tubule dipeptidases, it is marketed in combination with the dipeptidase inhibitor, cilastatin. Conversely, meropenem is stable to renal dipeptidases and requires no cilastatin (19). Since it is in the beta-lactam class of antibiotics it is likely that these imipenem/cilastin and meropenem can benefit from the addition of clavulanate 125 mg every 8–12 hours. Clavulanate was added to meropenem in one study of XDR-TB patients with reasonably good outcome results (13). (Clavulanate is not readily available alone and some give it as amoxicillin/clavulanate 500 mg/125 mg oral tablet). • High-dose isoniazid. Many experts feel that high-dose isoniazid can be used against strains resistant to low concentrations of isoniazid but susceptible to higher doses (20) (>1% of bacilli resistant to 0.2 mcg/ml but susceptible to 1 mcg/ml of isoniazid), whereas, isoniazid is not recommended for high-dose resistance (>1% of bacilli resistant to 1 mcg/ml of isoniazid). Some experts give 900 mg three times a week (21) in adults while others use as high as 16–20 mg/kg/day (22) Good data are not available on the safety of high-dose isoniazid and there may be possible associated higher rates of peripheral neuropathy, hepatitis and other unforeseen adverse effects. Experts also recommend not using isoniazid if the strain is documented to have a katG gene mutation. The katG mutation is detected by line probe assay tests available today. • Thioacetazone. While thioacetazone is a drug with known efficacy against TB, it is placed in Group 5 because its role in drug-resistant TB treatment is not well established. Overall, a weak bacteriostatic drug, thioacetazone has cross-resistance with ethionamide (23)

and isoniazid (24,25). Thioacetazone is contraindicated in HIV-infected individuals (26) due to a serious risk of adverse reaction that can result in Stevens-Johnson Syndrome and death. The drug is also not well-tolerated in persons of Asian origin. For all these reasons, this drug is rarely added as a Group 5 drug. Until there is more information on its role in MDR-TB therapy, most experts advise drug-resistant TB programmes not to include thioacetazone, especially if HIV status is unknown. • Clarithromycin. Clarithromycin is included in Group 5, but its activity against *M. tuberculosis* is uncertain. Some studies suggest that clarithromycin may have a synergistic effect with oral first-line agents (27,28) but synergy data with second-line drugs is absent. Most experts consider clarithromycin a very weak anti-TB drug and consider it to have no role in MDR-TB treatment.

Standard code for TB treatment regimens

There is a standard code for writing TB treatment regimens. Each anti-TB drug has an abbreviation. A drug-resistant TB regimen consists of two phases: the first phase is the period in which the injectable agent is used, and the second is after it has been stopped. These two phases are generally separated by a backslash (/). The number before each phase stands for phase duration in months, and this number is the minimum amount of time that the stage should last. The number in subscript (e.g. 3) after a letter is the number of drug doses per week. If there is no number in subscript, treatment is daily (injectables are generally given for 5–6 days per week). The drugs in the higher groups are written first followed by others in descending group order.

KNOWN CROSS RESISTANCE BETWEEN ANTITUBERCULOSIS AGENTS

- Cross-resistance and lack of understanding of the molecular mechanisms underlying TB drug resistance further confound the interpretation of DST results. Emerging evidence shows a clear association between phenotypic drug resistance and specific molecular mutations for most drugs; however, not all mutations conferring resistance to second-line drugs have been described, neither have the underlying molecular mechanisms for the detected mutations been elucidated.
- Summary of known cross-resistance between anti-TB drugs
- Rifamycins All rifamycins (rifampicin and rifabutin) have high levels of cross-resistance.
- Isoniazid There is high cross-resistance between isoniazid and ethionamide if the *inhA* mutation is present.
- Aminoglycosides and polypeptides Amikacin and kanamycin have (very) high cross-resistance. Amikacin/kanamycin and capreomycin can have cross-resistance, which is associated with the *rrs* mutation (clinical implications are not clear).
- Streptomycin has low cross-resistance with amikacin/kanamycin and capreomycin.
- Fluoroquinolones Fluoroquinolones are believed to have variable cross-resistance between themselves, with *in vitro* data suggesting that later-generation fluoroquinolones (levofloxacin, gatifloxacin, moxifloxacin) remain effective when lower generation fluoroquinolones (ofloxacin) are demonstrating resistance. It is unknown if the *in vitro* data translates into clinical relevance. When levofloxacin (a third generation fluoroquinolone) is demonstrating resistance, it is not known if fourth generation quinolones (moxifloxacin and gatifloxacin) remain effective, and their use in such cases is not standardized. It is not known if cross-resistance is complete between fourth generation fluoroquinolones (i.e. between moxifloxacin and gatifloxacin), but is generally considered complete in *in vitro* studies. Laboratories should test isolates for resistance to each fluoroquinolone used by their TB programme (i.e. if a TB

programme uses levofloxacin in the standardized regimen the fluoroquinolone DST of choice for the programme is levofloxacin, not ofloxacin as is often being done). Thiamides Prothionamide and ethionamide have 100% cross-resistance.

Role of drug susceptibility testing

Countries vary greatly in their access to reliable mycobacterial laboratories, and many do not have regular access to DST. The inability to do routine DST in all patients should not be a barrier for patients that need Category IV treatment. Fully standardized regimens using second-line anti-tuberculosis drugs have been shown to be feasible and cost-effective in DR-TB treatment. In countries where reliable DST is not available, every effort should be made to improve laboratory capacity, for the following reasons:

- DST surveys are needed to identify groups of patients that are at high risk for DR-TB. General nationwide surveys may not reflect DST patterns of specific groups of patients. For example, the DST patterns of all previously treated patients may be very different from those that failed SCC.
- Even in the setting of a strong DOTS programme, some patients in high-risk groups (e.g. Category II failures) will not have DR-TB. These guidelines strongly recommend confirming treatment failure by culture and testing for DR-TB through the use of DST of at least isoniazid and rifampicin.
- In the era of HIV and rapid spread of highly resistant (e.g. XDR) strains, a detailed history of previous tuberculosis treatment may not adequately predict the resistance pattern of the infecting strain, as many patients with DR-TB may have been infected originally with a resistant strain.

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

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

In summary, regular access to quality-assured DST is recommended for all programmes, even those using a standardized regimen. Delays in treatment while awaiting DST can result in increased morbidity and mortality, as well as longer periods of infectiousness. Too many of the second-line drugs should not be relied upon for individual regimen design.

Designing and administrating an MDR regimen

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

- Early MDR-TB detection and the prompt initiation of an effective treatment are important factors in obtaining successful outcomes.
- The intensive phase of MDR-TB treatment should consist of at least four second-line anti-TB drugs that are likely to be effective (including an injectable anti-TB drug), as well as pyrazinamide (conditional recommendation, very low quality evidence) Where there is unclear evidence about the effectiveness of a certain drug, this drug can still be part of the regimen, however, it should not be depended upon for success.
- MDR regimens should include at least pyrazinamide, a fluoroquinolone, an injectable anti-TB drug, ethionamide (or prothionamide) and either cycloserine or PAS (para- aminosalicylic acid) if cycloserine cannot be used (conditional recommendation, very low quality evidence).
- The drugs in the regimen should be judged to be “likely effective”. An anti-TB drug is considered “likely to be effective” when: – The drug has not been used in a regimen that failed to cure the individual patient; – DST performed on the patient’s strain indicates that it is susceptible to the drug (DST for isoniazid, rifampicin, Groups 2 and 3 drugs is considered reliable; DST for all other drugs is considered not reliable enough for individual patient management); – No known resistance to drugs with high cross-resistance– No known close contacts with resistance to the drug; – Drug resistance surveys demonstrate that resistance is rare to the drug in patients with similar TB history. This final criterion is relevant in the absence of DST or for drugs in which individual DST is not reliable. Note: It is not always possible that information of all five criteria can be ascertained. Therefore, clinical judgment is often necessary on whether to count a drug as “likely effective”.
- There are conditions when more than five drugs are used. These conditions would be applicable when the effectiveness for a drug(s) is unlikely or questionable. One such relatively common condition is the treatment of XDR-TB.
- Drugs that the patient is known to have a strong contraindication of usage due to – drug– drug interactions, overlying toxicities, co-morbidities, history of severe allergy or other adverse reactions, and/or pregnancy – should not be used.
- A fluoroquinolone should be used (strong recommendation, very low quality evidence) (1).
- A later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (conditional recommendation, very low quality evidence) (1).
- In the treatment of patients with MDR-TB, ethionamide (or prothionamide) should be used (strong recommendation, very low quality evidence) (1). This recommendation assumes the recommended drugs meet the criteria of “likely to be effective” and there are no contraindications to its use (such as a severe adverse effects).
- The intensive phase (i.e. the initial part of treatment during which a Group 2 injectable agent is used) lasts at least eight months in total, but the duration can be modified according to the patient’s response to treatment (1). The optimal duration of intensive phase following culture conversion, which is associated with treatment success, could not be inferred directly from the analysis used to revise the WHO programmatic management of drug-resistant TB guidelines in 2011. Some clinical

experts may prefer that the intensive phase is continued for at least four months past culture conversion (see Section 5.9 on length of intensive phase).

- The total length of treatment is expected to be at least 20 months in most patients not previously treated for MDR-TB (1). Some clinical experts may prefer that total treatment be for at least 12 months past the point at which culture converts to negative and, some others may prefer not to give less than 20 months in total (see Section 5.10 on length of treatment).
- Each dose is given under a patient-centred directly observed therapy throughout the treatment. A treatment card is marked for each observed dose (see Part 4 – Forms for drug-resistant TB programmes). DOT can be performed either at facility-based or community-based levels, keeping in mind that social support is an essential component of care and treatment delivery.
- Any adverse effects of drugs should be managed immediately and adequately to relieve suffering, minimize the risk of treatment interruptions, and prevent morbidity and mortality due to serious adverse effects.
- Antiretroviral therapy (ART) is recommended for all patients with HIV and drug-resistant TB, irrespective of CD4 cell-count, as early as possible (within the first eight weeks) following initiation of the anti-TB treatment (strong recommendation) .
- The drug dosage is usually determined by age and weight.
- Pyrazinamide, ethambutol and fluoroquinolones should be given once a day. Depending on patient tolerance, once-a-day dosing is also used for oral second-line anti-TB drugs from Group 4, however, ethionamide/prothionamide, cycloserine and PAS have traditionally been given in split doses during the day to reduce adverse effects.
- All anti-TB drugs can be started at full dose. However, if tolerance is an issue, cycloserine, ethionamide and PAS dosing can be increased gradually over a two-week period.
- Injectable drugs can be given five to seven days a week depending on the availability of a skilled medical person to give the intramuscular injections. Injectable anti-TB drugs should be given once daily, i.e. do not split the dose over the day. If adverse effects are problematic in a patient, the injectable agent may be given three times a week, preferably only after culture conversion.
- When possible oral drugs are to be given seven days a week under directly observation. Some programmes suggest giving all drugs six days a week, but it is not known if this is equal to seven days a week. Oral drugs should not be given five days a week (only the injectable agent is allowed to be on a five days a week schedule, see above).
- Pyrazinamide can be used for the entire treatment. Many drug-resistant TB patients have chronically inflamed lungs, which theoretically produce the acidic environment in which pyrazinamide is more effective. Alternatively, in patients doing well, pyrazinamide can be stopped with the injectable drug if the patient can continue with at least three likely effective drugs.
- In MDR treatment strategies that initially enrol patients based on their strain being resistant to rifampicin alone, isoniazid may be included in the MDR regimen until DST to isoniazid can be done to determine if the isoniazid should be continued.
- Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization (conditional recommendation, very low quality evidence) .

Adjusting an empiric standardized regimen or designing an individualized regimen:

Empiric standardized regimens often need to be adjusted based on patient clinical history, once additional history or when DST results becomes available. Individual regimens are designed based on DST of the infecting strain, patient's history of TB treatment and contact history.

Building an MDR-TB Regimen:

STEP 1 Choose an injectable (Group 2) Kanamycin/ Amikacin/Capreomycin Choose a drug based on DST and treatment history. Streptomycin is generally not used because of high rates of resistance in patients with MDR-TB.

STEP 2 Choose a higher generation fluoroquinolone (Group 3) Levofloxacin Moxifloxacin Use a later generation fluoroquinolone. If levofloxacin (or ofloxacin) resistance is documented, use moxifloxacin. Avoid moxifloxacin if possible when using bedaquiline (see Annex 4).

STEP 3 Add Group 4 drugs Cycloserine/terizidone Para-aminosalicylic acid (PAS) Ethionamide/prothionamide Add two or more Group 4 drugs until there are at least four second-line anti-TB drugs likely to be effective. Ethionamide/prothionamide is considered the most effective Group 4 drug. Consider treatment history, side-effect profile, and cost. DST is not considered reliable for the drugs in this group.

STEP 4 Add Group 1 drugs Pyrazinamide Ethambutol Pyrazinamide is routinely added in most regimens; ethambutol can be added if the criteria for an effective drug are met . If isoniazid is unknown or pending it can be added to the regimen until DST results become available.

STEP5 Add Group 5 drugs Bedaquiline Linezolid Clofazimine Amoxicillin/clavulanate/Imipenem/cilastatin plus clavulanate Meropenem plus clavulanate High-dose isoniazid Clarithromycin Thioacetazone Consider adding Group 5 drugs if four second-line anti-TB drugs are not likely to be effective from Groups 2–4. If drugs are needed from this group, it is recommended to add two or more. DST is not standardized for the drugs in this group.

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

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

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

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

When using an empiric standardized regimen, TB programmes are strongly encouraged to also order drugs from groups and classes that are not routinely included in the standardized regimen. For example, a programme that uses an empiric standardized regimen that does not include PAS will still need PAS in the following situations: (i) patients intolerant to one of

the core drugs; (ii) pregnant patients with drug-resistant TB who cannot take all the drugs in the standard regimen; (iii) as part of a regimen in whom the standardized MDR treatment regimen has failed or in regimens for XDR-TB. All programmes are encouraged to have regimens designed to treat XDR-TB for when the standardized MDR regimen fails.

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

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

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

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

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

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

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

Usually, pyrazinamide is continued for the entire treatment, especially if there is extensive parenchymal lung damage. However, there is no data on the optimal length of time to use pyrazinamide in MDR-TB treatment. If the patient has minimal disease, some clinicians stop pyrazinamide with the injectable agent at the end of the intensive phase. In all situations, the patient should at the very least continue with three of the most potent second-line anti-TB drug that are determined to be effective against the patient's infecting strain of M. tuberculosis.

Total duration of treatment

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

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

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

Extra-pulmonary and central nervous system drug-resistant TB

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

Surgery in treatment of drug-resistant TB

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

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

successful resection, the intensive phase and total treatment duration should be guided by the recommendations in Sections 5.9 and 5.10.

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

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

Adjuvant therapies in drug-resistant TB treatment

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

Corticosteroids

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

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

Adjunctive therapy using immunotherapeutic interventions

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

Nutritional support

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

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

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

Individual drug dosages are given in drug annexure sheets.

Children: Children with drug-resistant TB generally have initial resistance transmitted from a primary case with drug-resistant TB. When DST is available it should be used to guide therapy. The treatment of culture negative children with clinical evidence of active TB disease and a contact with a documented case of drug-resistant TB should be guided by the results of DST and the history of the contact's exposure to anti-TB drugs.

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

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

In general, anti-TB drugs should be dosed according to body weight. Monthly monitoring of body weight is therefore especially important in paediatric cases, with adjustment of doses as children gain weight.

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

Dosing of anti-TB drugs in children is weight-based.

In children, microbiological monitoring of the response to treatment is often difficult (for the same reasons it is difficult to obtain a microbiological diagnosis). This makes it difficult to diagnose treatment failure in children. Persistent abnormalities on chest radiographs do not necessarily signify a lack of improvement. In children, weight loss or, more commonly, failure to gain weight adequately in the presence of proper nutritional intake, is of particular concern and often one of the first (or only) signs of treatment failure. This is another key reason to monitor weight carefully in children.

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

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

Diabetes mellitus:

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

Renal insufficiency: Renal insufficiency caused by longstanding TB infection itself or previous use of aminoglycosides is not uncommon. Great care should be taken in the administration of second-line drugs in patients with renal insufficiency, and the dose and/or the interval between dosing should be adjusted according to Table 6B. The dosing is based on the patient's creatinine clearance, which is an estimate of the glomerular filtration rate or renal function.

Calculate the number of ml to draw up in the syringe based on the mg/ml concentration of the preparation. Mix 1 gram in 5 ml sterile water, which gives a 200 mg/ml solution. Give 1.0 ml of the prepared solution daily (200 mg). • Levofloxacin: Levofloxacin is not recommended for children under 10 kg, however it is among the most important drugs in the treatment of MDR-TB. The risks and benefits should be discussed with the mother and if the mother agrees give $\frac{1}{4}$ of a 250 mg tablet twice a day. (This is based on the dosing of 15–20 mg/kg per day split into two doses for children under five years of age.) • Prothionamide: Give $\frac{1}{2}$ of a 250 mg tablet daily. If tolerance is an issue (nausea and vomiting), give $\frac{1}{4}$ tablet in the morning and $\frac{1}{4}$ tablet in the evening. • Cycloserine: Give $\frac{1}{2}$ of a 250 mg capsule daily (125 mg daily). Dissolve a full capsule in 10 ml of water and give 5 ml once daily. If tolerance is an issue, give 2.5 ml in the morning and 2.5 ml in the evening. • Pyrazinamide: Give $\frac{1}{2}$ of a 500 mg tablet = 250 mg – or – $\frac{3}{4}$ of a 400 mg tablet = 300 mg.

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

EXAMPLES OF STANDARDIZED REGIMEN DESIGN

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

Answer: Given the above circumstances, one strategy is to test all relapse patients with a rapid DST such as Xpert MTB/RIF. If rifampicin resistance is found, it is likely there will also be isoniazid resistance. The use of Xpert MTB/RIF as a diagnostic tool in a population with an MDR-TB prevalence of 15% (and rifampicin resistance prevalence of 15 + 1.5 =

16.5%) will result in a high positive predictive value of rifampicin resistance. Therefore, we can be confident that most Xpert RIF-positive results from this group of relapse patients are true positives. Information from drug resistance surveys is important to determine if isoniazid should be added routinely to a standardized MDR regimen while awaiting DST results to isoniazid. If a line probe assay rapid test for isoniazid can be done then isoniazid can be included for those testing susceptible (high-dose isoniazid can be considered for those testing positive for inhA gene on line probe assay rapid test). If a longer DST test for isoniazid is being done, then isoniazid can be included in the regimen until results are known. An example of an empiric standardized regimen for those with RR-TB or MDR-TB could be:

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

- Other options for drugs in this regimen include Km or Cm as the injectable drug, ethionamide instead of prothionamide, other fluoroquinolones (later-generation ones are much preferred), and PAS can replace cycloserine if the latter cannot be used.
- Isoniazid is given in normal doses until DST results become available; isoniazid can be continued if susceptible, stopped if resistant or adjusted to high-dose isoniazid if low level resistance is present (or InhA gene is present).
- Pyrazinamide can be stopped in the continuation phase for those patients with minimal lung damage and who are doing well. DST to second-line drugs should be done at the start of treatment. If resources for DST to second-line drugs are constrained, it can be done in those patients that do not respond to the standard regimen. For example, those still smear- or culture- positive at month three.

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

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

8 Cm-Lfx-Eto-Cs-PAS-Z/12 Lfx-Eto-Cs-PAS-Z. Other options for drugs in this regimen include prothionamide instead of ethionamide; later-generation fluoroquinolone must be used in this regimen with moxifloxacin being an option. There is little value of routinely adding isoniazid in the empiric regimen, but it can be added if further DST reveals susceptibility. DST for second-line drugs for all MDR-TB cases at the start of treatment is instrumental to the programmatic design of an effective regimen under these circumstances. If the patient

does have resistance to second-line drugs the empiric standard regime will need to be adjusted.

WHO INTERIM GUIDANCE ON USE OF BEDAQUILINE AND DELAMANID

Drug resistance is a major threat to global tuberculosis (TB) care and control. WHO estimates that globally, 5% of TB cases are estimated to have MDR-TB. Among new TB cases (that account for most of the global TB burden), an estimated 3.5% have MDR-TB. The proportion is higher among people previously treated for TB, at 20.5%. Levels of drug resistance among new cases are <3% in 108 (75%) of the 144 countries with drug resistance surveillance data. This includes almost all countries in the Region of the Americas, most countries in the African and South-East Asia regions, most countries in western Europe and several countries in the Western Pacific.

Source: *RESISTANT TB SURVEILLANCE & RESPONSES SUPPLEMENT GLOBAL TUBERCULOSIS REPORT 2014*

Current treatment regimens for drug-resistant TB are complex, lengthy, toxic and expensive. Only about one half of MDR-TB patients started on treatment globally are reported to be treated successfully, largely due to a high frequency of death and loss to follow-up, commonly associated with adverse drug reactions and high costs of treatment. In addition, it is estimated that up to a third of MDR-TB cases may have strains with additional resistance to fluoroquinolones and/or injectable second-line drugs (aminoglycosides or capreomycin), rendering their treatment even more difficult, with recourse only to highly toxic drugs. The landscape of drug development for treatment of TB has evolved over the past ten years and novel drugs are presently or soon entering Phase III trials for the treatment of MDR-TB. Considering the global MDR-TB crisis, the limited therapeutic options available for this life-threatening condition, and the need to promote safe and responsible use of TB drugs, WHO convened an Expert Group in April 2014 to review the available evidence on the efficacy, safety and effectiveness of delamanid, a new drug for the treatment of MDR-TB, with the view to issue interim recommendations on its use in conjunction with WHO-recommended MDR-TB treatment.

It is acknowledged that developing interim guidance on the use of a new TB drug on the basis of Phase IIb trial data is a novel step for WHO. Issuing interim guidance carries with it the responsibility of ensuring that it provides specific recommendations on the conditions for the use of the drug that reflect the limited data currently available. It will also be necessary for WHO to review, revise and/or update the interim guidance as additional substantive data on efficacy and safety become available. Acceleration of Phase III trials and completion at the earliest opportunity is imperative, as is timely analysis of emerging operational data on the use of the drug. It should also be noted that, in the absence of interim guidance from WHO, uncontrolled and potentially irresponsible use of the drug may adversely affect TB care and control efforts overall – potentially prompting the emergence of bedaquiline resistance and the possible loss of the first new TB chemotherapeutic drug in over 40 years.

Evidence assessment

Data on the pre-clinical and clinical development of the drug provided by the manufacturer, as well as publicly available data were reviewed to assess efficacy, safety and tolerability of the drug. In addition, modeling work to assess the potential cost-effectiveness of

programmatic implementation was commissioned to an independent expert. The comprehensive review of these data was conducted according to the GRADE process for evidence assessment, as required by WHO.

WHO Interim policy recommendations

In view of the aforementioned evidence assessment and advice provided by the EG, WHO recommends that bedaquiline and Delamanid may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB (conditional recommendation, very low confidence in estimates of effects). Given the limited data available on bedaquiline and delamanid and its use under the various situations that may be encountered in different clinical settings, adequate provisions for safe and effective use of the drug must be in place. Consequently, countries are advised to follow a phased approach to bedaquiline and delamanid implementation, ideally through observational cohorts, where the following measures are in place.

The WHO recommendation for the inclusion of bedaquiline and delamanid in the adult treatment regimen of MDR-TB is subject to the following five conditions being met:

1. Treatment is administered under closely monitored conditions, adhering to best practices in treatment delivery, to enable optimal drug effectiveness and safety.
2. Proper patient inclusion. The current recommendation for the use of bedaquiline applies to adults (≥ 18yrs) with pulmonary disease.
3. Patient informed consent obtained. Health-care providers should ensure that the patient is: (i) aware of the novel nature of bedaquiline; (ii) appreciates the reason why the drug is being proposed to be included in the regimen; and (iii) recognizes the benefits and potential harms. In addition, health-care workers should obtain the patient's agreement on the inclusion of bedaquiline in the prescribed treatment regimen. This informed consent process must be documented and signed by the patient, and applies to all situations where bedaquiline is employed, including under compassionate use programmes.
4. Adherence to principles of designing a WHO-recommended MDR-TB regimen.
5. Pharmacovigilance and proper management of adverse drug reactions and prevention of drug–drug interactions.

SESSION –VII

Monitoring and outcome definitions

This Session describes the Monitoring and Outcome definitions.

The participants will learn:

-) Resistance and Treatment outcome definitions
-) Treatment Monitoring Strategy
-) Designing of XDR-TB treatment regimen

Monitoring and Outcome definitions

This session explains the parameters and activities necessary for monitoring interventions in tuberculosis (TB) patients infected with drug-resistant TB strains, including patient care, programme supervision, as well as planning and measurement of progress toward universal access. It explains the definitions in use to identify register and assign outcomes to drug-resistant TB patients who require second-line anti-TB medication. Following extensive consultations since 2010, the definitions and minimal reporting requirements included in this session have been updated from the ones in the WHO 2011 Guidelines for the programmatic management of drug-resistant tuberculosis. An attempt has been made to simplify methods, to introduce indicators on coverage of drug susceptibility testing (DST) and to adapt the monitoring parameters to address today's fast-changing landscape in TB care. The advent of novel diagnostic technologies and the release of new anti-TB drugs make this particularly relevant. The outcome definitions have been revised in 2013 and can be applied to both second-line TB regimens recommended by WHO (which are on average about 20 months long) and to regimens that are substantially shorter. The minimum indicators to monitor multidrug-resistant TB (MDR-TB) patients, which were released in 2010, have been adapted in this chapter to accommodate testing centres relying on X-pert MTB/RIF1 for the diagnosis of rifampicin-resistant TB (RR-TB).

Implementing an effective information system.

The organization of information on drug-resistant patients facilitates the:

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

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

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

computation errors can be reduced. When adopting electronic systems it becomes important to employ standard formats for data elements which may need to be linked, such as registration numbers, district names, treatment unit codes, dates, patient names and identifiers.

2. Monitoring the detection, enrolment and treatment outcomes of drug-resistant TB patients. Many programmes need to decide when and how to computerize their systems. In 2012, WHO and its technical partners produced guidance on the electronic recording and reporting of TB in terms of the necessary organization, scope, capabilities, resources and infrastructure. Different patterns of drug resistance carry different implications for treatment and management. For the purposes of monitoring, drug-resistant cases are classified in categories based on DST in clinical isolates confirmed to be M. tuberculosis (note, the categories are NOT mutually exclusive):

Treatment outcome	Definition
Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase ^a
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase ^a
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: <ul style="list-style-type: none"> • Lack of conversion by the end of the intensive phase^a; or • Bacteriological reversion^b in the continuation phase after conversion to negative; or • Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs; or • Adverse drug reactions.
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for two consecutive months or more. Not evaluated A patient for whom no treatment outcome is assigned. (This includes cases “transferred out” to another treatment unit and whose treatment outcome is unknown).
Treatment success	The sum of Cured and Treatment completed.

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

b The terms “conversion” and “reversion” of culture as used here are defined as follows: Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the

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

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

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

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

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

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

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

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

For the purposes of registration on second-line treatment for MDR-TB, patients are considered New if DST was performed within one month of the start of treatment, even if

they had received more than one month of first-line drug treatment for TB by the time that the DST results returned and they were registered for second-line TB treatment.

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

If the patient is transferred-in from a different second-line treatment centre, it is indicated here with the name of the original centre. To simplify recording in the Second-line TB treatment register, Transfer in is included as one of the Registration groups.

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

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

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

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

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

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

Cohort Analysis

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

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

The recommended timeframe for Category IV treatment cohort analysis reflects the long duration of Category IV regimens. Cohort analyses should be carried out at 24 months and, if

needed, repeated at 36 months after the last patient starts treatment. For each treatment cohort, an interim status should be assessed at 6 months after the start of treatment to monitor programme progress

This focuses on monitoring the progress of treatment and identifying failure of treatment that indicates the need for a change in treatment strategy. The response to second-line anti-TB drugs is often slow with the median time to conversion being three months. Performing monthly culture tests is the best strategy in identifying failures earlier. Sputum smear microscopy alone results in delayed detection of failure. The WHO 2011 Guidelines for programme management of drug-resistant tuberculosis made the following recommendation: The use of sputum smear microscopy and culture rather than sputum smear microscopy alone is recommended for the monitoring of patients with multidrug-resistant TB (MDR-TB) during treatment (conditional recommendation/very low quality evidence)

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

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

Monitoring the progress of treatment Patients should be monitored closely for signs of treatment failure. Monitoring response to treatment is done through regular history taking, physical examination, chest radiograph and laboratory monitoring. The classic symptoms of TB – cough, sputum production, fever and weight loss – generally improve within the first few weeks. Cough and sputum production can persist after sputum conversion in patients with extensive lung damage, but even in those with extensive lung damage, improvement is often seen within a month or two of effective treatment. Persistent fever, weight loss or recurrence of any of the classic symptoms of TB should prompt investigation of treatment failure or untreated comorbidities. The recurrence of TB symptoms after sputum conversion may be the first sign of treatment failure. For children, height and weight should be measured monthly to ensure that they are growing normally. Normal growth rate usually resumes after a few months of successful treatment. For adults too weight should be recorded monthly (height is only recorded at the start of treatment).

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

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

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

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

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

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

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

A key component of monitoring the progress of treatment is patient-centred directly observed therapy (DOT). All treatment should be given under direct observation and DOT providers should be trained on the signs of treatment failure. Systemic reviews have shown that DOT for MDR-TB patients is an independent predictor of success; MONITORING EVALUATION RECOMMENDED FREQUENCY

Evaluation by clinician during the intensive phase: Every day during the first weeks if hospitalized and at least every week if treated as outpatient, until the treatment is well tolerated. Once stable the patient is seen twice a month or once a month. During the continuation phase: Monthly assessments unless there is a medical necessity to see the patient more often. The DOT supporter sees the patient daily between consultations and signals any concerns to the clinician. Treatment adherence and tolerance Daily at every DOT encounter by the DOT provider. Sputum smears and culture Monitoring smears and culture monthly throughout treatment. (Note: programmes with limited resources may choose to do monthly smears and cultures until conversion and then monthly smears with every other month cultures.)

Weight- At baseline, then every two weeks for first three months and then monthly. Height- At start of treatment for all (to be able to assess BMI throughout treatment); monthly for children (to assess growth).

Drug susceptibility testing -At baseline for first- and second-line anti-TB drugs. Repeat DST for patients who remain culture-positive or revert after month four.

Chest radiograph- At baseline, and then every six months.

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

- The treatment card should be reviewed to confirm that the patient has fully adhered to treatment. The supervisor of the DOT provider should confirm that the patient has taken all the prescribed medicines. A non-confrontational interview with the patient

should be undertaken with and without the DOT provider being present. Questions should be asked to rule out the possible manipulation of the DOT provider by the patient, or of the DOT provider(s) not fulfilling their duties. If manipulation is suspected, the DOT provider should be removed of DOT responsibilities with the patient, receive additional training and get closer supervision whenever he/she is assigned another DOT provider role. If the DOT provider is not fulfilling his/her duties even then, removal from the job may be required.

- Look for undetected comorbidities. Some undetected comorbidities mimic treatment failure through clinical and chest radiographical deterioration that occurs simultaneously with repeated culture- and smear-negative results. These comorbidities, such as NTMs, fungal infections, lung infections, or a pulmonary malignancy should be diagnosed and treated appropriately. Illnesses that may decrease absorption of medicines (e.g. chronic diarrhoea) or may result in immune suppression (e.g. HIV infection) should also be excluded.
- The bacteriological data should be reviewed. One single positive culture in the presence of an otherwise good clinical response can be caused by a laboratory contaminant or error. In this case, subsequent cultures that are negative help prove that the apparently positive result did not reflect treatment failure. Positive smears with negative cultures may be caused by the presence of dead bacilli and therefore may not indicate treatment failure.
- Review the DST. If there is evidence of acquired resistance to fluoroquinolones or second- line injectable drugs while on the MDR regimen, treatment failure is probable and a new regimen may need to be started.
- Review treatment regimen. The treatment regimen should be reviewed in relation to medical history, contacts and all DST reports. If the regimen does not meet the Patients who have persistent positive smears or cultures late into the continuation phase but who are doing well clinically and radiographically may not require a regimen change. Whenever a regimen change is indicated because of treatment failure, a new regimen is started (with at least four likely effective drugs) and options for adjunctive treatment – most commonly surgery – can be considered. Adding one drug to a failing regimen is always to be avoided.

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

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

Follow-up after successful completion of MDR-TB treatment: Patients should be followed up post treatment. Even though a patient has been cured of drug- resistant TB they may have sequelae from the disease that needs regular follow-up for care. For example, they may have

parenchymal damage in the lung and be at risk for bacterial pneumonias. Second, all cured patients are at risk for relapse of TB. Scheduled visits for the patient at three, six and 12 months post treatment is suggested, at a minimum. Also, instruct the patient to return to the clinic if there is cough of more than two weeks, or persistent fever and weight loss or for any medical concerns. Check sputum culture at six and 12 months after treatment completion date to evaluate for possible recurrence or whenever relapse is suspected.

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

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

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

Clinical Management of MDR and XDR-TB

XDR-TB was first defined in 2006 and is estimated to occur in about 9.6% of MDR-TB patients, however, it may vary from country to country. While it occurs all over the world, it has been reported as a significant problem in a number of countries. Likelihood of cure has proven to be much lower than in other MDR-TB cases and deaths are higher, especially in HIV-infected patients. There is very limited data on the different clinical approaches to XDR-TB and a recent review of treatment outcomes of XDR-TB patients could not find any associations between any specific drug or regimen and success; however, the analysis did indicate that success in XDR-TB patients was highest if at least six drugs were used in the intensive phase and four in the continuation phase. A different meta-analysis provides empiric evidence that the use of later-generation fluoroquinolones significantly improved treatment outcomes in patients with XDR-TB, even though DST demonstrated resistance to a representative fluoroquinolone.

While data on efficacy and safety is limited, the incorporation of bedaquiline into regimens designed to treat XDR-TB may be considered. However, the use of new drug depends on the country policy and resources for their use.

Treatment strategies for MDR-TB and XDR-TB

New anti-TB drugs are currently being developed and programme managers should keep abreast of WHO recommendations as they are released and updated through the website of the Task Force for New Drug Policy Development.

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

- Use pyrazinamide and any other Group 1 agent that may be effective.
- Use an injectable agent to which the strain is susceptible and consider an extended duration of use (12 months or possibly the whole treatment). If resistant to all injectable agents it is recommended to use one the patient has never used before or consider designing the regimen without an injectable agent. If toxicity is a limiting factor for the use of the injectable agent, and one of the injectable agents is considered effective, consider using inhaled version via a nebulizer..
- Use a higher-generation fluoroquinolone such as moxifloxacin or gatifloxacin.
- Use all Group 4 agents that have not been used extensively in a previous regimen or any that are likely to be effective.
- Add two or more Group 5 drugs (consider adding bedaquiline).
- Consider adding a new investigational drug eligible for use under the compassionate use scheme if policy of the WHO endorses its use for XDR-TB.
- Consider high-dose isoniazid treatment if low-level resistance or absence of the katG gene is documented.
- Consider adjuvant surgery if there is localized disease.
- Ensure rigorous respiratory infection control measures at the site where the patient is being treated.
- Consider the option of treatment in a hospital if the clinical condition of the patient is poor or major comorbidities coexist, or a shelter if the social condition of the patient prevents proper home care
- Manage HIV coinfection.
- Provide comprehensive monitoring and full social support to enable adherence to .
- Ensure that all patients have full access to palliative and end-of-life care services, with a patient-centred approach to relief the suffering of the disease and its treatment .
 - a. This recommendation is made because while the accuracy and reproducibility of DST to injectables are good, there is little data on clinical efficacy of DST. Options with XDR-TB are very limited and some strains may be affected in vivo by an injectable agent even though they are testing resistant in vitro.
 - b. No experience of the use of nebulization of injectable agents for TB has been published. Kanamycin and amikacin have been used via nebulization for cystic fibrosis. The effectiveness and safety of delivering injectable drugs via nebulization in TB is unknown. Do not count nebulized aminoglycosides as one of the four effective second-line anti-TB drugs needed to form an effective regimen. Renal toxicity and ototoxicity can still occur with nebulization.

EXAMPLES OF AN XDR-TB REGIMEN DESIGN

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

Answer: The patient may now have developed resistance to Eto as the patient was on only one or two effective drugs since the specimen collection and has remained smear-positive. Cs, while not tested for DST in this example, is also likely not effective with the strain being resistant. Furthermore, the DST is not reproducible or reliable enough for Eto, E or Z and we should depend on history more than DST – all of which are likely compromised. The later-generation fluoroquinolone Mfx may have some effect, even though Lfx is testing resistant. Options are limited and there is no expert consensus on a specific regimen that would be best for this patient. See Annex 4 for more information on the use of Bdq. Following the recommendations below would be considered acceptable (these are based on Figure 5.1 and Box 5.3). • Z-Mpm (plus Clv)-Mfx-PAS-Lzd-Cfz • Z-Mpm (plus CLV)-Bdq-PAS-Lzd-Cfz • Z-Mfx-PAS-Amx (plus CLV)-Cfz-Lzd.

Notes:

- Other possibilities exist apart from the above three regimens.
- The injectable drugs in the regimen are generally used for eight months but in cases where there is confidence in very few drugs and high confidence in the injectable agent, it can be used for a longer period.
- For dosing of drugs see Part 3 – Individual Drug Sheets.
- High-dose isoniazid can be added to any regimen if low-level resistance or absence of the katG gene is documented.
- If Bdq is added to the regimen, currently its maximum recommended duration of use is first six months of any treatment regimen.

SESSION –VIII

Monitoring & Management of adverse effects

This session describes the Monitoring & Management of adverse effects during treatment

The Participants will learn:

-) Pre treatment screening
-) Role of DOTS PLUS Committee
-) Management of adverse effects during treatment
-) Management of MDR TB in special conditions

Monitoring & Management of adverse effects

Monitoring for early detection of adverse reactions

Close monitoring of patients is necessary to ensure that the adverse effects of Category IV anti-TB drugs are recognized early by the DOT provider. DOT makes it possible to closely monitor patients. Patients will not be asked any leading question to elicit any adverse reaction. However, if the patient makes any spontaneous complaint, she/he will be interrogated in detail and the necessary action taken. Commonly, patients will volunteer if they experience any adverse effects.

The DOT provider should be trained to recognize adverse reactions like nausea, vomiting, diarrhoea, skin rash, ototoxicity, peripheral neuropathy, psychiatric symptoms and jaundice. Training should also be provided on the management of minor reactions and when the patients should be referred to the medical officer.

In addition to clinical monitoring, certain laboratory investigations may be required to detect certain occult adverse effects.

Pre-treatment screening and evaluation

The required initial pre-treatment clinical investigation includes a thorough medical history and physical examination. The initial evaluation serves to establish a baseline and may identify patients who are at increased risk for adverse effects or poor outcomes. The monitoring of treatment and the management of adverse effects may have to be more intensive in patients with pre-existing conditions or conditions identified at the initial evaluation (diabetes mellitus, renal insufficiency, acute or chronic liver disease, thyroid disease, mental illness, drug or alcohol dependence, HIV infection, pregnancy, lactation and others). The management of DR-TB when these conditions exist is described. Methods of avoiding pregnancy during treatment for women of childbearing age should be discussed.

Management of adverse effects

Second-line drugs have many more adverse effects than the first-line anti-tuberculosis drugs. Proper management of adverse effects begins with patient education. Before starting treatment, the patient should be instructed in detail about the potential adverse effects that could be produced by the prescribed drug regimen, and if and when to notify a health-care provider.

Prompt evaluation, diagnosis and treatment of adverse effects are extremely important, even if the adverse effect is not particularly dangerous. Patients may have significant fear and anxiety about an adverse effect if they do not understand why it is happening. These emotions in turn may augment the severity of the adverse effect, as in the case of nausea and vomiting. Long periods of time without medical evaluation also promote feelings of isolation and abandonment by the health-care system. Psychosocial support is an important component of the management of adverse effects. This is one of the most important roles played by DOT workers, who educate patients about their adverse effects and encourage them to continue treatment. Patient support groups are another means of providing psychosocial support to patients.

If the adverse effect is mild and not dangerous, continuing the treatment regimen, with the help of ancillary drugs if needed, is often the best option. In patients with highly resistant TB, a satisfactory replacement drug may not be available, so that suspending a drug will make the

treatment regimen less potent. Some adverse effects may disappear or diminish with time, and patients may be able to continue receiving the drug if sufficiently motivated.

The adverse effects of a number of second-line drugs are highly dose- dependent. Management often requires the use of ancillary medications to eliminate or lessen the adverse effects.

[**Management strategies of common adverse effect of second line anti-TB drugs** summarize, annex is placed at last page.

Role of DOTS Plus committee in the management of adverse reactions

Whenever a patient has serious adverse reactions necessitating hospitalization, reduction /withholding/ termination of any drug in the treatment regimen, the DOTS-Plus site committee should meet and arrange for specialist consultation, if required. The committee also should arrange for the drugs to be given for managing these reactions. Timely and intensive monitoring for identifying and management of adverse reactions to Category IV drugs are essential components of the DOTS-Plus programme. This will help to improve patient adherence to treatment, reduce mortality and obtain better treatment outcomes.

Management of MDR-TB in special conditions:

Objectives:

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

<ul style="list-style-type: none">● MDR-TB in special conditions
<ul style="list-style-type: none">● Breastfeeding
<ul style="list-style-type: none">● Contraception
<ul style="list-style-type: none">● Children
<ul style="list-style-type: none">● Diabetes mellitus
<ul style="list-style-type: none">● Renal insufficiency
<ul style="list-style-type: none">● Liver disorders
<ul style="list-style-type: none">● Seizure disorders
<ul style="list-style-type: none">● Psychiatric disorders
<ul style="list-style-type: none">● Substance dependence
<ul style="list-style-type: none">● HIV Infection

Pregnancy

All female patients of childbearing age should be tested for pregnancy upon initial evaluation. Pregnancy is not a contraindication for treatment of active drug-resistant TB, which poses great risks to the lives of both mother and fetus. However, birth control is strongly recommended for all non pregnant women receiving therapy for drug-resistant TB because of the potential consequences for both mother and fetus resulting from frequent and severe adverse drug reactions. Pregnant patients should be carefully evaluated, taking into consideration gestational age and severity of the drug-resistant TB. The risks and benefits of treatment should be carefully considered, with the primary goal of smear conversion to protect the health of the mother and child, both before and after birth.

Benefits and risks of treatment. Most pregnant patients should be started on treatment as soon as the diagnosis is made. However, since the majority of teratogenic effects occur in the first trimester, treatment may be delayed until the second trimester when the patient is

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

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

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

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

The total treatment duration is the same as for MDR-TB treatment National TB control programmes should provide clear instructions on the management of MDR-TB in pregnancy and standardized regimens need adjustments in almost all cases.

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

Breastfeeding

A woman who is breastfeeding and has active drug-resistant TB should receive a full course of anti-tuberculosis treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to her baby. In lactating mothers on treatment, most anti-tuberculosis drugs will be found in the breast milk in concentrations that would equal only a small fraction of the therapeutic dose used in an infant. However, any effects on infants of such exposure during the full course of MDR-TB treatment have not been established. Therefore, when resources and training are available, it is recommended to provide infant formula options as an alternative to breastfeeding. When infant formula is provided, fuel for boiling water and the necessary apparatus (stove, heating pans and bottles) must also be provided, as well as training on how to prepare and use the infant formula. All this should be free of charge to poor patients, and DR-TB control programmes should therefore, budget in advance for the estimated number of patients who might need this support. The mother and her baby should not be completely separated. However, if the mother is sputum smear-positive, the care of the infant should be left to family members until she becomes sputum smear-negative, if this is feasible. When the mother and infant are together, this common time should be spent in well-ventilated areas or outdoors. In some settings, the mother may be offered the option of using a surgical mask or an N-95 respirator until she becomes sputum smear negative.

Contraception

There is no contraindication to the use of oral contraceptives with the nonrifampicin containing regimens. Patients who vomit directly after taking an oral contraceptive can be at risk of decreased absorption of the drug and therefore of decreased efficacy. These patients should be advised to take their contraceptives apart from times when they may experience vomiting caused by the anti-tuberculosis treatment. Patients, who vomit at any time directly after, or within the first two hours after, taking the contraceptive tablet, should use a barrier method of contraception until a full month of the contraceptive tablets can be tolerated. For patients with mono- and poly-resistant TB that is susceptible to rifampicin, the use of rifampicin interacts with the contraceptive drugs resulting in decreased efficacy of protection against pregnancy. A woman on oral contraception while receiving rifampicin treatment may choose between two options: following consultation with a physician, use of an oral contraceptive pill containing a higher dose of estrogen (50 µg); or use of another form of contraception.

Children

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

The treatment of culture-negative children with clinical evidence of active TB disease and contact with a documented case of drug-resistant TB should be guided by the results of DST and the history of the contact's exposure to Anti-tuberculosis drugs.

There is only limited reported experience with the use of second-line drugs for extended periods in children. The risks and benefits of each drug should be carefully considered in designing a regimen. Frank discussion with family members is critical, especially at the outset of therapy. MDR-TB is life threatening, and no anti-tuberculosis drugs are absolutely

contraindicated in children. Children who have received treatment for drug-resistant TB have generally tolerated the second-line drugs well.

Although fluoroquinolones have been shown to retard cartilage development in beagle puppies, experience with the use of fluoroquinolones has not demonstrated similar effects in humans. It is considered that the benefit of fluoroquinolones in treating MDR-TB in children outweighs any risk. Additionally, ethionamide, PAS and Cycloserine have been used effectively in children and are well tolerated. In general, anti-tuberculosis drugs should be dosed according to body weight. Monthly monitoring of body weight is therefore especially important in pediatric cases, with adjustment of doses as children gain weight.

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

In children who are not culture-positive initially, treatment failure is difficult to assess. Persistent abnormalities on chest radiograph do not necessarily signify a lack of improvement. In children, weight loss or, more commonly, failure to gain weight adequately, is of particular concern and often one of the first (or only) signs of treatment failure. This is another key reason to monitor weight carefully in children.

Pediatric dosing of second-line anti-tuberculosis drugs

Drug	Daily Dose(MG/KG)	Frequency	Max. daily dose
Streptomycin	20–40	Once daily	1 g
Kanamycin	15–30	Once daily	1 g
Amikacin	15–22.5	Once daily	1 g
Capreomycin	15–30	Once daily	1 g
Ofloxacin	15–20	Twice daily	800 mg
Levofloxacin	7.5–10	Once daily	750 mg
Moxifloxacin	7.5–10	Once daily	400 mg
Ethionamide	15–20	Twice daily	1 g
Protionamide	15–20	Twice daily	1 g
Cycloserine	10–20	Once or twice daily	1 g
PAS	150	Twice or thrice daily	12 g

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

Diabetes mellitus

Diabetic patients with MDR-TB are at risk for poor outcomes. In addition, the presence of diabetes mellitus may potentiate the adverse effects of anti-tuberculosis drugs, especially renal dysfunction and peripheral neuropathy. Diabetes must be managed closely throughout the treatment of drug-resistant TB. The health-care provider should be in close

communication with the physician who manages the patient's diabetes. Oral hypoglycaemic agents are not contraindicated during the treatment of drug-resistant TB but may require the patient to increase the dosage.

Use of ethionamide or protionamide may make it more difficult to control insulin levels. Creatinine and potassium levels should be monitored more frequently, often weekly for the first month and then at least monthly thereafter.

Renal insufficiency

Renal insufficiency caused by longstanding TB infection itself or previous use of aminoglycosides is not uncommon. Great care should be taken in the administration of second-line drugs in patients with renal insufficiency, and the dose and/or the interval between dosing should be adjusted.

Adjustment of anti-tuberculosis medication in renal insufficiency

DRUG	CHANGE IN FREQUENCY	RECOMMENDED DOSE ^c AND FREQUENCY FOR PATIENTS WITH CREATININE CLEARANCE <30ML/MIN OR FOR PATIENTS RECEIVING HAEMODIALYSIS
Isoniazid	No change	300 mg once daily, or 900 mg three times per week
Rifampicin	No change	600 mg once daily, or 600 mg three times per week
Pyrazinamide	Yes	25–35 mg/kg per dose three times per week (not daily)
Ethambutol	Yes	15–25 mg/kg per dose three times per week (not daily)
Ofloxacin	Yes	600–800 mg per dose three times per week (not daily)
Levofloxacin	Yes	750–1000 mg per dose three times per week (not daily)
Moxifloxacin	No change	400 mg once daily
Cycloserine	Yes	250 mg once daily, or 500 mg/dose three times per week ^d
Terizidone	-	Recommendations not available
Protionamide	No change	250–500 mg per dose daily
ethionamide	No change	250–500 mg per dose daily
paminosalicylic acid ^e	No change	4 g/dose, twice daily
Streptomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily) ^f
Capreomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily) ^f
Kanamycin	Yes	12–15 mg/kg per dose two or three times per week (not daily) ^f
amikacin	Yes	12–15 mg/kg per dose two or three times per week (not daily) ^e

a. Adapted from *Treatment of tuberculosis*.

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

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

- d. The appropriateness of 250 mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity (if possible measure serum concentrations and adjust accordingly).
- e. Sodium salt formulations of PAS may result in an excessive sodium load and should be avoided in patients with renal insufficiency. Formulations of PAS that do not use the sodium salt can be used without the hazard of sodium retention.
- f. Caution should be used with the injectable agents in patients with renal function impairment because of the increased risk of both Ototoxicity and Nephrotoxicity.

Liver disorders

The first-line drugs isoniazid, rifampicin and pyrazinamide are all associated with hepatotoxicity. Of the three, rifampicin is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice. Pyrazinamide is the most hepatotoxic of the three first-line drugs. Among the second-line drugs, ethionamide, prothionamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with the fluoroquinolones. Patients with a history of liver disease can receive the usual drug-resistant TB chemotherapy regimens provided there is no clinical evidence of chronic liver disease, hepatitis virus carriage, past history of acute hepatitis or excessive alcohol consumption. However, hepatotoxic reactions to anti-tuberculosis drugs may be more common in these patients and should be anticipated. In general, patients with chronic liver disease should not receive pyrazinamide. All other drugs can be used, but close monitoring of liver enzymes is advised. If significant aggravation of liver inflammation occurs, the drugs responsible may have to be stopped. Uncommonly, a patient with TB may have concurrent acute hepatitis that is unrelated to TB or anti-tuberculosis treatment. In this case, clinical judgment is necessary. In some cases, it is possible to defer anti-tuberculosis treatment until the acute hepatitis has been resolved. In other cases when it is necessary to treat drug-resistant TB during acute hepatitis, the combination of four non hepatotoxic drugs is the safest option.

Seizure disorders

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

Cycloserine should be avoided in patients with active seizure disorders that are not well controlled with medication. However, in cases where Cycloserine is a crucial component of the treatment regimen, it can be given and the anti-seizure medication adjusted as needed to control the seizure disorder. The risks and benefits of using Cycloserine should be discussed with the patient and the decision on whether to use Cycloserine made together with the patient. In mono- and poly-resistant cases, the use of isoniazid and rifampicin may interfere with many of the anti-seizure medications. Drug interactions should be checked before their use (see Annex 2 for drug interactions). Seizures that present for the first time during anti-tuberculosis therapy are likely to be the result of an adverse effect of one of the anti-tuberculosis drugs.

Psychiatric disorders

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

Treatment with psychiatric medication, individual counseling and/or group therapy may be necessary to manage the patient suffering from a psychiatric condition or an adverse psychiatric effect caused by medication. Group therapy has been very successful in providing a supportive environment for MDR-TB patients and may be helpful for patients with or without psychiatric conditions. (Adequate measures to prevent infection risk should be in place for the group therapy.) The use of Cycloserine is not absolutely contraindicated for the psychiatric patient. Adverse effects from Cycloserine may be more prevalent in the psychiatric patient, but the benefits of using this drug may outweigh the potentially higher risk of adverse effects. Close monitoring is recommended if Cycloserine is used in patients with psychiatric disorders.

All health-care workers treating drug-resistant TB should work closely with a mental health specialist and have an organized system for psychiatric emergencies. Psychiatric emergencies include psychosis, suicidal ideation and any situation involving the patient's being a danger to him or herself or others.

Substance dependence

Patients with substance dependence disorders should be offered treatment for their addiction. Complete abstinence from alcohol or other substances should be strongly encouraged, although active consumption is not a contraindication for anti-tuberculosis treatment. If the treatment is repeatedly interrupted because of the patient's dependence, therapy should be suspended until successful treatment or measures to ensure adherence have been established. Good DOT gives the patient contact with and support from health-care providers, which often allows complete treatment even in patients with substance dependence.

Cycloserine will have a higher incidence of adverse effects (as in the psychiatric patient) in patients dependent on alcohol or other substances, including a higher incidence of seizures. However, if Cycloserine is considered important to the regimen, it should be used and the patient closely observed for adverse effects, which are then adequately treated.

HIV Infected persons

Key recommendations

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

General considerations

Recent global drug resistance surveillance suggests an association between HIV and MDR-TB in some parts of the world, although specific factors involved in this association have not been determined. HIV is a powerful risk factor for all forms of TB, and DR-TB outbreaks, including XDR-TB outbreaks in HIV-infected patients, appear to be common. DR-TB is often associated with higher mortality rates in the HIV infected compared with the non-infected; however, the use of ART in addition to treatment of DR-TB has been reported to improve outcomes of DR-TB in the HIV-infected.

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

The diagnosis of TB (including MDR-TB and XDR-TB) in HIV-infected people is more difficult and may be confused with other pulmonary or systemic infections. The presentation is more likely to be extra-pulmonary or sputum smear-negative than in HIV-uninfected TB patients, especially as immunosuppression advances. This can result in misdiagnosis or delays in diagnosis, and in turn, higher morbidity and mortality.

Algorithms have recently been published by the WHO with the aim of improving the diagnosis of smear-negative pulmonary and extra-pulmonary TB. The new algorithms emphasize the use of clinical criteria first and, if needed, the use of additional laboratory data (culture) and radiography to diagnose TB. Clinical criteria have been shown to have an 89–96% positive predictive value of smear-negative and extra-pulmonary TB when compared with culture. For patients with advanced HIV disease, mycobacterial culture of other fluids (e.g. blood, pleural fluid, ascetic fluid, cerebrospinal fluid and bone-marrow aspirates) and histopathology (e.g. lymph node biopsies) may be helpful in diagnosis.

In many programmes and areas, all HIV patients with TB are screened for drug-resistance with DST. Rapid drug-resistance testing is the DST technique of choice since this allows prompt diagnosis of MDR-TB, decreasing the time the patient may be on an inadequate

regimen and the period during which the patient may be spreading DR-TB. Programmes without facilities or resources to screen all HIV-infected patients for DR-TB should put significant efforts into obtaining them, especially if DR-TB rates are moderate or high. Some programmes may adopt a strategy of targeted DST for patients with increased risk of DR-TB (such as those in whom treatment has failed or who are contacts of DR-TB cases) Programmes may also choose to use targeted DST for those with lower CD4 counts (e.g. less than 200 cells/mm³) since these patients are at a very high risk of death due to unrecognized DR-TB.

Recommended collaborative TB/HIV activities

WHO recommends that certain collaborative activities are carried out to decrease the joint burden of TB and HIV. These activities are the backbone of the WHO TB/HIV collaborative strategy that, along with the implementation of effective DOTS programmes, will strengthen and increase the success of DR-TB/HIV control and treatment activities. These guidelines recommend whenever possible the highest standard of care.

- **Perform provider-initiated HIV testing and counseling in all TB suspects.**

Given the high levels of HIV and TB co-infection in many settings, provider-initiated HIV counseling and testing is recommended for all TB suspects. Provider-initiated testing can be done at the same time the sputum is sent for smear microscopy (or culture). This is more efficient and more likely to be successful than referring patients elsewhere for HIV testing and counseling. Provider-initiated counseling and testing can serve as a gateway to lifesaving prevention, care and treatment interventions.

- **Use standard algorithms to diagnose pulmonary and extra-pulmonary TB.**

New recommendations for improving the diagnosis and treatment of smear-negative pulmonary and extra-pulmonary TB have been put forth by WHO.

- **Use mycobacterial cultures and, where available, newer more rapid methods of diagnosis.**

Mycobacterial cultures of sputum or other fluids and tissues are recommended to help in the diagnosis of sputum smear negative and extra-pulmonary TB. The heavy reliance on smear microscopy has significant limitations and is insufficient to reliably diagnose a significant proportion of HIV-co-infected patients, especially as the degree of immuno-suppression advances. Rapid methods such as liquid culture or molecular techniques should be considered.

- **Perform DST at the start of anti-tuberculosis therapy.**

Unrecognized DR-TB carries a high risk of mortality in patients with HIV. Prompt initiation of appropriate anti-tuberculosis treatment (and subsequent initiation of ART) can reduce mortality among HIV-infected patients infected with DR-TB. Because unrecognized MDR-TB and XDR-TB are associated with such high mortality in HIV-infected patients, many international protocols dictate the performance of DST and/or rapid drug resistance testing for all HIV-infected patients with established active TB.

While performing DST for all TB/HIV co-infected patients is the standard of care for many areas, these guidelines recognize that this may be difficult or impossible in many resource-limited settings.

- **Determine the extent (or prevalence) of TB drug resistance in patients with HIV.**

Programmes should determine the extent of the overlap of the DR-TB and HIV epidemics. This can be done in two ways:

- (i) Data from population-based TB DRS can be linked with HIV testing of those TB patients included and/or
- (ii) When implementing HIV surveillance among TB patients (or provider-initiated testing and counseling for all TB patients), DST can be included in all, or an unbiased sub-set of, HIV infected patients. The latter technique is more complex if rates of DR-TB in HIV-infected and negative patients are to be compared, as a control group of HIV-negative TB infected patients would also need to be established.

- **Introduce ART promptly in DR-TB/HIV patients.**

These guidelines recommend the prompt initiation of ART in HIV-infected patients with DR-TB according to WHO guidelines.

- **Consider empirical therapy with second-line anti-tuberculosis drugs.**

Patients with a very high risk of DR-TB can be empirically started on Category IV regimens. This strategy can be applied to all patients regardless of HIV status but is especially important in those with HIV. (Note: empirical use of Category IV is reserved for patients who have an extremely high rate of MDR-TB, such as failures of Category II or very close contacts of DR-TB.

- **Provide Chemoprophylaxis Treatment (CPT) for patients with active TB and HIV.**

CPT should be provided to all patients with HIV according to WHO recommendations. This therapy is not known to interact significantly with any of the second line anti-tuberculosis agents. There are overlapping toxicities between ART, anti-tuberculosis therapy and CPT, and vigilance in terms of monitoring adverse effects is required.

- **Arrange treatment follow-up by a specialized team.**

The team of care providers should be familiar with the treatment of both DR-TB and HIV, with close monitoring of potential additive adverse effects and nutritional status as well as periodic assessments of therapeutic response for both infections.

- **Implement additional nutritional and socioeconomic support.**

Patients with DR-TB and HIV may suffer from severe wasting, diarrhoeal diseases, and malabsorption syndromes. Co-infected patients often come from socially marginalized groups or from families with low economic resources. Additionally, DR-TB therapy with second-line anti-tuberculosis medications may result in adverse effects that affect treatment adherence and require more frequent visits to health facilities. Wherever possible, patients with DR-TB/HIV and limited means should be offered socioeconomic and nutritional support.

- **Ensure effective infection control.**

Infection control procedures can reduce the risk of *M. tuberculosis* transmission in HIV/AIDS care facilities. Infection control issues concerning DR-TB, including issues regarding HIV.

- **Involve key stakeholders in DR-TB/HIV activities.**

The local/national TB/HIV coordinating bodies, community groups and key stakeholders should be involved in the planning and monitoring of DR-TB/HIV activities and programmes.

Concomitant treatment of DR-TB and HIV

The treatment of DR-TB in patients with HIV is very similar to that in patients without HIV.

- ART plays a crucial role, as mortality in MDR-TB/HIV patients without the use of ART is extremely high (91–100% as reported in one analysis of MDR-TB outbreaks in 9 different institutions).
- Adverse effects are more common in patients with HIV. The multiple medicines involved in DR-TB with recognized high toxicity risks, often combined with ART, results in a high incidence of adverse effects. Some toxicities are common to both anti-tuberculosis treatment and ART, which may result in added rates of adverse events.
- Monitoring needs to be more intense for both response to therapy and adverse effects.
- The use of thioacetazone is not recommended for patients with HIV or for routine use in populations with high rates of HIV.
- Immune Reconstitution Inflammatory Syndrome (IRIS) may complicate therapy.

Initiating ART treatment in patients with DR-TB

The use of ART in HIV-infected patients with TB improves survival for both drug-resistant and susceptible disease. As stated above, cohorts of patients treated for DR-TB without the benefit of ART have experienced mortality rates often exceeding 90%. However, the likelihood of adverse effects could compromise the treatment of either HIV or DR-TB if both treatments are started simultaneously. On the other hand, undue delay in the start of ART could result in significant risk of HIV-related death among patients with advanced disease. The optimal timing for the introduction of ART in patients receiving TB treatment is unknown.

Based on WHO guidelines for the treatment of HIV infection in adults and adolescents, provides recommendations for initiating ART in relationship to starting therapy for DR-TB.

Timing of ART in the ART-naive patient starting anti-tuberculosis therapy for DR-TB

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

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

The DR-TB inpatients already receiving ART

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

The second issue is whether the presentation of active DR-TB in a patient on ART constitutes ART failure. The principles of determining failure in such cases are described in other WHO documents. If ART failure has been diagnosed, it is not recommended to begin a new second-line ART regimen at the same time as initiation of a DR-TB regimen. Instead, continue the present ART regimen and switch to the second-line ART regimen 2–8 weeks after the start of DR-TB treatment. Important drug–drug interactions in the treatment of HIV and DR-TB Currently, little is known about drug–drug interactions between second-line anti-tuberculosis agents and antiretroviral therapy. There are several known interactions between drugs used to treat HIV and TB, which are summarized below.

- **Rifamycin derivatives.**

While rifamycin derivatives are not routinely used in DR-TB treatment, they are used in the treatment of rifampicin-sensitive poly- and mono-resistant TB. Guidance on use of rifamycin derivativebased regimens and ART (including with PI-based regimens) is available elsewhere.

- **Quinolones and didanosine.**

Buffered didanosine contains an aluminium/ magnesium-based antacid and, if given jointly with fluoroquinolones, may result in decreased fluoroquinolone absorption; it should be avoided, but if it is necessary it should be given six hours before or two hours after fluoroquinolone administration.

The enteric coated (EC) formulation of didanosine can be used concomitantly without this precaution.

- **Ethionamide/prothionamide.**

Based on limited existing information of the metabolism of the thiamides (ethionamide and prothionamide), this drug class may have interactions with antiretroviral drugs. Ethionamide/prothionamide is thought to be metabolized by the CYP450 system, although it is not known which of the CYP enzymes are responsible. Whether doses of ethionamide/prothionamide and/or certain antiretroviral drugs should be modified during the concomitant treatment of DR-TB and HIV is completely unknown.

- **Clarithromycin.**

Clarithromycin is a substrate and inhibitor of CYP3A and has multiple drug interactions with protease inhibitors and NNRTIs. If possible, the use of Clarithromycin should be avoided in patients co-infected with DR-TB and HIV because of both its weak efficacy against DR-TB and multiple drug interactions.

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

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

Adverse effects those are common to both antiretroviral and anti-tuberculosis drugs. It should be noted that relatively very little is known about the rates of adverse effects in the concomitant treatment of DR-TB and HIV, is meant to alert the clinician to potentially overlapping and additive toxicities, and as of the writing of these guidelines is based on preliminary, non-published data and expert opinion. When possible, avoid the use of agents with shared adverse effect profiles. Often, however, the benefit of using drugs that have overlapping toxicities outweighs the risk. Therefore, if two drugs with overlapping toxicities are determined to be essential in a patient's regimen, this guideline recommends increased monitoring of adverse effects rather than disallowing a certain combination.

Recommended treatment of TB, whether drug-susceptible or resistant, is the same for HIV-infected and non-HIV-infected patients, except for the use of Thioacetazone, which should not be used in HIV-infected patients.

However, the adverse events of drugs are more common in HIV patients. Deaths during treatment caused by TB itself or by other HIV related diseases are more frequent in HIV-infected patients, particularly in the advanced stages of immunodeficiency.

The use of Anti-Retro Viral (ART) in HIV-infected patients with TB improves survival and slows progression to AIDS. However, initiation of ART in HIV-infected patients with drug-susceptible or drug-resistant TB is often associated with adverse events that may lead to the interruption of both TB and/or HIV therapy.

Management of patients after MDR-TB Treatment failure

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

Assessment of patients at risk for treatment failure

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

The following steps are recommended in such patients:

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

Management of patients after MDR-TB treatment failure

- The bacteriological data should be reviewed. Often, the smear and culture data are the strongest evidence that a patient is not responding to therapy. One single positive culture in the presence of an otherwise good clinical response can be caused by a laboratory contaminant or error. In this case, subsequent cultures that are negative, or in which the number of colonies is decreasing, may help prove that the apparently positive result did not reflect treatment failure. Positive smears with negative cultures may be caused by the presence of dead bacilli and therefore may not indicate treatment failure. Repeated culture- and smear-negative results in a patient with clinical and radiographical deterioration may indicate that the patient has a disease other than MDR-TB.
- The health-care worker should confirm that the patient has taken all the prescribed medicines. A non-confrontational interview should be undertaken without the DOT worker present.
- A non-confrontational interview of the DOT worker alone should also be carried out. Questions should be asked to rule out the possible manipulation of the DOT worker by the patient. If manipulation is suspected, the DOT worker should be switched to another patient, and the patient with suspected treatment failure should be assigned to a new DOT worker.
- Other illnesses that may decrease absorption of medicines (e.g. chronic diarrhoea) or may result in immune suppression (e.g. HIV infection) should be excluded.
- If surgical resection is feasible, it should be considered.

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

Indications for suspending treatment

It takes 3–4 months to evaluate whether a change in treatment plan has been effective. If the patient continues to deteriorate despite the measures described in the previous section,

treatment failure should be considered. There is no single indicator to determine whether a treatment regimen is failing. Although there is no simple definition for treatment failure, there often comes a point during the treatment when it becomes clear that the patient is not going to improve. Signs indicating treatment failure include:

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

It is not necessary for all of these signs to be present to identify failure of the treatment regimen. However, a cure is highly unlikely when they are all present. The epidemiological definition of treatment failure for recording outcomes is often different from that used in the process of suspending therapy in a patient when the therapy is failing. The epidemiological definition is an outcome to account for the patient in a treatment cohort analysis, while the clinical decision to suspend therapy is made after the clinical search for all other options has been exhausted and cure of the patient is considered to be highly unlikely.

Suspending therapy

Treatment can be considered to have failed and suspension of therapy is recommended in cases where the medical personnel involved are confident that all the drugs have been ingested and there is no possibility of adding other drugs or carrying out surgery. There are two important considerations in suspending therapy or changing it to a supportive care regimen. The first is the patient's quality of life: the drugs used in MDR-TB treatment have significant adverse effects, and continuing them while the treatment is failing may cause additional suffering. The second is the public health concern: continuing a treatment that is failing can amplify resistance in the patient's strain, resulting in highly resistant strains such as XDR-TB that may cause subsequent infection of others.

Approach to suspending therapy

The approach to suspending therapy should start with discussions among the clinical team, including all physicians, nurses and DOT workers involved in the patient's care. Once the clinical team decides that treatment should be suspended, a clear plan should be prepared for approaching the patient and the family. This process usually requires a number of visits and takes place over several weeks. Home visits during the process offer an excellent opportunity to talk with family members and the patient in a familiar environment. It is not recommended to suspend therapy before the patient understands and accepts the reasons to do so, and agrees with the supportive care offered.

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

A number of supportive measures can be used once the therapy has been suspended. It is very important that medical visits continue and that the patient is not abandoned. The supportive measures are described in detail in the Integrated Management of Adolescent and Adult Illness guidelines produced by WHO in a booklet titled *Palliative care: symptom management and end-of-lifecare. (Year of publication-2004)*

Management of Adverse Effects during treatment, Individual drug profiles and Drug interactions are given in Annexure- I, II and III respectively.

SESSION –IX

Delivery of Patient Care

This session describes the strategy for delivery of patient care in different treatment delivery settings.

The participants will learn:

- Treatment delivery settings
- Community based care and support

Treatment delivery settings:

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

Community-based care.

Although early in the history of DR-TB treatment, strict hospitalization of patients was considered necessary; community-based care provided by trained lay and community health workers (CHWs) can achieve comparable results and, in theory, may result in decreased nosocomial spread of the disease. In each setting, care should be delivered by a multidisciplinary team of providers, including physicians, nurses, social workers and CHWs. The roles and responsibilities of each of these groups of providers will vary depending on the needs and resources available in specific settings.

● **Clinic-based treatment.**

Some DR-TB treatment strategies involve the patient travelling to a clinic each day to receive DOT. This system works provided there is no barrier to travel or if the patient lives near a facility offering DOT of DR-TB; the patient should be given an enabler for travel in situations other than these. The patient should be smear-negative if travelling on public transportation or waiting in common waiting rooms. Some facilities have a separate area with infection control measures for smear positive patients. Special early morning appointments can be made for patients who need to get to work. An alternative version of this strategy is to have the clinic act as a “day hospital” where patients can rest or get a meal as an incentive for coming each day. Special attention must be taken in clinic-based programmes so that HIV-infected patients are not exposed to smear-positive patients.

● **Hospitalization.**

Hospitals should provide acceptable living conditions, sufficient activities so that patients avoid boredom, adequate food, a heating system in cool areas, fans or cooling systems in hot climates and proper infection control measures. Prisons require specific measures to improve adherence, which are described in detail in the WHO guidelines for TB control in prisons

Adherence

Following Adherence promotion strategies for DOTS-Plus are recommended

1. Providing Counseling to Patient and Family on disease education
2. Directly observed therapy (DOT)
3. Socio economic intervention
4. Psychosocial & emotional support
5. Early and Effective management of adverse drug effects
6. Monitoring & Follow-up of the Non-adherence patients

Patients with MDR-TB may be more likely to have had problems with non-adherence due to prolonged duration of treatment, drug side effects and large number of drugs (Pill load).

Adherence is important to prevent the generation of pan-resistant strains with the potential for community-wide spread and virtually no chance of cure for the patient

1. Providing Counseling to Patient and Family on disease education:

Providing counseling and health education to the MDR-TB patient about the disease and about the taking regular and adequate treatment is of utmost importance, for they must clearly understand that by taking the drugs irregularly or inadequately, or by defaulting, they had fallen into a category that was difficult to treat and that required a prolonged therapy. It is vital for them to realize that this is their last chance of treatment. Hence, it is extremely essential to strictly adhere to the prescribed line of treatment, as well as, to the scheduled follow-up of sputum and other lab investigations. Health education and counseling is provided to all patients and family members at different levels of health care, right from one at the periphery to those at the DOTS-Plus site facility. It is started at the initial point of contact and carried on a continuous basis at all visits by the patient to a health facility. The counseling and motivation is required to be done not only of the patient but also of the family members. In addition to the emphasis on regular treatment, health education also attempts to cross check the manner and the number of drugs/injections being taken, the occurrence of side effects like yellowish skin and/or eyes, pain and swelling of joints, imbalance etc. if any, and the frequency of sputa examinations being performed. Education can be provided by the attending doctors, nurses, community health workers, and other health care workers.

3. DOT for MDR TB patients

Directly observed treatment (DOT)

Because MDR-TB treatment is the last therapeutic chance for patients and there is a high public health consequence if a patient with MDR-TB fails therapy, it is recommended that all patients receiving Category IV treatment for MDR-TB receive daily DOT wherever they are receiving the treatment.

Who can deliver DOT?

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

Maintaining confidentiality

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

3. Socio economic intervention

Socioeconomic interventions have included:

- Health care free of charge;
- Food parcels for DR-TB patients and their dependents;

- Temporary shelter in a housing facility or in a rented home for DR-TB patients;
- School fees for dependent children;
- Transportation fees;
- Advice and assistance in administrative matters relating to the treatment;
- Assistance in defending rights and/or reinforcing the responsibilities of patients;
- Providing skills training and livelihood to patients both while on treatment as well as to prepare them with skills that can support them as they reintegrate into the community upon treatment completion.

4. Psychosocial & emotional support

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

5. Early and effective management of adverse drug reactions

Adverse drug reaction among patients on MDR-TB treatment may be one reason for non-adherence. So management of adverse drug reaction should be done in a simple and cost effective way without compromising the MDR-TB treatment regimen.

MDR-TB treatment can be successful with high overall rates of adherence when adequate support measures are provided as follows.

- Reimbursement of travel expenses to patient.
- Team approach for treatment adherence
- DOTS-Plus site in-door facility
- Patient, family and peer's education on MDR-TB treatment
- Early and effective management of adverse drug reactions

6. Monitoring & Follow-up of the Non-adherence patients

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

Community-based care and support

Community-based care and support is any action or help provided *by, with or from* the community, including situations in which patients are receiving ambulatory treatment. This support contributes to, and may even be necessary to, patient recovery. Political will from the health and local community authorities is vital to these efforts, and in settings with no

tradition of community participation, it may help to involve organizations that have expertise in social mobilization and community organizing.

- **Community care supporters.**

There are numerous potential supporters who can be brought into the effort to address programmatic needs on a local level. These include local health centre nurses, paid (and in some cases volunteer) CHWs, former and current patients, affected families, associations, cooperatives, grassroots organizations, local NGOs, community volunteers and many more.

- **Function of the community care supporters.**

Community care supporters can provide assistance in clinical management, DOT, contact tracing, infection control, recording and reporting, training, advocacy and social support.

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

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

This solidarity is vital to new patients, who often feel isolated and vulnerable.

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

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

— *Recording and reporting.* Data obtained within the family and community can contribute to better comprehensive management. This can include documenting processes occurring outside the health centre and closer to the patient's home. Recording certain variables during a home visit can better assess risks for the patient and family (such as leaky roofs, insufficient living space or poor sanitary conditions). Community-based support in recording and reporting may require close supervision and validation by health facility staff, and should be done in a manner that underlines "partnership," *Training/education.* Community-based training and education can come in the form of peer educators (i.e. former patients) or trained advocates. Topics can include general information on TB, how DR-TB develops, the treatment of DR-TB and the importance of adherence and infection control. Training and education on DR-TB will be most effective Treatment deli very and community-based DR-TB supportive with the aid of materials written in lay language. WHO has issued guidelines for the development of teaching materials under strategies referred to as advocacy, communication and social mobilization (ACSM).

These materials will be more effective if they contain input from patients. Patients can become part of a team that designs the text and visuals of materials for DR-TB patients.

Topics such as the rights and responsibilities of patients as stated in the *Patients' charter for tuberculosis care* should also be included. When former patients and care supporters participate in this health education process, it is more credible locally and serves also to raise awareness of TB in the wider community, strengthening basic TB control and care.

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

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

The relationship of community-based support and hospitalization for DR-TB,

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

Costs & sustainability

When care is rooted in the community, ownership by the community supporters will make the support more sustainable. The CHW is often the backbone of a community-based support network. These guidelines advocate for trained CHWs who are a certified part of the health system and who receive a regular stipend that is a reasonable compensation for the amount of time that they spend each day participating in community-based care. The added cost of a strong CHW network is often cost effective because it contributes to lower rates of failure and prevention of further drug resistance.

Monitoring the CHW

As stated, the CHW is often the backbone of the community-based network. Monitoring of the CHW can involve supervisors who perform unannounced or ad hoc visits to the patient. At these visits, they can perform pill counts, examinations of the treatment card and assess how activities are being carried out. Whenever a patient is doing poorly, a home visit and assessment of DOT should be performed. It

is important to monitor the health status of CHWs and teach them how to protect themselves against TB transmission as well to ensure that they themselves do not develop disease. Weekly/monthly reports from the CHWs or those providing care in the community should be required. A communication network should be clear and in place, making sure that community volunteers have easy access to professional health staff should there be problems that arise in the community, e.g. adverse events or questions asked by patients that the CHWs cannot answer.

Conclusion

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

SESSION –X

Operational considerations for MDR TB patients management

This session describes the Operational considerations for MDR TB management

The participants will learn:

-) Management of DR & Infection Control
-) Role of Rapid test in infection control & key recommendations
-) Procurement of second line anti-TB drugs

OPERATIONAL COMPONENTS FOR MDR-TB PATIENTS MANAGEMENT

Management of Drug Resistance & Infection Control

Chapter objectives

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

The priorities of infection control

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

The management of DR-TB does not significantly alter the basic TB infection control strategies. However, in view of its seriousness, every programme attempting to treat DR-TB should also undertake a systematic review of current practices and ensure that everything possible is done to prevent transmission among patients and to staff.

Recommendations for infection control to prevent DR-TB are essentially the same as those to prevent the spread of drug-susceptible TB, with only minor differences in emphasis. Further information is provided in the WHO/CDC/IUATLD Guidelines for prevention of tuberculosis in health care facilities in resource-limited settings.

This chapter reviews briefly the recommendations that have a specific focus on DR-TB. TB infection control has three components. By order of importance, they are: administrative controls, environmental or engineering controls, and personal respiratory protection.

The administrative controls are the most effective and least expensive and therefore have highest priority in resource-constrained settings.

Administrative controls

Administrative controls include policies and procedures intended to promptly identify infectious cases so that additional precautions can be taken. They necessitate the appointment of a director of infection control for the institution, and an infection control committee representing key departments of the facility. The initial task of the committee is the formulation of a comprehensive infection control plan for the institution, including a programme for the education of all staff on infection control policies and procedures. An important aspect of administrative control measures is the physical separation of patients known or suspected to have TB or DR-TB (especially smear-positive cases) from other patients, especially those who are immuno-compromised. In many resource-limited settings, however, isolation rooms are not available and patients are mixed together in open wards. A second, less satisfactory but practical, solution is to separate rather than isolate patients.

In this approach, patients with TB are grouped together and apart from those with suspected DR-TB, who are grouped together. This separation may be difficult as wards are usually

separated by sex, which increases the number of different areas required. The presence of a substantial number of HIV-infected patients further complicates separation as they are not only potentially infectious but also highly vulnerable to inter-current infection and re-infection from others. Placing HIV- infected patients on wards with known or suspected TB together with other TB or MDR-TB patients should always be avoided. Infectious patients with XDR-TB, whether infected with HIV or not, should not be placed on general wards. Given the high mortality associated with XDR-TB, isolation until the patient is no longer infectious is recommended.

Another administrative issue is the length of time patients spend in the hospital. In many resource-limited countries, patients are traditionally treated for prolonged periods in the hospital, particularly when they come from great distances. However, this practice involves an increased risk of nosocomial transmission. The risk of transmission to patients and healthcare workers decreases when community-based ambulatory treatment is established and hospital stays are reduced. Although most transmission is likely to have occurred before the diagnosis and start of treatment, ambulatory patients should be advised to avoid contact with the general public and with particularly susceptible people, such as young children or individuals with HIV infection. Health-care workers visiting TB patients at home before treatment is well established should wear properly fitted personal respirator masks. Attention should also be paid to outpatient clinical settings. Because of the risk of severe morbidity and mortality in HIV-infected persons from DR-TB, persons with known DR TB should receive routine care outside of normal HIV care settings.

Environmental controls

Environmental (or engineering) controls assume that unsuspected, untreated TB patients will enter hospitals despite all efforts to identify them. In addition, there are certain high-risk settings, such as sputum induction rooms, bronchoscopy rooms and rooms for the evaluation of newly admitted patients who may have untreated TB or DR-TB, where engineering interventions are necessary to reduce risk. Engineering controls attempt to reduce the concentration of infectious droplet nuclei in the air. They include natural and/or mechanical ventilation, ultraviolet germicidal irradiation (UVGI) and high efficiency particulate air filtration. Environmental methods should never replace administrative controls; in fact, they work together. In warm climates, infection control often depends on natural ventilation. The efficacy of natural ventilation has not been studied, but it probably depends heavily on climatic conditions. In warm climates, patients spend much of their time outdoors where transmission is highly unlikely. However, at night, for security and warmth, patients stay indoors with doors and windows usually closed tightly. Thus, patients in sub-Saharan Africa (warm climate) and in Siberia (cold climate) may endure similar high-risk conditions, at least some of the time. The use of extraction fans to improve ventilation in closed rooms through wall vents can be extremely useful. Mechanical ventilation systems are uncommon in resource-poor settings and, when present, are often poorly maintained. However, a little ventilation is better than none, and in facilities with mechanical ventilation systems, efforts should be made to ensure that they function correctly. Clinics in warm climates should be designed without interior hallways, which tend to trap air and with waiting areas that are open on at least three sides.

Ventilation can be supplemented with upper-room UVGI. This has long been known to be extremely effective in inactivating infectious particles in the air above people's heads, while not exposing them to skin or eye irritation, which is the only practical safety concern. Normal convection currents or low velocity ceiling fans usually ensure good room air mixing, thereby decontaminating air in the breathing zone. Upper-room UVGI is intended for use

while rooms are occupied, but not to sterilize empty rooms as is commonly done in some parts of the world. It is much more important to decontaminate air while the infectious source and other occupants are present, and upper-room UVGI is designed to do so without significant radiation risks. A growing number of manufacturers of fixtures designed for upper-room use are established in low-income countries and can provide products at relatively low cost. However, there are currently no standards for these products; the buyer should obtain advice from an engineer knowledgeable in the field. In addition to UVGI designed for upper-room use, germicidal UV is sometimes used in ventilation ducts or in fan-driven air sterilizing devices mounted on ceilings or walls, or portable units that can be moved from room to room. However, the efficacy of these systems is limited by the number of air turnovers they can produce, especially in large spaces. By irradiating large volumes of upper room air at one time, upper-room systems have a quantitative advantage, especially when combined with low-velocity ceiling fans to ensure room air mixing. Laboratories that process specimens that may be DR-TB require particularly strict environmental controls.

Personal respiratory protection (special masks)

Because administrative and engineering controls cannot provide complete protection, the third line of defence against nosocomial TB transmission is the use of personal respirators. Personal respirators are fundamentally different from, and more expensive than, the more familiar surgical masks which they resemble. Surgical masks are designed to protect the operating field from relatively large respiratory droplets generated by surgeons and surgical nurses. They are relatively loose fitting and made of paper or cloth; they are not adequate for prevention of TB infection.

Masks that prevent TB transmission are known as “particulate respirators” or simply “respirators”. They are designed to protect the wearer from tiny (1–5 μm) airborne infectious droplets. The filtration media through which air passes must capture these minute particles; most importantly, the respirator must fit tightly on the face, especially around the bridge of the nose. Ideally, respirators should be “fit tested” for individual wearers. In addition to choosing the proper model for each worker, this process serves to educate workers on how to put on their respirators correctly to minimize face-seal leakage. Men with beards cannot be properly fitted with personal respirators. Institutions purchasing respirators are advised to look for models that are specifically designed to protect against TB and that meet international standards of quality. Because they are visible and relatively expensive, it is sometimes assumed that personal respirators alone will prevent TB transmission. However, they cannot be worn continuously and are likely not to be in use when unsuspected TB cases, or unsuspected DR-TB, are encountered. For these reasons, administrative controls that aim to detect and separate cases, and engineering controls that can reduce the risk even for unsuspected cases, are more important.

Role of rapid tests in infection control

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

Management of contacts of MDR-TB patients

Objective

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

Key recommendations

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

General considerations

Opportunities to halt the transmission of resistant mycobacteria in communities and to treat MDR-TB in a timely fashion are often squandered. The main reasons are lack of investigation of contacts of MDR-TB patients, failure to ask patients presenting with active TB disease about any history of exposure to MDR-TB, and lack of access by national treatment programmes to second line regimens and/or DST. Close contacts of MDR-TB patients are defined as people living in the same household, or spending many hours a day together with the patient in the same indoor living space. The available data indicate that close contacts of MDR-TB patients who develop active TB most commonly have drug-resistant disease. While all contacts of TB require investigation, DR-TB requires the most vigilance. Because of the severe risk of morbidity and mortality of XDR-TB, contact tracing of cases of XDR-TB should be given the highest level of alertness and priority. NTPs should consider contact investigation of XDR-TB as an emergency situation.

Management of symptomatic adult contacts of patients with MDR-TB

All close contacts of MDR-TB cases should be identified through contact tracing and evaluated for active TB by a health-care provider. If the contact appears to have active TB disease, culture and DST should be performed. If DST is not available, or while DST results are awaited, an empirical regimen based either on the resistance pattern of the index case or on the most common resistance pattern in the community may be started. Delay in the diagnosis of MDR-TB and start of appropriate treatment can lead to increased morbidity and mortality as well as unchecked amplification and transmission of drug-resistant strains of TB. When investigation of a symptomatic adult contact yields no evidence of TB, a trial of a broad-spectrum antibiotic, particularly one that is not active against TB, such as trimethoprim/sulfamethoxazole, can be used. If the patient continues to have symptoms, chest computed tomography and/or directed bronchoscopy for smear and culture should be considered if available. Where these diagnostic tools are not available or the results are not conclusive, a diagnosis should be based on the clinical information at hand. If the initial investigation is not suggestive of active TB but the contact remains symptomatic, repeat physical examinations, smears and cultures should be performed monthly with repeat chest X-ray as needed.

Management of symptomatic pediatric contacts of patients with MDR-TB

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

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

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

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

Symptomatic paediatric household contacts should receive:

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

Children with MDR-TB who are incorrectly entered in SCC may suffer significant and protracted morbidity as a result of ongoing active disease, with the possibility of lifelong disability or even death. Because children with TB may never become sputum smear-positive, it is reasonable to initiate empirical MDR-TB therapy based on the DST pattern of the contact. If DST of the contact is not available, therapy can be based on the common DST patterns of resistance in the community.

Chemoprophylaxis of contacts of MDR-TB index cases

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

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

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

Management of Logistics Supply

Objectives:

This chapter provides information on the procedures for inventory management of the second-line drugs used in the treatment of drug-resistant TB.

Category IV regimen: second-line anti-TB drugs

Drug management cycle of second-line anti-TB drugs

The management cycle of second-line anti-TB drugs comprises five elements:

-) Drug selection;
-) Quantitative assessment of drug requirements;
-) Management of procurement and distribution;
-) Assurance of drug quality; and
-) Ensuring rational drug use.

**Second-line anti-tuberculosis drugs included in the
WHO Model List of Essential Medicines**

kanamycin	levofloxacin	ofloxacin
cycloserine	amikacin	capreomycin
	ethionamide	<i>p</i>-aminosalicylic acid
While ciprofloxacin has not yet been removed from the WHO Model List of Essential Medicines and second-line anti-tuberculosis drugs, it is no longer recommended for the treatment of any forms of TB		

A number of factors must be considered when selecting second-line anti-TB drugs, including the efficacy of the drugs, success of the treatment regimen, adherence, the treatment strategy, possible side effects, and the cost of the treatment.

Accurate demand forecasting of second-line anti-TB drugs, i.e. correct quantification of the drug needs for a specific period of time, is one of the elements that guarantees an uninterrupted drug supply.

There are two main approaches for demand forecasting:

- Usually, the most precise method for demand forecasting is the consumption based approach, consisting of projection of future needs based on records of past consumption of individual drugs. This method assumes that the data are complete, accurate, and properly adjusted for stock-outs and anticipated changes in demand and use. This method is recommended once DOTS-Plus activities have been established for a period of time.
- The morbidity-based approach method is recommended for the initial phase of DOTS Plus activities. In this method, the re-treatment regimen (the number of patients to be treated with each regimens are taken into account.

Several other key factors must also be considered, including the existing stock, lead time for delivery, safety stock needed and the shelf lives of the drugs. Shelf-lives of second-line drugs is shorter than those of first-line drugs, ranging from 18 to 36 months. It is recommended that stock should be sufficient for a period of 2–3 times the delivery delay.

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

In the initial years, the drugs for the treatment of MDR TB patients will be supplied directly to the DOTS-Plus site by National TB Control Programme.

Drug supply to patient will be according to National guideline on Logistic system for second line drugs. As for example from India, as described as below:

Drugs for 3 months duration (inclusive of the dosages received at the hospital and at the time of discharge) shall be issued to the District tuberculosis officer (DTO)/ representative. In the Intensive Phase (IP) period, the drugs shall be issued to the DTO / representative in 3 monthly supplies. Before the consumption of this stock of drugs, i.e. in the beginning of the 3rd month, the DTO/ representative shall collect the drugs for the subsequent 3 months from the state level DOTS-Plus site. If the IP of the patient is required to be extended, the state level DOTS-Plus site committee shall inform the DTO who themselves or through their representative, will collect the drugs for the treatment extension of up to 3 months duration. In case, the extended IP of the patient is continued for the full 3 months, the drugs for Continuation Phase (CP) will be collected by the DTO / representative during the 9th month of treatment. Otherwise, when the state level DOTS Plus site committee takes a decision to

switch the patient on to the CP, the DTO shall be notified who them self or through their representative, will collect the drugs for initiation of CP. The drugs in the CP shall be issued for a period of 6 months. During the period between when the DTO has been notified of the decision to change over to CP and collection and delivery of drugs, the patient's IP shall be continued until the drugs for the CP are delivered. When the patient is initiated on the CP, the DTO shall return any left over drugs from the IP of the extension period to the state level DOTS-Plus site. Before consumption of the 6 months supply of the CP i.e. in the beginning of the 6th month of CP, the DTO shall get the drugs collected for another 6 months and so on until completion of the CP.

The quality assurance component of the NTCP drug supply system makes certain that each drug used by a patient is safe, efficacious, and has appropriate standards of quality.

Under NTCP, the second-line anti-TB drugs will be procured at the national level annually, with 6 monthly supply lots. After the initial 2 years of implementation, drugs will be delivered from the manufacturer to the respective logistic division of National programme. From the logistic division, need based release to DOTS-Plus sites would be made every quarter based on the submission of reports.

NTCP will assist the sites in storing of drug supplies by providing guidelines for drug stores at the respective sites. Oral drugs will be supplied in single drug blister strips, in individual boxes. These will be re-packed into individual boxes containing drug requirements for 3 months in the IP and 6 months in the CP.

Drugs will be supplied to cover three months requirements of a patient in the intensive and 6 months in continuation phases of treatment. PAS will also be procured and supplied to deal with patients who need individual drugs substitution due to adverse drug reactions

Main elements to consider when planning Procurement of second-line anti-TB drugs

<input type="checkbox"/> Drug forecast based on treatment regimen, cohort size and expected cases to be treated in 1 year.
<input type="checkbox"/> Drug labeling
<input type="checkbox"/> Shelf-life of the products
<input type="checkbox"/> Lead-time for delivery of full drug request
<input type="checkbox"/> Delivery period
<input type="checkbox"/> No. of Supply Lots
<input type="checkbox"/> Estimated size of buffer stock

Recording and Reporting

This chapter describes the information system for Category IV patients, with the objective of recording information needed to monitor programme performance and treatment outcomes. It presents the instruments and minimum variables necessary to implement and monitor Category IV treatment. Tools are also introduced to track screening and enrolment efforts. Lastly, the chapter presents additional optional components.

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

Aims of the information system and performance indicators

The aims of the information system are two folds:

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

The performance indicators include:

- The number of patients at risk of developing MDR TB
- The number of patients in whom MDR-TB is detected in the laboratory.
- The number of MDR-TB patients started on treatment.
- Interim treatment outcome at 6-months of MDR-TB cases.
- Final outcome of MDR-TB treatment.

Scope of the information system

The information system for treatment of DR-TB is based upon, and is an extension of, the basic DOTS information system. The forms have therefore been designed to be as similar as possible to the standard forms used in DOTS programmes. The core information system should be consistent across settings to permit comparison. The forms may be modified as necessary to suit the local context. For instance, additional variables that are considered valuable in specific situations can be included.

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

Main forms/register and flow of information

The forms and registers include the following:

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

Reports include:

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

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

When Category IV treatment is being introduced, there may be a large group of patients who are still sputum smear-positive after supervised Category II treatment from previous years. There may also be patients who have received several unsuccessful treatments, are considered incurable by health staff and who have lived with active TB disease with no or inadequate treatment for a period of time. While preparing for Category IV treatment, TB control programmes should keep a list of these patients. When Category IV treatment becomes available, such cases with evidence of active disease should follow the national protocol for Category IV treatment start, ideally having a DST done at the start to confirm MDR-TB. The number of patients waiting for Category IV treatment should be estimated in all programmes, as this will facilitate planning of drug and other resource needs. As the Category IV treatment programme progresses, the list of chronic cases will become smaller and eventually include only patients who have failed Category IV treatment.

Assuring the quality of the recording and reporting system

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

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

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

Computerized systems

The recording and reporting system can be managed by hand. However, an electronic system is highly desirable since it facilitates better quality of information as well as data analysis; it will also obviate the need for transcription and repeated entry into different forms. Patient data may be entered in a format similar to the Category IV Treatment Card, and lists similar to the Category IV Register can then be generated. Print-outs of the list may be compared with the handwritten Category IV Register to ensure completeness of the system. The corrected database may then be used to generate quarterly and annual reports.

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

ANNEX I

I Adverse effects, suspected agent(s) and management strategies

ADVERSE EFFECT	SUSPECTED AGENT(S)	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Seizures	Cs, H, fluoroquinolones	<ol style="list-style-type: none"> 1. Suspend suspected agent pending resolution of seizures. 2. Initiate anticonvulsant therapy (e.g. phenytoin, valproic acid). 3. Increase pyridoxine to maximum daily dose (200 mg per day). 4. Restart suspected agent or reinitiate suspected agent at therapy, lower dose, if essential to the regimen. 5. Discontinue suspected agent if this can be done without compromising regimen. 	<ol style="list-style-type: none"> 1. Anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agent discontinued. 2. History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well controlled and/or the patient is receiving anticonvulsant therapy. 3. Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy.
Peripheral neuropathy	Cs, H, S, Km, Am, Cm, Vi, Eto/ Pto, fluoroquinolones	<ol style="list-style-type: none"> 1. Increase pyridoxine to maximum daily dose (200 mg per day). 2. Change injectable to Capreomycin if patient has documented susceptibility to capreomycin. 3. Initiate therapy with tricyclic antidepressants such as amitriptyline. Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms. 4. Lower dose of suspected agent, if this can be done without compromising regimen. 5. Discontinue suspected agent if this can be done without compromising regimen. 	<ol style="list-style-type: none"> 1. Patients with co-morbid disease (e.g. diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here. 2. Neuropathy may be irreversible; however, some patients may experience improvement when offending agents are suspended.

Hearing loss	S, Km, Am, Cm, Clr	<ol style="list-style-type: none"> 1. Document hearing loss and compare with baseline audiometry if available. 2. Change parenteral treatment to capreomycin if patient has documented susceptibility to capreomycin. 3. Increase frequency and/or lower dose of suspected agent if this can be done without compromising the regimen (consider administration three times per week). 4. Discontinue suspected agent if this can be done without compromising the regimen. 	<ol style="list-style-type: none"> 1. Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of MDR-TB therapy. 2. Hearing loss is generally not reversible. 3. The risk of further hearing loss must be weighed against risks of stopping the injectable in the treatment regimen.
Psychotic symptoms.	Cs, H, fluoro-Quinolones, Eto/Pto	<ol style="list-style-type: none"> 1. Stop suspected agent for a short period of time (1–4 wks.) while psychotic symptoms are brought under control. 2. Initiate antipsychotic therapy. 3. Lower dose of suspected agent if this can be done without compromising regimen. 4. Discontinue suspected agent if this can be done without compromising regimen. 	<ol style="list-style-type: none"> 1. Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy. 2. Previous history of psychiatric disease is not a contraindication to the use of agents listed here but may increase the, psychotic symptoms developing during treatment. 3. Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending
Depression	Socio-economic circumstances, chronic disease, Cs, fluoro-quinolones H, Eto/pto	<p>Improve socio economic conditions Group or individual counseling initiate antidepressant therapy lower dose of suspected agent if this can be done without compromising the regimen Discontinue suspected agent if this can be done without compromising regimen</p>	<ol style="list-style-type: none"> 1. Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression. 2. Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated. 3. History of previous depression is not a contraindication to the use of the agents listed but may increase the likelihood of depression developing during treatment.

Hypo-thyroidism	PAS, Eto/ Pto	1. Initiate thyroxine therapy	1. Completely reversible upon discontinuation of PAS ethionamide/protionamide.
Nausea and vomiting	Eto/Pto, PAS, H, E,Z,	1. Assess for dehydration; initiate rehydration if indicated 2. Initiate antiemetic therapy 3. Lower dose of suspected agent, if this can be done without compromising regimen 4. Discontinue suspected agent if this can be done compromising regimen – rarely necessary	1. Nausea and vomiting universal in early weeks of therapy and PAS, and usually abate with time on treatment and adjunctive 2. Electrolytes should be monitored and repleted if vomiting is severe. 3 Reversible upon discontinuation of suspected agent. 4. Severe abdominal distress and acute abdomen have been reported with the use of clofazimine. Although these reports are rare, if this effect occurs, clofazimine should be suspended
Gastritis	PAS, Eto/Pto	1. H2-blockers, proton-pump inhibitors, or antacids.. 2. Stop suspected agent(s) for short periods of time (e.g, one to seven days). 3. Lower dose of suspected agent, if this can be done without compromising regimen. medications). 4. Discontinue suspected agent if this can be done without compromising regimen.	1. Severe gastritis, as manifested by haematemesis, melaena or haematechezia, is rare 2. Dosing of antacids should be carefully timed so as to not interfere with the absorption of anti-tuberculosis drugs (take 2 hours before or 3 hours after anti-tuberculosis. 3. Reversible upon discontinuation of suspected agent(s)

ADVERSE EFFECT	SUSPECTED AGENT(S)	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Hepatitis	Z, H, R, Eto/Pto, PAS, E, fluoro- quinolones	<ol style="list-style-type: none"> 1. Stop all therapy pending resolution of hepatitis. 2. Eliminate other potential causes of hepatitis. 3. Consider suspending most likely agent. Reintroduce remaining drugs, one at a time with the most hepatotoxic agents first, while monitor liver function. 	<ol style="list-style-type: none"> 1. History of previous hepatitis should be carefully analyzed to determine most likely causative agent(s); these should be avoided in future regimens 2. Generally reversible upon discontinuation of suspected agent.
Renal	S, Km, Am, Cm, Vm	<ol style="list-style-type: none"> 1. Discontinue suspected agent. 2. Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen. 3. Consider dosing 2 to 3 times a week if drug is essential to the regimen and patient can tolerate (close monitoring of creatinine). 4 Adjust all TB medications according to the creatinine clearance. 	<ol style="list-style-type: none"> 1. History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these co-morbidities may be at increased risk for developing renal failure. 2. Renal impairment may be permanent.

<p>Rash, allergic reaction and anaphylaxis</p>	<p>Any drug</p>	<ol style="list-style-type: none"> 1. For serious allergic reactions, stop all therapy pending resolution of reaction. In the case of anaphylaxis manage with standard emergency protocols. 2. Eliminate other potential causes of allergic skin reactions (like scabies or other environmental agents). 3. For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They include • Antihistamines • Hydrocortisone cream for localized rash • Prednisone in a low dose of 10 to 20 mg per day for several weeks can be tried if other measures are not helpful • Phototoxicity may respond to sunscreens, but these can also cause rash • Dry skin may cause itching (especially in diabetics), liberal use of moisturizing lotion is recommended. Dry skin is a common and significant problem with clofazimine. 4. Once the rash resolves, reintroduce remaining drugs, one at a time with the one most likely to cause the reaction last. Consider not reintroducing even as a challenge any drug that is highly likely to be the cause. 5. Suspend permanently any drug identified to be the cause of a serious reaction. 	<ol style="list-style-type: none"> 1. History of previous drug allergies should be carefully reviewed. Any known drug allergies should be noted on the treatment card. 2. Flushing reaction to rifampicin or pyrazinamide is usually mild and resolves with time. Antihistamines can be used. Hot flushes, itching, palpitations can be caused with isoniazid and tyramine- containing foods (cheese, red wine). If this occurs advise patients to avoid foods that precipitate the reaction. 3. Any of the drugs can cause hives (urticaria). To identify the drug, introduce the drugs one at a time. In the case of hives a desensitization attempt can be made (methods are described elsewhere . 4. Any drug that resulted in anaphylaxis or Stevens– Johnson syndrome should never be reintroduced, not even as a challenge.
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<p>Nausea and vomiting</p>	<p>Eto, Pto, PAS, Bdq H, E, Z, Amx/Clv, Cfz</p>	<p>Assess for danger signs including dehydration, electrolyte disturbances and hepatitis. Initiate rehydration therapy if indicated and correct any electrolyte disturbances. If there is blood in the vomit, check haemoglobin and treat for possible bleeding ulcers. 2. Initiate a stepwise approach to manage nausea and vomiting.</p> <ul style="list-style-type: none"> • Phase 1: Adjust medications and conditions without lowering the overall dose: –Give Eto/Pto at night –Give Eto or PAS twice or thrice daily –Give a light snack (biscuits, bread, rice, tea) before the medications –Give PAS two hours after other anti-TB drugs. <p>Phase 2: Start antiemetic(s): –Metoclopramide 10 mg, 30 minutes before anti-TB medications. –Ondansetron 8 mg, 30 minutes before the anti-TB drugs and again eight hours after. Ondansetron can either be used on its own or with metoclopramide. (If ondansetron is not available, promethazine can be used.) For refractory nausea give 24 mg, 30 minutes before the dose can be tried.</p> <p>Phase 3: Decrease dose of the suspected drug by one weight class if this can be done without compromising the regimen. It is rarely necessary to suspend the drug completely.</p>	<ol style="list-style-type: none"> 1. Nausea and vomiting are universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy. Some nausea and even vomiting may need to be tolerated at least in the initial period. 2. Creatinine and electrolytes should be checked if vomiting is severe. Give intravenous fluids and replace electrolytes as needed. 3. Another strategy is to stop the responsible medicine for two or three days and then add it back gradually increasing the dose (advise the patient that the medicine will be increased back to a therapeutic dose in a manner that will be better tolerated). 4. Ondansetron is a serotonin 5-HT₃ receptor antagonist and considered to have strong antiemetic properties. It is on the WHO essential drug list. A number of other antiemetics from this class of serotonin 5-HT₃ receptor antagonists exist. Trying different antiemetics, even if from the same class may be helpful for some patients. Ondansetron prolongs the QT interval; avoid with bedaquiline. 5. For patients particularly anxious about the nausea, (and with “anticipatory nausea and vomiting”) a small dose of an anti-anxiety medicine (5 mg of diazepam) can help when given 30 minutes prior to the intake of anti-TB drugs.
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Gastritis and abdominal pain	PAS, Eto, Pto, Cfz, FQs, H, E, and Z	<p>1. Abdominal pain can also be associated with serious adverse effects, such as pancreatitis, lactic acidosis and hepatitis. If any of these are suspected, obtain appropriate laboratory tests to confirm and suspend the suspected agent. 2. If symptoms are associated consistent with gastritis (epigastric burning or discomfort, a sour taste in mouth associated with reflux) initiate medical therapy with the use of H2-blockers (ranitidine 150 mg twice daily or 300 mg once daily) or proton-pump inhibitors (omeprazole 20 mg once daily). Avoid the use of antacids as they decrease absorption of fluoroquinolones. 3. For severe abdominal pain stop suspected agent(s) for short periods of time (one to seven days). 4. Lower the dose of the suspected agent, if this can be done without compromising the regimen. 5. Discontinue the suspected agent if this can be done without compromising the regimen.</p>	<p>1. Severe gastritis, as manifested by blood in the vomit or stool is relatively rare. 2. If antacids must be used, they should be carefully timed so as to not interfere with the absorption of fluoroquinolones (take two hours before or three hours after anti-TB drugs). 3. Stop any nonsteroidal anti-inflammatory drugs the patient may be taking. 4. Diagnose and treat for <i>Helicobacter pylori</i> infections. 5. Severe abdominal distress has been reported with the use of clofazimine. Although these reports are rare, if this occurs, clofazimine should be suspended.</p>
Diarrhoea and/or flatulence	PAS, Eto/Pto	<p>1. Encourage patients to tolerate some degree of loose stools and flatulence. 2. Encourage fluid intake. 3. Treat uncomplicated diarrhoea (no blood in stool and no fever) with loperamide 4 mg by mouth initially followed by 2 mg after each loose stool to a maximum of 10 mg per 24 hours. 4. Check serum electrolytes (especially potassium) and dehydration status if diarrhoea is severe. 5. Fever and diarrhoea and/or blood in the stools indicate that diarrhoea may be</p>	<p>1. Consider other causes of diarrhoea: • Pseudo-membranous colitis related to broad-spectrum antibiotics (such as the fluoroquinolones) is a serious and even life threatening condition. Fever, bloody diarrhoea, intense abdominal pain and increased white blood cells are warning signs of possible pseudo- membranous colitis. • Parasites and common waterborne pathogens in the area should be evaluated in the patient</p>

		secondary to something other than the simple adverse effect of anti-TB drugs.	and treated. • Lactose intolerance, especially if patient has been exposed to new foods in a hospital not normally part of their diet. 2. Loperamide can be used in children over two years of age.
Hepatitis	Z, H, R, Pto / Eto, and PAS	1. If enzymes are more than five times the upper limit of normal, stop all hepatotoxic drugs and continue with at least three non hepatotoxic medications (for example, the injectable agent, fluoroquinolone and cycloserine). If hepatitis worsens or does not resolve with the three-drug regimen, then stop all drugs. 2. Eliminate other potential causes of hepatitis (viral hepatitis and alcohol induced hepatitis being the two most common causes) and treat any that is identified. 3. Consider suspending the most likely agent permanently. Reintroduce remaining drugs, one at a time with the least hepatotoxic agents first, while monitoring liver function by testing the enzymes every three days, and if the most likely agent is not essential consider not reintroducing it.	1. History of previous drug hepatitis should be carefully analysed to determine the most likely causative agent(s); these drugs should be avoided in future regimens. 2. Viral serology should be done to rule out other aetiologies of hepatitis if available, especially to hepatitis A, B and C. 3. Alcohol use should be investigated and alcoholism addressed. 4. Generally, hepatitis due to medications resolves upon discontinuation of the suspected drug.
Hypo- thyroidism	PAS, Eto/ Pto	1. Most adults will require 100–150 mcg of levothyroxine daily. Start levothyroxine in the following manner: • Young healthy adults can be started on 75–100 mcg daily • Older patients should begin treatment with 50 mcg daily •	1. Symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, as well as occasional depression and inability to concentrate. 2. Do not start treatment unless

		<p>Patients with significant cardiovascular disease should start at 25 mcg daily. 2. Monitor TSH every one to two months and increase the dose by 12.5–25 mcg until TSH normalizes. Adjust the dose more slowly in the elderly and in patients with cardiac conditions.</p>	<p>TSH is above 1.5– 2.0 times of the upper normal limit. 3. It is completely reversible upon discontinuation of PAS and/or ethionamide/protionamide. 4. The combination of ethionamide/protionamide with PAS is more frequently associated with hypothyroidism than when each individual drug is used.</p>
Arthralgia	Z, Bdq, Fluoroquinolones	<p>1. Initiate therapy with nonsteroidal anti-inflammatory drugs (indomethacin 50 mg twice daily or ibuprofen 400 to 800 mg three times a day). 2. Lower the dose of the suspected agent (most commonly pyrazinamide) if this can be done without compromising the regimen. 3. Discontinue the suspected agent if this can be done without compromising the regimen.</p>	<p>1. Symptoms of arthralgia generally diminish over time, even without intervention. 2. Uric acid levels may be elevated in patients on pyrazinamide. There is little evidence to support the addition of allopurinol for arthralgias, although if gout is present it should be used. 3. If acute swelling, redness and warmth are present in a joint, consider aspiration for diagnosis of gout, infections, autoimmune diseases, etc.</p>
Tendonitis and tendon rupture	Fluoroquinolones	<p>1. If significant inflammation of tendons or tendon sheaths occur: • Consider stopping fluoroquinolones • Give a non steroidal anti-inflammatory drug (ibuprofen 400 mg four times daily) • Rest the joint. 2. If treatment failure is likely without the fluoroquinolone • Reduce dose if possible • Ensure joint is strictly rested • Inform patient of the possible risk of tendon rupture and discuss the risks and benefits of ongoing use of the fluoroquinolone.</p>	<p>1. Tendon rupture with fluoroquinolone use is more likely in patients doing new physical activities and more common among older patients and diabetics. 2. Tendon rupture is relatively rare in patients on MDR-TB regimens with fluoroquinolones.</p>

<p>Electrolyte disturbances (hypokalaemia and hypomagnesaemia)</p>	<p>Cm, Km, Am, S</p>	<p>Check potassium. 2. If potassium is low, also check for magnesium and calcium (if unable to check for magnesium, consider empiric treatment with magnesium in all cases of hypokalaemia). 3. Replace electrolytes as needed. Dose oral electrolytes apart from fluoroquinolone as they can interfere with fluoroquinolone absorption.</p> <p>Also see Annex 7 – Management of electrolyte disturbances</p>	<p>1. If severe hypokalaemia is present, consider hospitalization. 2. Amiloride, 5–10 mg daily, or spironolactone, 25 mg daily, may decrease potassium and magnesium wasting, and thus useful in refractory cases. 3. Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhoea.</p>
<p>Nephrotoxicity (renal toxicity)</p>	<p>S, Km, Am, Cm</p>	<p>1. Discontinue the suspected agent.</p> <p>2. Consider using capreomycin if an aminoglycoside had been the prior injectable drug in the regimen.</p> <p>3. Consider other contributing aetiologies (non steroidal anti-inflammatory drugs, diabetes, other medications, dehydration, congestive heart failure, urinary obstruction, etc.) and address as indicated.</p> <p>4. Follow creatinine (and electrolyte) levels closely, every one to two weeks. 5. Consider dosing the injectable agent two to three times a week if the drug is essential to the regimen and the patient can tolerate (close monitoring of creatinine). If the creatinine continues to rise despite twice/thrice a week dosing, suspend the injectable agent. 5. Adjust all TB medications according to the creatinine clearance.</p>	<p>1. History of diabetes or renal disease is not a contraindication to the use of agents listed here, although patients with these comorbidities may be at increased risk for developing renal failure.</p> <p>2. An example of how to calculate a creatinine clearance based on the serum creatinine is provided in Chapter 7, Box 7.2.</p> <p>3. Renal impairment may be permanent.</p>

Vestibular toxicity (tinnitus and dizziness)	S, Km, Am, Cm, Cs, FQs, H Eto, Lzd	1. If early symptoms of vestibular toxicity appear, change the dosing of the injectable agent to twice/thrice a week. Also, consider using capreomycin if an aminoglycoside had been the prior injectable in the regimen. 3. If tinnitus and unsteadiness worsen with the above adjustment, stop the injectable agent. This is one of the few adverse reactions that cause permanent intolerable toxicity and can necessitate discontinuation of a class of agents.	1. Ask the patient about tinnitus and unsteadiness every week. 2. Fullness in the ears and intermittent ringing are early symptoms of vestibular toxicity. 3. A degree of disequilibrium can be caused by Cs, FQs, Eto/Pto, INH or linezolid. Some clinicians will stop all drugs for several days to see if symptoms are attributed to these drugs. Symptoms of vestibular toxicity generally do not improve on withholding medications.
Hearing loss (also see vestibular toxicity above)	S, Km, Am, Cm, Clr	1. Document hearing loss and compare with baseline audiogram if available. (Some degree of hearing loss occurs with most patients starting with high frequency loss.) 2. If early symptoms of hearing loss are documented, change the dosing of the injectable agent to twice/thrice a week. Also, consider using capreomycin if an aminoglycoside had been the prior injectable in the regimen. 3. Discontinue the injectable agent if hearing loss continues despite dose adjustment and add additional drugs to reinforce the regimen. Even when additional drugs are not available, stopping the injectable agent can be considered based on the patient's desire to maintain hearing. Also see Annex 7 – Management of hearing loss	1. Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of MDR-TB therapy. 2. Hearing loss is almost always permanent. Continuing the injectable agent despite hearing loss almost always results in irreversible deafness. 3. While the benefit of hearing aids is minimal to moderate in auditory toxicity, consider a trial use to determine if a patient with hearing loss can benefit from their use.
Peripheral neuropathy	Cs, Lzd, H, S, Km, Amk, Cm, H, Fluoroquinolones, rarely Pto/Eto, E	1. Correct any vitamin or nutritional deficiencies. Increase pyridoxine to the maximum daily dose (200 mg per day). 2. Consider whether the dose of cycloserine can be reduced without compromising the regimen. If isoniazid is being used (especially high dose isoniazid), consider stopping it. If possible,	1. Patients with comorbid disease (e.g. diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here. 2. Neuropathy may be

		<p>switching the aminoglycoside to capreomycin may also be helpful. 3. Initiate medical therapy: • Nonsteroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms. • Therapy with tricyclic antidepressants such as amitriptyline (start with 25 mg at bedtime, the dose may be increased to a maximum of 150 mg) can be tried. Do not use tricyclic antidepressants with selective serotonin reuptake inhibitors and antidepressant drugs. • Carbamazepine, an anticonvulsant, at 100 to 400 mg twice daily can be tried. • Gabapentin (used off-label) at 300 mg thrice a day; it can be used at a maximum dose of 3600 mg/day in three or four divided doses. 4. Rarely, medication may be discontinued, but only if an alternative drug is available and the regimen is not compromised.</p>	<p>irreversible but many patients experience improvement when the offending agents are suspended. The neuropathy associated with linezolid is common after prolonged use and often permanent. For this reason, suspension of this drug should be strongly considered when neuropathy develops due to linezolid.</p>
Headache	Cs, Bdq,	<p>Rule out more serious causes of headache including meningitis, and other infections of the central nervous system. (HIV coinfecting patients should receive a head computed tomography scan and cerebrospinal fluid analysis.) Start analgesics like ibuprofen or paracetamol. Also encourage good hydration. Consider low dose tricyclic antidepressants for refractory headaches.</p>	<p>Headaches are common during the initial months of MDR-TB therapy. They can present as migraine or cluster headaches. 2. To minimize headaches at the start of therapy, cycloserine can be started at lower doses of 250– 500 mg and gradually increased over one to two weeks to achieve the target dose. 3. Headaches due to cycloserine and bedaquiline are usually self-limited. 4. Pyridoxine (vitamin B6) should be given to all patients receiving cycloserine to help prevent neurotoxicity. The recommended dose is 50 mg for every 250 mg of cycloserine prescribed.</p>

Depression	Socioeconomic circumstances, chronic disease, Cs, fluoroquinolones, H, Eto/Pto	1. Assess and address underlying socioeconomic issues (see Chapter 12 on Social support). 2. Assess patients for coexisting substance abuse and refer to treatment if appropriate. 3. Initiate individual counselling (or group counselling if the patient is sputum smear and culture negative). 3. When depression is more significant, initiate antidepressant therapy (amitryptiline, fluoxetine or similar). Tricyclic antidepressants and selective serotonin reuptake inhibitors should be given together and should not be given to patients on linezolid. 4. Lower the dose of the suspected agent if this can be done without compromising the regimen. (Reducing the dose of cycloserine and ethionamide to 500 mg daily to see if the depression is lessened is a common strategy). 5. Discontinue the suspected agent if this can be done without compromising the regimen.	1. Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression. 2. Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated. 3. History of previous depression is not a contraindication to the use of agents listed but may increase the likelihood of depression developing during treatment. If significant depression is present at the start of treatment, avoid a regimen with cycloserine, if possible. 4. Question the patient regarding suicidal ideation any time the depression is judged to be more than mild.
Suicidal ideation	Cs, H, Eto/Pto	1. Hospitalize the patient and put under 24-hour surveillance. 2. Discontinue cycloserine. 3. Request psychiatric consultation. 4. Initiate antidepressant therapy. 5. Lower the dose of Eto/Pto to 500 mg daily until the patient is stable.	1. Keep the patient in the hospital until risk of suicide has passed. 2. If no improvement occurs after holding cycloserine, hold H and/or Eto/Pto.
Psychotic symptoms	Cs, H, fluoroquinolones	1. Stop the suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control. The most likely drug is cycloserine followed by high dose isoniazid. 2. If moderate to severe symptoms persist, initiate antipsychotic therapy (haloperidol). 3. Hospitalize in a ward with psychiatric expertise if patient is at risk to himself/herself or others. 4. Increase pyridoxine to the maximum daily dose (200 mg per day). 5. Lower	1. Some patients will need to continue antipsychotic treatment throughout MDR-TB treatment (and discontinued upon completion of treatment). 2. Previous history of psychiatric disease is not a contraindication to cycloserine, but its use may increase the likelihood of psychotic symptoms developing during treatment. 3. Some patients will tolerate cycloserine with

		<p>the dose of the suspected agent (most commonly cycloserine to 500 mg a day) if this can be done without compromising the regimen. 6. Discontinue the suspected agent if this can be done without compromising the regimen. 7. Once all symptoms resolve and patient is off cycloserine, antipsychotic therapy can be tapered off. If cycloserine is continued at a lower dose, antipsychotic therapy may need to be continued and any attempts of tapering off should be done after referring to a psychiatrist trained in the adverse effects of second-line anti-TB drugs.</p>	<p>an antipsychotic drug but this should be done in consultation with a psychiatrist, as these patients will need to be under special observation; this should only be done when there is no other alternative. 4. Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent. 5. Always check creatinine in patients with new onset psychosis. A decrease in renal function can result in high blood levels of cycloserine, which can cause psychosis.</p>
Seizures	Cs, H, fluoroquinolones	<p>1. Hold cycloserine, fluoroquinolones and isoniazid pending resolution of seizures. 2. Initiate anticonvulsant therapy (carbamazepine, phenytoin or valproic acid are most commonly used). 3. Increase pyridoxine to the maximum daily dose (200 mg per day). 4. Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium and chloride. 5. When seizures have resolved, restart medications one at a time. Cycloserine should not be restarted unless it is absolutely essential to the regimen. If cycloserine is reinitiated, start a dose one weight band lower.</p>	<p>1. An anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agent is discontinued. 2. History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well controlled and/ or the patient is receiving anticonvulsant therapy. (Do not include cycloserine if an alternative drug is available.) 3. Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy. 5. Always check creatinine in patients with new onset seizures. A decrease in renal function can result in high blood levels of cycloserine, which can cause seizures. Adjusting the dose of cycloserine in the presence of low creatinine may be all that is needed to control the seizures.</p>

Optic neuritis	E, Eto/Pto, Lzd, Cfz, rifabutin, H, S	1. Stop ethambutol. Do not restart. 2. Refer patient to an ophthalmologist.	1. The most common drug responsible is ethambutol and it usually reverses with cessation of the drug. 2. Improve diabetes control in diabetic patients.
Metallic	tasteEto/Pto, Clr, FQs	1. Encourage the patient to tolerate this side effect. 2. Sucking hard candy or chewing gum can be helpful.	1. Normal taste returns when treatment is stopped.
Gynaecomastia	Eto/Pto	1. Breast enlargement can be a troublesome side effect of Eto/Pto therapy, especially for male patients. Galactorrhoea has also been reported. 2. Encourage patients to tolerate this side effect.	1. Resolution occurs after treatment is stopped.
Alopecia	H, Eto/Pto	1. Hair loss can occur or there can be significant thinning of the hair, but this is temporary and not progressive during treatment. 2. Encourage patients to tolerate this side effect.	1. Significant cosmetic change has not been reported.
Superficial fungal infection and thrush	Fluoroquinolones and other antibiotics with antibacterial properties	1. Topical antifungal agents or short-course oral antifungal drugs are helpful. 2. Exclude other diseases if response to treatment is not prompt (such as HIV).	1. Vaginal or penile candidiasis, oral thrush or cutaneous candidiasis in skin folds may occur with antibiotic treatment.
Lactic acidosis	Lzd	1. Stop linezolid if lactic acidosis occurs.	1. Lactic acidosis can be monitored with a blood test that measures lactic acid.
Dysglycaemia and hyperglycaemia	Gfx, Eto/Pto	1. Stop gatifloxacin and replace with different later-generation fluoroquinolone like moxifloxacin. 2. Treat diabetes as needed. Good glucose control is important during treatment.	
QT prolongation	Bdq, fluoroquinolones,	Any patient found to have a QTc value greater than 500 ms should be managed carefully. • Repeat ECG and confirm the prolongation. • Bedaquiline should	1. The QT interval is measured from the end of the QRS complex to the beginning of the T wave on a standard ECG. The QT is

	clarithromycin clofazimine	be stopped for QTc value greater than 500 ms. Consider stopping other drugs that prolong the QT interval. • Check potassium, calcium and magnesium levels. Electrolyte levels should be maintained in the normal range. • It is suggested to maintain potassium levels of more than 4 mEq/l and magnesium levels of more than 1.8 mg/dl. • Avoid other drugs that increase the QT interval. Monitor the patient's renal and hepatic function and adjust the dose of fluoroquinolones if impairment is present. Consider suspension of fluoroquinolone if risk of torsades de pointes outweighs the benefits of the drug. Also see Annex 4 for more information on QT interval monitoring with bedaquiline.	corrected for heart rate, which is referred to as the QTc and calculated by most ECG machines. A normal QTc is generally <440 ms. 2. Values above QTc 440 ms are referred to as prolonged. Patients with prolonged QTc are at risk for developing cardiac arrhythmias like torsades de pointes, which can be life threatening. Patients with QTc greater than 500 ms are at the greatest risk for developing these arrhythmias. 3. The fluoroquinolones cause prolongation of the QTc. Moxifloxacin and gatifloxacin cause the greatest QTc prolongation, while levofloxacin and ofloxacin have a lower risk. 4. Currently, ECG monitoring prior to initiation and during MDR-TB therapy is only required with the use of bedaquiline.
Haematological abnormalities	Lzd	Stop linezolid if myelosuppression (suppression of white blood cells, red blood cells or platelets) occurs. Consider restarting with a lower dose of linezolid (300 mg instead of 600 mg) if myelosuppression resolves and if linezolid is considered essential to the regimen. Consider nondrug related causes of the haematological abnormality. Consider blood transfusion for severe anaemia.	1. Haematological abnormalities (leukopenia, thrombocytopenia, anaemia, red cell aplasia, coagulation abnormalities, and eosinophilia) can rarely occur with a number of other anti-TB drugs. (See individual drug sheets, Part 3.) 2. There is little experience with prolonged use of linezolid.

Pharmacovigilance in programmatic management of drug-resistant TB

Pharmacovigilance is defined by WHO as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem”. Many of the second-line anti-TB drugs are more prone to cause toxic reactions in patients than first-line drugs, making pharmacovigilance more important in the programmatic management of drug-resistant TB. By recording the occurrence of adverse drug reactions for patients on treatment, many programmes are already undertaking basic data collection inherent to pharmacovigilance. However, the collection of such data and the measurement of indicators on pharmacovigilance are not part of the standard parameters used in monitoring of TB patients on treatment. Consequently, in most programmes, the nature and frequency of harms caused by the drugs themselves are poorly profiled and can only be inferred indirectly from the interruption or failure of treatment. As programmes start to incorporate newly released drugs into treatment regimens, WHO recommends that they also improve their capacity to undertake pharmacovigilance.

This section provides some introductory advice on pharmacovigilance; for more details refer to A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis (7) (called the pharmacovigilance handbook for short in this section). The pharmacovigilance handbook provides a step-by-step approach to undertaking the pharmacovigilance of anti-TB drugs, explaining the different methodologies and how to make inferences based on the findings. This document contains a list of other general WHO publications (8,9) and non WHO resources on pharmacovigilance. Before embarking on pharmacovigilance activities, TB practitioners, health officials, planners, public health teams, drug regulatory authorities and others should become familiar with these publications.

Good pharmacovigilance will identify the risks within the shortest possible time after the medicine has been marketed and will help to establish or identify risk factors. It will thus support the safe, rational and more effective (and more cost effective) introduction of new anti-TB drugs. Good pharmacovigilance will also pick up adverse effects quicker from the second-line anti-TB drugs in use.

11.4.1 Basic definitions used in pharmacovigilance (7) • Adverse event (AE): Any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment. • Adverse (drug) reaction (ADR): A response to a medicine, which is noxious and unintended, and which occurs at doses normally used in humans. • Risk factor: A characteristic associated with an increased probability of occurrence of an event. In the presence of a risk factor, a patient is more likely to develop an adverse reaction. • Serious reaction: A serious reaction is an adverse drug reaction which involves any of the following: death or a life-threatening experience; hospitalization or prolongation of hospitalization; persistent significant disability; congenital anomaly.

• Signal: Reported information on a possible causal relationship between an adverse event and a medicine; the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information.

Three methods of pharmacovigilance are identified and described in the pharmacovigilance handbook: (i) spontaneous reporting, (ii) targeted reporting, and (iii) cohort event monitoring (CEM) (10). The first two methods can be built into national programmes of routine pharmacovigilance and/or TB control. CEM is an active form of surveillance and is similar in design and management to an epidemiological cohort study with baseline and prospective,

periodic measurement of patient parameters. The guidance and templates in the pharmacovigilance handbook are a useful basis for developing adequate long term monitoring of the outcomes of treatment with new TB drugs. It is recommended that each pharmacovigilance programme follows as much as possible the forms presented in the handbook, and adapts these to the specific programme needs, as collecting data in a similar manner will indeed facilitate the combination of data sets and the interpretation of associations between effects and exposures.

Best practices for data collection and organization of the pharmacovigilance dataset will need to be defined at the country level. It is important that these build upon the existing reporting structures inherent to the programmatic management of drug-resistant TB, particularly the monitoring of patients in annual “cohorts” for the assignment of standard end-of-treatment outcomes.

11.4.2 What to monitor In spontaneous pharmacovigilance, the main object of reporting is an adverse drug reaction, while in cohort-based methods, adverse events are recorded. The detection of serious adverse events, which lead to hospitalization, or prolongation of hospitalization, a persistent significant disability, a congenital anomaly, a life-threatening condition, or death, will be a priority for monitoring. Reporting of serious adverse events as per ICH10 definition is a necessity. All deaths are to be reported and as much information as possible relevant to ascertainment of the cause of death should be consistently collected; this may require recovering information from vital registration coding. Reporting of other adverse events and other events (e.g. pregnancy, lactation exposure) may be required, primarily based on what is known about the safety profile of the new agent and also for other possible harms which have not yet been described.

Of the three methods above, the cohort-based method (i.e. CEM) is the best approach for pharmacovigilance for new anti-TB drugs. Every person receiving the new drug should be registered and data collected on a periodic as well as a sporadic, event-driven basis. A cohort approach is essential to avoid bias in selection of patients or in measurement of events. It is also best suited to infer on the potential association of an event with the given exposure. Lastly, it provides denominators and baseline data for analysis.

Using a cohort-based method will require a set of tools to standardize the collection of data.

- Treatment initiation and Treatment review forms to register baseline and follow-up patient data (Annexes 6 and 7 in the pharmacovigilance handbook): Instructions for the completion of these two forms – including definitions of terms and specifying what, how, when, and how long to report each event or other necessary data elements;
- Forms for the spontaneous reports of suspected adverse drug reaction (Annex 2 in the pharmacovigilance handbook). These are to be completed upon the presumption of a reaction and referred to the national body responsible for pharmacovigilance in the country. Some countries (e.g. Kenya) have developed utilities for the electronic reporting of such episodes; and
- An electronic database which is kept up-to-date with data reported by the different units undertaking the CEM and which can also capture sporadic reports.

The implementation of the system will require the following.

- The development of a CEM protocol, which defines clearly the activities and the standard operating procedures.
- A training programme for the staff involved at the different levels of health care.
- The proper implementation, management and supervision of the pharmacovigilance programme. This should be preferably built into the management and supervision of the programmatic management of drug-resistant TB programme but will demand extra resources for planning, supervision, data entry and sharing of results.
- The

creation of an electronic database or the adaptation of an existing one to ensure proper safekeeping of the data. This is indispensable for the analysis of data and will facilitate the sharing of data between centres. • Plans for identification of signals (pharmacovigilance handbook; Sections I–L) and data analysis. • Ethical approval must be applied consistently to the CEM protocol and activities. Pharmacovigilance activities should be considered as a standard of patient care and needs to be seen as another facet of public health surveillance rather than a research activity, not dissimilar from the way many countries operate for the routine surveillance of TB drug resistance based on diagnostic testing. • The constitution of a CEM committee at the national programme level.

11.4.3 Roles and responsibilities For CEM to fulfil its objectives, an effective coordination of the many diverse functions including data collection, sharing of data between different units, complex statistical analyses, effective communication and human resource development, will be needed. This will be under the responsibility of two main players: (i) the national pharmacovigilance (NPV) centre, and (ii) the health ministry’s TB control programme.

Table 11.5 below proposes the main lead responsibilities for the different components of CEM and could be useful in assigning the complementary functions and associated funding needs.

TABLE 11.5 Lead responsibilities for the different components of cohort event monitoring

CEM COMPONENT LEAD RESPONSIBILITY

Protocol preparation NPV centre Staff training NPV centre Management and supervision - At start: NPV centre - At “maintenance” stage: TB control programme Design and production of forms for data collection NPV centre Collection of data on forms TB control programme Electronic database - If none exist: NPV centre - If programmatic management of drug-resistant TB database exists: TB control programme Data analysis plan, signal identification, communications NPV centre

Ethical approval and conformity NPV centre Secretariat/animation of CEM committee NPV centre

a In cases where the private sector is also involved in active pharmacovigilance, the national TB control programme needs to maintain an effective liaison with these providers to ensure that there is consistent and comprehensive monitoring of drug safety. Likewise, when TB care is provided in general hospitals and specialist centres outside of the usual span of control of the national TB control programme, then a good rapport is needed to ensure that the required activities are conducted to good effect.

Annexure-II

Anti-TB drug information sheets

Amikacin (Amk)
Amoxicillin/Clavulanate (Amx/Clv)
Bedaquiline2 (Bdq)
Capreomycin (Cm)
Clofazimine (Cfz)
Cycloserine (Cs) [and Terizidone (Trd)]
Ethambutol (Emb)
Ethionamide (Eto)/Protionamide (Pto)
Gatifloxacin (Gfx)
Imipenem (Imp)/Cilastatin (Cln)
Isoniazid (Inh)
Kanamycin (Km)
Levofloxacin (Lfx)
Linezolid (Lzd)
Meropenem (Mpm)
Moxifloxacin (Mfx)
Para-aminosalicylic acid (PAS)
Pyrazinamide (Pza)
Rifabutin (Rfb)
Rifampin (Rif)
Rifapentine (Rpt)
Streptomycin (Sm)

Adapted from Tuberculosis Drug Information Guide.2nd Edition. California: Curry International Tuberculosis Center and California Department of Public Health; 2012, except where otherwise referenced. Common presentations of the drugs are described; actual preparations may vary depending on the manufacturer.

Amikacin (Amk)

DRUG CLASS: AMINOGLYCOSIDE

Activity against TB, mechanism of action, and metabolism	Bactericidal: Inhibits protein synthesis. Cross-resistance with kanamycin is considered complete and some data suggesting cross-resistance with capreomycin can occur. Primarily excreted unchanged through the kidney by glomerular filtration.
Dose	Adults: 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 gram). 15 mg/kg/dose, 3 times per week can be used after culture conversion is documented after initial period of daily administration. >59 years of age: 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. Alternatively, 15 mg/kg/dose 3 times per week. Children: 15–30 mg/kg/day (max 1 gram) 5–7 days per week. 15–30 mg/kg/day (max 1 gram) 3 days per week after initial period daily.

Preparation and administration	Given intravenous (IV) or intramuscular (IM). Not absorbed orally. For IV solution, mix with D5W or other solutions (in at least 100 ml of fluid for adults or 5 mg/ml for children). IM absorption can be delayed if same site is used consistently. For IV administration, infuse over 30–60 minutes for adults; 1–2 hours for children; IM absorption is complete within 4 hours.
Storage	Solution is stable at room temperature (15–25 °C); diluted solution is stable at room temperature for at least 3 weeks or in the refrigerator for at least 60 days.
CSF Penetration	Variable penetration; appears to penetrate inflamed meninges better.
Special Circumstances	Use in pregnancy/breastfeeding: Generally avoided during pregnancy due to congenital deafness seen with streptomycin and kanamycin. Can be used while breastfeeding. Use in renal disease: Use with caution. Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. 12–15 mg/kg/dose after dialysis 2–3 times weekly (not daily). The drug is variably cleared by haemodialysis. Use in hepatic disease: Drug concentrations not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution in patients with severe liver disease as it may progress rapidly to hepatorenal syndrome.
Adverse Reactions	Common: Local pain with intramuscular injections. Proteinuria. Occasional: Nephrotoxicity, ototoxicity (hearing loss), vestibular toxicity (vertigo, ataxia, dizziness). All increases with advanced age and prolonged use. Electrolyte abnormalities, including hypokalaemia, hypocalcaemia, and hypomagnesaemia. Rare: Neuropathy, rash.
Contraindications	Pregnancy — relative contraindication (congenital deafness). Hypersensitivity to aminoglycosides. Caution with renal, hepatic, vestibular or auditory impairment
Drug Interactions	Co-administration of loop diuretics (furosemide) and aminoglycoside antibiotics carries an increased risk of ototoxicity.
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly audiology exam; follow monthly electrolytes, magnesium and calcium. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough concentrations at baseline if there is any question about renal function. Some experts monitor aminoglycoside concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.

Patient instructions and alerting symptoms	Instruct patients to inform their health care provider right away if any of the following occurs: • Problems with hearing, dizziness or balance • Rash or swelling of your face • Trouble breathing • Decreased urination • Swelling, pain or redness at your IV site • Muscle twitching or weakness.
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Amoxicillin/Clavulanate (Amx/Clv)

DRUG CLASS: PENICILLIN/BETA-LACTAM INHIBITOR

Activity against TB, mechanism of action, and metabolism	Conflicting and limited reports, but possible early bactericidal activity. Clavulanate is a beta-lactam inhibitor. Amoxicillin component is renally excreted and clavulanate is cleared by the liver.
Dose¹	Expressed in amoxicillin component Adult (and child >30 kg): 80 mg/kg/day in 2 divided doses Child under 30 kg: 80 mg/kg/day in 2 divided doses Maximum dose: 3000 mg daily
Preparation and administration	An oral drug with different preparations: • 875 mg amoxicillin/125 mg clavulanic acid tablet (ratio 7:1) • 400 mg amoxicillin/57 mg clavulanic acid/5 ml, powder for oral suspension (ratio 7:1) • 500 mg amoxicillin/62.5 mg clavulanic acid tablet (ratio 8:1) • 500 mg amoxicillin/62.5 mg clavulanic acid/5 ml, powder for oral suspension (ratio 8:1).
Storage	Tablets are stable at room temperature (15–25 °C); reconstituted suspension should be stored in the refrigerator and discarded after 7 days.
Oral absorption	Good oral absorption, best tolerated and well absorbed when taken at the start of a standard meal.
CSF penetration	Approximately 5% of the plasma concentration reaches the CSF.
Special circumstances	Use in pregnancy/breastfeeding: Probably safe in pregnancy (no known risk); can be used while breastfeeding. Use in renal disease: Amoxicillin is renally excreted and the dose should be adjusted for renal failure. For creatinine clearance 10–30 ml/min dose 1000 mg as amoxicillin twice daily; for creatinine clearance <10 ml/min dose 1000 mg as amoxicillin once daily. It is cleared by dialysis, so should be dosed after dialysis – single dose every 24 hours and after each dialysis session. Use in hepatic disease: Clavulanate is cleared by the liver, so care should be used when using in patients with liver failure.

Adverse reactions	Common: Diarrhoea and abdominal discomfort are most common. Nausea and vomiting. Uncommon: Hypersensitivity and rash. Rare side effects have been reported in other organ systems.
Contraindications	Penicillin allergy; use with caution with cephalosporin allergies.
Monitoring	No specific monitoring is required.
Patient instructions and alerting symptoms	Take at beginning of a meal Instruct patients to inform their health care provider right away if any of the following occurs: • Rash or swelling • Trouble breathing • Severe diarrhoea.

- **Tuberculosis: Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries. Médecins Sans Frontières and Partners In Health; 2013 (http://refbooks.msf.org/msf_docs/en/tuberculosis/tuberculosis_en.pdf, accessed 24 March 2014).**

Bedaquiline² (Bdq)

DRUG CLASS: DIARYLQUINOLINE

Activity against TB, mechanism of action, and metabolism	Bactericidal. Inhibits ATP synthesis; novel method of action; The drug has a 5.5-month half-life. CYP3A4 is the major CYP isoenzyme involved in the metabolism of bedaquiline. The metabolism leads to the formation of N-monodesmethyl metabolite (M2). M2 is not thought to contribute significantly to clinical efficacy given its lower average exposure (23–31%) in humans and lower antimycobacterial activity (4- to 6-fold lower) compared to the parent compound. M2 concentrations appeared to correlate with QT prolongation. Bedaquiline is mainly eliminated in faeces. The renal clearance of unchanged drug is insignificant.
Dose	Adults: 400 mg once daily for 2 weeks, followed by 200 mg, 3 times per week for 22 weeks with food. Children: Not yet determined. If a dose is missed during the first 2 weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule. From week 3 onwards, if a 200 mg dose is missed, patients should take the missed dose as soon as possible, and then resume the 3 times a week regimen.
Preparation and administration	100 mg tablets.
Storage	Store tablet at room temperature (15–25 °C).
Oral absorption	Better absorption is obtained if taken with food.
CSF penetration	No data are available regarding CNS penetration.

Special circumstances	Use in pregnancy/breastfeeding: Not recommended during pregnancy or breastfeeding due to limited data. Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus. Use in renal disease: No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution). Use in hepatic disease: No dosage adjustment is required in patients with mild to moderate hepatic impairment. Dosing and toxicity not well established in severe hepatic impairment, use with caution and only when the benefits outweigh the risks.
Adverse reactions	Common: Gastrointestinal distress (nausea, vomiting, abdominal pain, loss of appetite), joint pain (arthralgia), headache. (Note: haemoptysis and chest pain were also more frequently reported in the group receiving bedaquiline than in the placebo treatment group). Less common: QT prolongation, hyperuricaemia, phospholipidosis (the accumulation of phospholipids in the body's tissues), elevated aminotransferases. Possibly an increased risk of pancreatitis. WARNINGS: A significant imbalance in fatalities was noted in Trial C208 Stage 2, with a higher number of deaths in the bedaquiline group (10 vs 2 in the placebo group; RR=5.1; p=0.017). ³ There was no sudden death reported in the study. There was no discernible pattern for cause of deaths and the reason for the imbalance in deaths is not clear.
Contraindications	Do not use or discontinue bedaquiline • Clinically significant ventricular arrhythmia. • A QTcF interval of >500 ms (confirmed by repeat ECG). • Severe liver disease. Use with caution in the following situations (with more frequent ECG monitoring and evaluation of risk versus benefit): • Use with other QT prolonging drugs (see drug interactions) • A history of torsade de pointes • A history of congenital long QT syndrome • A history of hypothyroidism and bradyarrhythmias • A history of uncompensated heart failure • Serum calcium, magnesium or potassium levels below the lower limits of normal.
Drug interactions	Bedaquiline is metabolized by CYP3A4. Rifampicin (a CYP3A4 inducer) reduces bedaquiline in blood by half. Efavirenz based on a single dose study appears to reduce the amount of bedaquiline though inducing CYP3A4. CYP3A4 inhibitors (e.g. azole anti-fungal drugs, some macrolides, protease inhibitors, and many others) can raise the level of bedaquiline but can be considered for use if the benefits outweigh the risk. Avoid use with other drugs that prolong the QT interval as additive QT prolongation may occur (e.g. clofazimine, fluoroquinolones, delamanid, azole anti-fungal drugs, and many others); any syncopal event (fainting) should prompt an immediate medical evaluation and ECG.

Monitoring	An ECG should be obtained before initiation of treatment, and at least 2, 12 and 24 weeks after starting treatment. More frequently if heart conditions, hypothyroidism or electrolyte disturbances are present. Liver function tests should be done monthly.
Patient instructions and alerting symptoms	The patient should be informed that bedaquiline is a new anti-TB drug and there could be unknown risks and side effects. The following serious side effects can occur with bedaquiline: death, heart rhythm abnormalities, and/or hepatitis. This medicine should be taken with food. Avoid alcohol. The patient should be informed that in one clinical trial, more deaths were seen in people who were treated with bedaquiline compared to people who did not receive. Instruct patients to inform their health care provider right away if any of the following occurs: • Abdominal pain • Yellowing of your skin or eyes • Palpitations • Chest pain • Fainting and near fainting events.

- Highlights of drug prescribing information for Sirturo (bedaquiline). Titusville, NJ 08560: Janssen Therapeutics, Division of Janssen Products. (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf, accessed 24 March 2014).
- Anti-Infective Drugs Advisory Committee Meeting Briefing Document: TMC207 (bedaquiline), treatment of patients with MDR-TB. NDA 204–384, Janssen Pharmaceutical companies of Johnson & Johnson, 28 November 2012.

Capreomycin (Cm)

DRUG CLASS: CYCLIC POLYPEPTIDE

Activity against TB, mechanism of action, and metabolism	Bactericidal; has strong anti-TB activity; inhibits protein synthesis. Some data suggest cross-resistance with amikacin and kanamycin.
Dose	Adults: 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 gram, but a large, muscular person could receive more and should have the concentrations monitored). 15 mg/kg/dose, 2–3 times per week after an initial period of daily administration (some experts use up to 25 mg/kg/dose for intermittent therapy; monitor concentrations). >59 years of age: 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after the initial period. Alternatively, 15 mg/kg/dose, 3 times per week. Children: 15–30 mg/kg/day (max 1 gram), 5–7 days per week. 130 mg/kg/day (max 1 gram), 2–3 days per week after initial period daily. Renal failure/dialysis: 12–15 mg/kg/dose, 2–3 times weekly (not daily). Markedly obese individuals should have an adjusted dose due to decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give suprathreshold concentrations. For dosing, use adjusted weight as follows: Ideal body weight + 40% of excess weight Ideal body weight (men): 50 kg plus 2.3 kg/ inch over 5 ft. Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft.

	Serum concentrations should be followed closely when possible.
Route of administration	IV or IM.
Preparation	Capreomycin is available in vials of 1 gram for either IM or IV administration. The contents of the vial should be reconstituted with 2 ml or more of normal saline or sterile water.
Storage	Package insert indicates that reconstituted capreomycin can be stored in the refrigerator up to 24 hours prior to use. Other data suggest that it may be held for 14 days in the refrigerator or 2 days at room temperature (15–25 °C).
Oral absorption	There is no significant oral absorption. Intramuscular absorption may be delayed if the same site is used consistently.
CSF penetration	There is a paucity of data regarding capreomycin's penetration of the meninges.
Special circumstances.	Use in pregnancy/breastfeeding: Generally avoided during pregnancy due to congenital deafness seen with streptomycin and kanamycin. There are case reports of its safe use in pregnancy (unaffected newborns). Can be used while breastfeeding. Use in renal disease: Use with caution. Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See section above for dosage under renal disease or dialysis. Use in hepatic disease: Drug concentrations are not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution – some patients with severe liver disease may progress rapidly to hepatorenal syndrome
Adverse reactions	Similar to the aminoglycosides. Nephrotoxicity: 20–25% including proteinuria, reduced creatinine clearance, and depletion of potassium and magnesium. Ototoxicity (hearing loss): Occurs more often among the elderly or those with pre-existing renal impairment and vestibular toxicity. Local pain with intramuscular injections. Electrolyte abnormalities, including hypokalaemia, hypocalcaemia and hypomagnesaemia.
Contraindications	Hypersensitivity to capreomycin. Some experts would not use capreomycin if vestibular side effects resulted from aminoglycoside use. Generally avoided during pregnancy due to congenital deafness seen with aminoglycosides and mechanism of ototoxicity may be similar with capreomycin. There are case reports of its safe use during pregnancy (unaffected newborns).
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal

	impairment or any other concerns; document baseline and monthly audiology exam; follow monthly electrolytes, magnesium and calcium. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough concentrations at baseline if there is any question about renal function. Some experts monitor capreomycin concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.
Patient instructions and alerting symptoms	Instruct patients to inform their health care provider right away if any of the following occurs: • Rash • Fever or chills • Bleeding or bruising • Problems with hearing, dizziness or balance • Bleeding or a lump where the shot is given • Decreased urination • Trouble breathing • Muscle weakness.

Clarithromycin (Clr)

DRUG CLASS: MACROLIDE

Activity against TB, mechanism of action, and metabolism	Much more active against nontuberculous mycobacteria, especially <i>Mycobacterium avium</i> -complex (MAC), but some isolates of TB are susceptible in vitro. Does not have proven value for the treatment of TB in humans, and in vitro data are not particularly encouraging (<i>M. tuberculosis</i> is intrinsically resistant to macrolides, a characteristic associated with expression of the <i>erm(37)</i> gene). ⁴ Inhibits protein synthesis by binding to the 50S ribosomal subunit. The drug is cleared both hepatically and renally. Because of high intracellular concentrations, tissue levels are higher than in the serum.
Dose	Adults: 500 mg twice daily or 1 gram daily of extended release formulation. Children: 7.5 mg/kg q 12 hours up to 500 mg. Renal failure/dialysis: The drug is cleared both hepatically and renally. In severe renal impairment, the interval doses should be increased, i.e. 500 mg/day.
Preparation	Oral tablets of 250 and 500 mg. Also available in extended release tablets for once daily use. Oral suspension 125 mg/5 ml and 250 mg/5 ml.
Storage	Store tablets and unmixed granules for suspension at room temperature (15–25 °C) in a well-sealed container and protect from light. The mixed suspension should not be refrigerated and can be stored for 14 days.
Oral absorption	The drug is rapidly absorbed after oral administration and is about 50% bioavailable. It can be given without regard to food. Food slightly delays the peak serum level but also slightly increases the peak concentration achieved.
CSF penetration	There is no information available about CNS penetration.

Special circumstances	Pregnancy/breastfeeding: Pregnancy category C and generally should not be used during pregnancy unless no other alternative is available. It is not known if the drug is excreted in human breast milk. Use in renal disease: In severe renal impairment, the interval between doses should be increased, i.e. 500 mg daily. Use in hepatic disease: No adjustment is necessary.
Adverse reactions	Common: Diarrhoea, nausea, abnormal taste, dyspepsia, abdominal pain /discomfort, headache. Rare allergic skin reactions, liver toxicity, QT prolongation, Clostridium difficile colitis, hearing loss.
Contraindications	Patients with known hypersensitivity to macrolide antibiotics. Should not be given with the any of the following drugs: bedaquiline, cisapride, pimozide, astemizole, terfenadine, and ergotamine or dihydroergotamine.
Monitoring	No routine laboratory monitoring is indicated.
Patient instructions and alerting symptoms	This medication may be taken with or without food. Be sure to tell your health care provider what other medications you are taking. Do not take cisapride, pimozide, astemizole, terfenadine, and ergotamine or dihydroergotamine when taking clarithromycin. Instruct patients to inform their health care provider right away if any of the following occurs: <ul style="list-style-type: none"> • Severe diarrhoea. • Rash.

- Andini N, Nash KA. Intrinsic macrolide resistance of the Mycobacterium tuberculosis complex is inducible. Antimicrobial Agents and Chemotherapy 2006;50(7):2560–2562.

Clofazimine (Cfz)

DRUG CLASS: IMINOPHENAZINE

Activity against TB, mechanism of action, and metabolism	In vitro activity against M. tuberculosis without much in vivo data. Generally reserved for cases with few other options. Tissue half-life estimated to be around 70 days.
Dose	Adults: 100–200 mg daily (oral) has been used. A regimen of 200 mg daily for 2 months, followed by 100 mg daily has been used. Children: Limited data, but doses of 1 mg/kg/day have been given.
Preparation and administration.	50 and 100 mg capsules. Oral, not available parenterally. Improved tolerance and absorption with food.
Storage	Room temperature (15–25 °C).

Oral absorption	70% absorption after an oral dose.
CSF penetration	Limited data are available regarding CNS penetration.
Special circumstances	Use in pregnancy/breastfeeding: Not recommended due to limited data (some reports of normal outcomes, some reports of neonatal deaths). Avoided with breastfeeding due to pigmentation of the infant. Use in renal disease: No dosage adjustment required. Use in hepatic disease: Partially metabolized by the liver; use caution and/or adjust the dose for severe hepatic insufficiency.
Adverse reactions	Common: Orange/red discoloration of skin, conjunctiva, cornea and body fluids. Dry skin, pruritus, rash, ichthyosis, xerosis. Gastrointestinal intolerance. Photosensitivity. Less common: retinopathy, severe abdominal symptoms, bleeding and bowel obstruction; QT prolongation.
Contraindications	Allergy to clofazimine.
Drug interactions	Using with drugs that prolong the QT interval may cause additive QT prolongation (e.g. bedaquiline, fluoroquinolones, delamanid, azole anti-fungal drugs, and many others); further research is needed to understand potential interactions with antiretrovirals.
Monitoring	Symptomatic monitoring.
Patient instructions and alerting symptoms	Take with food to avoid stomach upset and improve absorption. This medicine may discolor your skin and body secretions are orange, red or brownish-black. This should go away after stopping the medicine, but may take a long time. Avoid the sun and use strong sunscreens. Instruct patients to inform their health care provider right away if any of the following occurs: • Bloody or black stools or diarrhoea • Yellowing of skin or eyes • Severe nausea, vomiting, abdominal pain, cramps or burning • Depression or thoughts of hurting oneself.

Cycloserine (Cs) [and Terizidone (Trd)]

DRUG CLASS: ANALOG OF D-ALANINE.

Activity against TB, mechanism of action, and metabolism	Bacteriostatic; inhibits cell wall synthesis.
Dose	Adults: 10–15 mg/kg/day usually (max. 1000 mg/day); Usually 500–750 mg/day given in two divided doses or once a day if tolerated. Some patients may require only alternate day 250 mg and 500 mg dosing to avoid toxicity. Children: 10–20 mg/kg/day divided every 12 hours (daily maximum 1 gram). Pyridoxine (vitamin B6): Although supporting data are not extensive, MDR-TB experts recommend that all

	patients should receive vitamin B6 while taking cycloserine. Adults need 100 mg or more (or 50 mg per 250 mg of cycloserine) and children should receive a dose proportionate to their weight (1–2 mg/kg/day, with a usual range of 10–50 mg/day). Renal failure/dialysis: 250 mg once daily or 500 mg, 3 times per week; monitor drug concentrations to keep peak concentrations <35 mcg/ml.
Route of administration	Oral; not available parenterally.
Preparation	250 mg capsule.
Storage	Room temperature (15–25 °C) in airtight containers.
Oral absorption	Modestly decreased by food (best to take on an empty stomach); not significantly affected by antacids or orange juice.
CSF penetration	Concentrations approach those in serum.
Special circumstances	Use in pregnancy/breastfeeding: Not well studied, but no teratogenicity documented. Use if there are not better choices. Can be used while breastfeeding (dose the infant with vitamin B6 if breastfed). Use in renal disease: Cycloserine is cleared by the kidney and requires dose adjustment for renal failure (see above). Use with caution. Use in hepatic disease: Not associated with hepatotoxicity.
Adverse reactions	CNS toxicity, including inability to concentrate and lethargy. More serious CNS side effects, including seizure, depression, psychosis and suicidal ideation, usually occur at peak concentrations >35 mcg/ml, but may be seen in the normal therapeutic range. Other side effects include peripheral neuropathy and skin changes. Skin problems include lichenoid eruptions and Stevens-Johnson syndrome.
Contraindications	Relative contraindications include seizure disorder, psychotic disease or alcohol abuse.
Monitoring	Peak concentrations should be obtained within the first 1–2 weeks of therapy and monitored serially during therapy. The peak concentration should be kept below 35 mcg/ml. Baseline and monthly monitoring for depression using a tool such as the Beck Depression Index should be done.
Patient instructions and alerting symptoms	If food is taken, avoid a large fatty meal. Avoid alcohol. You must also take a high-dose vitamin B6 supplement while on this drug. Instruct patients to inform their health care provider right away if any of the following occurs: • Seizures • Shakiness or trouble talking • Depression or thoughts of hurting yourself • Anxiety, confusion or loss of memory • Personality changes, such as aggressive behavior • Rash or hives • Headache.

Ethambutol (Emb)

DRUG CLASS: UNSPECIFIED

Activity against TB, mechanism of action, and metabolism	Bacteriostatic; inhibitor of cell wall synthesis; bactericidal only at the high end of the dosing range. At doses used over long periods of time, ethambutol protects against further development of resistance.
Dose	Adults: 15–25 mg/kg/day. Higher doses should be used only during the initial months of therapy. For prolonged therapy, the dose should be closer to 15 mg/kg/day to avoid toxicity. Children: 15–25 mg/kg/day; doses closer to 15 mg/kg/day should be used if the drug is used for more than 2 months. Renal failure/dialysis: 15–25 mg/kg/dose, 3 times weekly (not daily). Obesity: For obese patients, base dosing on adjusted weight as follows: Ideal body weight + 40% of excess weight Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft
Route of administration	Oral; not available parenterally in the US
Preparation	100 mg tablets; scored 400 mg tablets; coated 100 mg tablets; coated, scored 400 mg tablets.
Storage	Room temperature (15–25 °C).
Pharmacokinetics	Peak oral absorption occurs 2–4 hours after the dose. Draw a peak serum concentration 2–3 hours after the dose; a second sample 6 hours post-dose could be obtained if there is concern about late absorption and in order to estimate the serum half-life. Peak concentrations of 2–6 mcg/ml are expected with daily dosing. Intermittent doses of 50 mg/kg can be expected to produce peaks of 4–12 mcg/ml.
Oral absorption	80% bioavailability independent of food.
CSF penetration	Ethambutol penetrates meninges poorly
Special circumstances	Use in pregnancy/breastfeeding: Safe in pregnancy; can be used while breastfeeding. Use in renal disease: Use with caution – cleared by the kidneys; dose adjustment required for renal failure. Increased risk of toxicity with renal failure. If needed for use in the regimen, consider therapeutic drug monitoring. Use in hepatic disease: Safe in liver disease.
Adverse reactions	Retrobulbar neuritis (dose-related – exacerbated during renal failure).
Contraindications	Pre-existing optic neuritis; visual changes on ethambutol.
Monitoring	Patients should be counselled to report any changes in vision. Baseline and monthly visual acuity and colour discrimination monitoring should be performed (particular attention should be given to individuals on higher doses or with renal impairment).
Patient instructions and	Can be taken with food or on an empty stomach. Instruct patients to inform their health care provider right away if any of the following

alerting symptoms	occurs: • Any problems with your eyes: vision changes, blurring, colour blindness, trouble seeing or eye pain • Swelling of face • Rash, hives or trouble breathing • Numbness, pain or tingling in hands or feet • Joint pain • Fever or chills • Nausea, vomiting, poor appetite or abdominal pain • Headache or dizziness.
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Ethionamide (Eto)/Protionamide (Pto)

DRUG CLASS: CARBOTHIONAMIDES GROUP, DERIVATIVES OF ISONICOTINIC ACID

Activity against TB, mechanism of action, and metabolism	Weakly bactericidal; blocks mycolic acid synthesis.
Dose.	Adults: 15–20 mg/kg/day frequently divided (max dose 1 gram per day); usually 500–750 mg per day in 2 divided doses or a single daily dose. Children: 15–20 mg/kg/day usually divided into 2–3 doses (max dose 1 gram per day). A single daily dose can sometimes be given at bedtime or with the main meal. Many individuals require gradual ramping up of the dose and treatment for gastrointestinal upset. Pyridoxine (vitamin B6): Although there is little supporting data, most MDR-TB experts recommend that all patients should receive vitamin B6 while taking ethionamide. Suggested dose for adults is 100 mg and children should receive a dose proportionate to their weight (1–2 mg/kg/day, with a usual range of 10–50 mg/day). Renal failure/dialysis: No change
Route of administration	Oral; not available parenterally.
Preparation	Coated 250 mg tablet.
Storage	Store at room temperature (15–25 °C).
Oral absorption	Erratic absorption, possibly due to gastrointestinal disturbances associated with the medication.
CSF penetration	Concentrations approach those in the serum; one paediatric study evaluating drug concentrations in the CSF suggests that ethionamide should be dosed on the high end of the range for patients with meningitis.
Special circumstances	Use in pregnancy/breastfeeding: Generally avoided during pregnancy due to reports of teratogenicity; little data about use during breastfeeding – an estimated 20% of the infant

	therapeutic dose will be passed on to the baby in the breast milk (dose the infant with vitamin B6 if breastfed). Use in renal disease: No precautions are required for renal impairment. Use in hepatic disease: Can cause hepatotoxicity similar to that of isoniazid – use with caution in liver disease.
Adverse reactions	Gastrointestinal upset and anorexia: sometimes intolerable (symptoms are moderated by food or taking at bedtime). Premedication with an antiemetic like ondansetron is often helpful. Low dose Ativan 0.5 mg has also been used successfully. Metallic taste. Hepatotoxicity. Endocrine effects: Gynaecomastia, hair loss, acne, impotence, menstrual irregularity, and reversible hypothyroidism – treat with thyroid replacement. Neurotoxicity (patients taking ethionamide should take high doses of vitamin B6). Side effects may be exaggerated in patients also taking cycloserine.
Contraindications	Sensitivity to ethionamide.
Monitoring	Monitor thyroid stimulating hormone for evidence of hypothyroidism requiring replacement; therapeutic drug monitoring required if malabsorption is suspected. Monitor liver function tests.
Patient instructions and alerting symptoms	Take this medicine with food. You must also take a high-dose vitamin B6 supplement while on this drug. Instruct patients to inform their health care provider right away if any of the following occurs: <ul style="list-style-type: none"> • Any problems with your eyes: eye pain, blurred vision, colour blindness or trouble seeing • Numbness, tingling or pain in your hands or feet • Unusual bruising or bleeding • Personality changes such as depression, confusion or aggression • Yellowing of your skin or eyes • Dark-colored urine • Nausea and vomiting • Dizziness • Swollen breasts (in men).

Gatifloxacin (Gfx)

DRUG CLASS: FLUOROQUINOLONE

Activity against TB, mechanism of action, and metabolism	Bactericidal; acts by inhibiting the A subunit of DNA gyrase (topoisomerase), which is essential in the reproduction of and metabolism bacterial DNA.
Dose	400 mg/day
Route of administration	Oral.
Preparation	Tablets, 200 or 400 mg.
Storage	Room temperature (15–25 °C), airtight containers protected from light.
Oral absorption	Readily absorbed from the gastrointestinal tract with an absolute bioavailability of 96%. Gatifloxacin in an anion and taking with divalent cations will result in bonding and not being absorbed. Administrate two hours before or four hours after ingestion of milk- based products, antacids or other medications containing divalent cations (iron, magnesium, calcium, zinc, vitamins, didanosine, sucralfate).
CSF penetration	Widely distributed in body fluids including CSF.
Special circumstances	Pregnancy/breastfeeding: safety class C. Fluoroquinolones are not recommended during breastfeeding due to the potential for arthropathy. Animal data demonstrated arthropathy in immature animals, with erosions in joint cartilage. Renal disease: doses of gatifloxacin should be reduced in patients with renal impairment. When creatinine clearance is less than 30 ml/min, the recommended dosing is 400 mg, 3 times per week.
Adverse reactions	Generally well tolerated. Occasional: gastrointestinal intolerance; Rare CNS-headache; malaise; insomnia; restlessness; dizziness; allergic reactions; diarrhoea; photosensitivity; increased liver function tests; tendon rupture (increased incidence seen in older men with concurrent use of corticosteroids). Severe dysglycaemia, hypoglycaemia and hyperglycaemia, and diabetes have been reported (many countries have removed the drug from their national formularies for this reason).
Contraindications	Pregnancy Intolerance of fluoroquinolones Diabetes. Gatifloxacin can worsen diabetes and glycaemic control.
Monitoring	Glucose monitoring every 1–2 weeks.
Patient instructions and alerting symptoms	Instruct patients to inform their health care provider right away if any of the following occurs: • Rashes, hives, bruising or blistering, trouble breathing • Pain, swelling or tearing of a tendon or muscle or joint pain. • Diarrhoea • Yellow skin or eyes • Anxiety, confusion or dizziness (signs of hypoglycaemia or hyperglycaemia) • Increased thirst or frequent urination (sign of hyperglycaemia)

Imipenem (Imp)/Cilastatin (Cln)

DRUG CLASS: BETA-LACTAM – CARBAPENEM (IT IS RELATED TO THE PENICILLIN/ CEPHALOSPORIN FAMILY OF ANTIBIOTICS BUT IS CLASSIFIED AS BELONGING TO THE CARBAPENEM CLASS).

Activity against TB, mechanism of action, and metabolism	In vitro activity – very limited clinical experience. Given that imipenem is rapidly degraded by renal proximal tubule dipeptidases, it is used in combination with the dipeptidase inhibitor, cilastatin. (Conversely, meropenem a similar drug as imipenem is stable to renal dipeptidases and requires no cilastatin). Cilastatin is partially metabolized renally.
Dose	Adults: 1000 mg IV every 12 hours. (Dosed on the imipenem component). Should be given with clavulanate (available as amoxicillin/clavulanate) 125 mg every 8–12 hours. Children: Meropenem preferred. See Meropenem, drug sheet for dosing.
Route of administration IV or IM (total recommended IM dose is not more than 1.5 gram/day and therefore not very practical for treatment of drug-resistant TB). No oral absorption.	
Preparation	Lyophilized powder 1:1 ratio of imipenem and cilastatin. Vials available as 250 mg, 500 mg, 750 mg, or 1 gram and contain equal amounts of both drugs. (i.e. a “500 mg vial” contains 500 mg of imipenem and 500 mg cilastatin)
Storage	Powder should be kept at room temperature (15–25 °C); suspended product should be kept no more than 4 hours at room temperature or no more than 24 hours refrigerated.
CSF penetration	Good CSF penetration, but children with meningitis treated with imipenem had high rates of seizures (meropenem preferred for meningitis and for children).
Special circumstances	Use in pregnancy/breastfeeding: Little information is known regarding use in pregnancy; unknown safety during breastfeeding. Use in renal disease: Adjustment in dose based on severity of renal failure – for example, 750 mg every 12 hours for creatinine clearance 20–40 ml/min, 500 mg every 12 hours for creatinine clearance <20 ml/min. Dose after dialysis. Use in hepatic disease: Elevated liver function tests have been noted in up to 6% of patients, but no definite liver damage has been documented.
Adverse reactions	Common: Diarrhoea, nausea, or vomiting. Less common: Seizure (noted with CNS infection), palpitations, pseudomembranous colitis.

Contraindications	Carbapenem intolerance; meningitis (use meropenem rather than imipenem).
Monitoring	Symptomatic monitoring.
Patient instructions and alerting symptoms	Make sure your health care provider knows if you are also taking ganciclovir or have allergy to penicillins or cephalosporins. Instruct patients to inform their health care provider right away if any of the following occurs: • Fast or irregular heartbeat • Seizures • Severe diarrhoea (watery or bloody) • Skin rash, hives, or itching • Swelling of the face, throat or lips • Wheezing or trouble breathing.

Isoniazid (Inh)

DRUG CLASS: ISONICOTINIC ACID HYDRAZIDE

Activity against TB, mechanism of action, and metabolism	Bactericidal; Especially for rapidly dividing cells. Affects mycolic acid (cell wall) synthesis. Inclusion of isoniazid in the regimen of patients with strain W MDR-TB was also associated with improved outcomes.
Dose	Adults: 4–6 mg/kg/day (oral or IV); usual adult dose 300 mg daily; high dose isoniazid (600 to 1500 mg daily, see Annex 2 for weight- based dosing) used for patients with low-level isoniazid resistance or documented isoniazid resistance other than due to the Kat G gene mutation. Children: 10–15 mg/kg/day up to 300 mg (oral or IV); – Patient <30 kg: 7 to 15 mg/kg once daily – Patient ≥ 30 kg: 4 to 6 mg/kg once daily – Maximum dose: 300 mg daily Renal failure/dialysis: 300 mg once daily or 900 mg thrice weekly. Pyridoxine (vitamin B6) should be used when high-dose isoniazid is administered and in patients with diabetes, uraemia, HIV infection, seizure disorders, alcohol abuse, malnutrition or peripheral neuropathy. Additionally, pregnant and postpartum women and exclusively breastfed infants should receive vitamin B6 while taking isoniazid. (Normal dose of pyridoxine when used prophylactically for prevention of neuropathy in patients taking isoniazid is 10–25 mg/day.)
Route of administration	Oral, IV or IM.
Preparation	50 mg, 100 mg or 300 mg scored or unscored tablets; 50 mg/5 ml oral suspension in sorbitol; solution for injection is 100 mg/ml. When given IV, dilute in 25 ml normal saline and infuse as a slow bolus over 5 minutes. Since compatibility information is not available, do not infuse “piggyback” with other drugs through a shared IV line.
Storage	Suspension must be kept at room temperature (15–25 °C).
Oral absorption	Well absorbed orally or intramuscularly; best absorbed on an empty stomach; up to 50% reduction in peak concentration with a fatty meal.

CSF penetration	Concentration equivalent to plasma in inflamed meninges. 20% of concentrations in plasma in noninflamed meninges.
Special circumstances	Use in pregnancy/breastfeeding: Safe during pregnancy; safe during breastfeeding (both baby and mother should receive pyridoxine supplementation). Up to 20% of the infant therapeutic dose will be passed on to the baby in the breast milk. Use in renal disease: No dose adjustment for renal failure, but pyridoxine supplementation should be used. Use in hepatic disease: May exacerbate liver failure. Use with caution. Drug Interactions: Isoniazid is a CYP3A4 inhibitor. Isoniazid may increase the concentrations of certain cytochrome P450 enzyme substrates, including phenytoin and carbamazepine.
Adverse reactions	Hepatitis (age-related). Peripheral neuropathy. Hypersensitivity reactions. Other reactions, including optic neuritis, arthralgias, CNS changes, drug- induced lupus, diarrhoea, and cramping with liquid product.
Contraindications	Patients with high-level isoniazid resistance who have failed an isoniazid-containing regimen should not receive isoniazid. History of allergic reaction to isoniazid.
Drug Interactions	Monitor concentrations of phenytoin or carbamazepine in patients receiving those drugs (increases phenytoin concentrations and risk of hepatotoxicity with carbamazepine), especially when undergoing isoniazid monotherapy. Rifampin tends to lower concentrations of these drugs and balance the effect of isoniazid.
Monitoring	Clinical monitoring of all patients on isoniazid is essential. Routine laboratory monitoring is not recommended for patients receiving isoniazid monotherapy for latent TB infection. For patients receiving multiple TB drugs or other hepatotoxic drugs, or with underlying liver disease (including viral hepatitis), baseline liver function testing is recommended. Follow-up liver function testing is determined by baseline concerns and symptoms of hepatotoxicity.
Alerting symptoms	Instruct patients to inform their health care provider right away if any of the following occurs: • Loss of appetite for a few days that does not go away • Tiredness, weakness • Moderate stomach pain, nausea or vomiting • Numbness, pain or tingling of your fingers or toes • Blurred vision, eye pain • Yellow skin or eyes or dark-colored urine.

Kanamycin (Km)

DRUG CLASS: AMINOGLYCOSIDE

Activity against TB, mechanism of action, and metabolism	Bactericidal; has strong anti-TB activity. Cross-resistance with amikacin and some data suggesting cross-resistance with capreomycin; inhibits protein synthesis.
Dose	Adults: 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 gram, but a large, well-built person could receive more and should have concentrations monitored). >59 years of age: 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after initial period. Alternatively, 15 mg/kg/dose, 3 times per week. Children: 15–30 mg/kg/day (max 1 gram) 5–7 days per week. Renal failure/dialysis: 12–15 mg/kg/dose, 3 times weekly. Markedly obese individuals should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give suprathereapeutic concentrations. For dosing, use adjusted weight as follows: Ideal body weight + 40% of excess weight Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft If possible, concentrations should be followed closely.
Route of administration	IV or IM; not absorbed orally.
Preparation	250 mg/ml in vials of 500 mg or 1 gram; 1 gram in 3 ml vial; or 75 mg/vial for infants. Can be mixed with D5W or normal saline for intravenous infusion. Adult IV doses should be mixed in at least 100 ml of fluid, and paediatric IV doses should be mixed to a concentration of at least 5 mg/ml. For intravenous administration, infuse over 60 minutes for adults; 1–2 hours for children.
Storage	Store in the refrigerator.
Oral absorption	Not absorbed orally; 40–80% of the dose is absorbed intramuscularly.
CSF penetration	Minimal and variable CSF penetration – slightly better with inflamed meninges.
Special circumstances risk of ototoxicity.	Use in pregnancy/breastfeeding: Generally avoided in pregnancy due to documented congenital deafness. Can be used while breastfeeding. Use in renal disease: Use with caution. Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See section above for dosage under renal disease or dialysis. The drug is variably cleared by haemodialysis. Use in hepatic disease: Drug concentrations are not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution because patients with severe liver disease may progress

	rapidly to hepatorenal syndrome. Diuretic use: Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased
Adverse reactions	Nephrotoxicity: Appears to be more nephrotoxic than streptomycin. Ototoxicity (hearing loss) and vestibular toxicity: Increases with advanced age and prolonged use; appears to occur slightly more commonly with kanamycin than with streptomycin and about the same frequency as amikacin. Kanamycin seems to have slightly less vestibular toxicity.
Contraindications	Pregnancy (congenital deafness seen with streptomycin and kanamycin use in pregnancy); hypersensitivity to aminoglycosides; caution with renal, vestibular or auditory impairment; patients with intestinal obstructions.
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment is present); document creatinine clearance if there is baseline renal impairment or any other concern; document baseline and monthly audiology exam. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough concentrations at baseline if there is any question about renal function. Some experts monitor aminoglycoside concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.
Alerting Symptoms	Instruct patients to inform their health care provider right away if any of the following occurs: • Problems with hearing, dizziness or balance • Rash or swelling of your face • Trouble breathing • Decreased urination • Watery or bloody diarrhoea • Swelling, pain, or redness at your IV site • Muscle twitching or weakness.

Levofloxacin (Lfx)

DRUG CLASS: FLUOROQUINOLONE (FQN)

Activity against TB, mechanism of action, and metabolism	Bactericidal; has strong anti-TB activity. Cross-resistance with other fluoroquinolones but may not be complete. Data suggests greater activity than ciprofloxacin or ofloxacin. Inhibits DNA gyrase.
Dose	Adults: For treatment of TB disease 10–15 mg/kg once daily. (also see Annex 2 Weight-based dosing for adults): Children: 5 years and under: 15–20 mg/kg split into two doses (morning and evening). Over 5 years: 10–15 mg/kg once daily (also see Annex 3 Weight-based dosing for children). Renal failure/dialysis: 750–1000 mg/dose, 3 times weekly (not daily) for creatinine clearance <30 ml/min.
Route of administration	Oral or intravenous.

Preparation	Coated tablets (250 mg, 500 mg, 750 mg); solution for injection 25 mg/ml; 250 mg in 50 ml container; 500 mg in 100 ml container; 750 mg in 150 ml container. Oral suspension is 25 mg/ml.
Storage	Oral forms, undiluted solution, and pre-mixed solutions are stored at room temperature (15–25 °C). Once diluted, the solution can be kept at room temperature for 3 days, in the refrigerator for 2 weeks, or frozen for 6 months.
Oral absorption	Excellent oral absorption. Levofloxacin is an anion and taking with divalent cations will result in bonding and not being absorbed: administrate two hours before or four hours after ingestion of milk-based products, antacids, or other medications containing divalent cations (iron, magnesium, calcium, zinc, vitamins, didanosine, sucralfate).
CSF penetration	Concentrations are 65% of that in the serum.
Special circumstances	Use in pregnancy/breastfeeding: Fluoroquinolones are generally avoided during pregnancy and breastfeeding due to possibility of arthropathy. However, there are a few case reports of fluoroquinolones being used safely during pregnancy. Use in renal disease: Dosage adjustment is recommended if creatinine clearance is <50 ml/min. The drug is not cleared by haemodialysis; supplemental doses after dialysis are not necessary. Use in hepatic disease: Drug concentrations are not affected by hepatic disease. Presumed to be safe in severe liver disease.
Adverse reactions	Nausea and bloating. Headache, dizziness, insomnia or tremulousness. Rare tendon rupture, arthralgias (can usually be treated symptomatically). QTc prolongation, hypoglycaemia.
Contraindications	Fluoroquinolone intolerance, prolonged QTc, pregnancy (relative contraindication).
Monitoring	Side effect monitoring, but no specific laboratory monitoring required.
Patient instructions and alerting symptoms	You can take levofloxacin with food. Drink plenty of beverages. Do not take milk-based products, antacids (especially aluminum-containing), mineral supplements such as iron or magnesium, or multivitamins within 2 hours of this medication or within 4 hours after. This medicine may cause sun sensitivity; use sunscreens. Do not undertake new strenuous activities. Instruct patients to inform their health care provider right away if any of the following occurs: • Pain, swelling or tearing of a tendon (such as the back of your ankle, elbow, etc.), or muscle or joint pain • Rashes, hives, bruising or blistering, trouble breathing or tightness in your chest • Diarrhoea • Yellow skin or eyes • Anxiety, confusion or dizziness.

Linezolid (Lzd)

DRUG CLASS: OXAZOLIDINONES

Activity against TB, mechanism of action, and metabolism	Has in vitro bactericidal activity – increasing clinical experience; inhibits protein synthesis.
Dose	Adults: 600 mg, once daily. (Reduce to 400–300 mg/day if serious adverse effects develop). Children: 10 mg/kg three times daily in children up to 11 years of age and 10 mg/kg (maximum dose 600 mg) twice daily in older children. ⁵ 10 mg/kg/dose every 12 hours. Vitamin B6: All patients should receive vitamin B6 while receiving linezolid.
Preparation	Coated tablets: 400 and 600 mg; intravenous solution: 2 mg/ml: 100, 200 or 300 mg bags. Intravenous doses are administered over 30–120 minutes. Oral powder for suspension: 100 mg/5 ml, 240 ml bottle.
Storage	Store tablet at room temperature (15–25 °C). Reconstituted oral suspension may be stored at room temperature for 21 days. Parenteral preparation should be stored at room temperature (protect from light and do not freeze).
Oral absorption	Nearly complete oral absorption.
CSF penetration	CSF concentrations are about 1/3 of those in serum in animal models, and linezolid has been used to treat meningitis in humans.
Special circumstances	Use in pregnancy/breastfeeding: Not recommended during pregnancy or breastfeeding due to limited data. Use in renal disease: No dose adjustment is recommended, but metabolites may accumulate. Use in hepatic disease: Rarely associated with increased transaminases.
Adverse reactions lactic acid blood test.	Myelosuppression (decreased level of platelets, decreased level of white blood cells, and/or anaemia). Diarrhoea and nausea. Optic and peripheral neuropathy may be irreversible and linezolid should be stopped if these develop; weigh against the risk of permanent blindness or disabling permanent neuropathy. Lactic acidosis – patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving linezolid should receive immediate medical evaluation, including a
Contraindications	Hypersensitivity to oxazolidinones. Symptoms of neuropathy (pain, numbness, tingling or weakness in the extremities).
Drug Interactions	Avoid use with patients taking serotonergic agents, such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (e.g. fluoxetine, paroxetine), lithium, tricyclic antidepressants, etc. as it may cause serious CNS reactions such as serotonin syndrome.

Monitoring	Monitor for peripheral neuropathy and optic neuritis (visual eye tests every two months or if symptoms develop, clinical examination for peripheral neuropathy monthly or if symptoms develop). Monitor a complete blood count weekly during the initial period, then monthly, and then as needed based on symptoms; there is little clinical experience with prolonged use.
Patient instructions and alerting symptoms or vomiting.	This medicine may be taken with or without food. Take it with food if it irritates the stomach. Avoid food and drinks that contain tyramine: aged cheeses, dried meats, sauerkraut, soy sauce, tap beers and red wines. Make sure your doctor knows if you are taking medicines for colds, congestion or depression. Instruct patients to inform their health care provider right away if any of the following occurs: • Pain, numbness, tingling or weakness in the extremities • Black, tarry stools or severe diarrhoea • Unusual bleeding or bruising • Unusual tiredness or weakness • Headache, nausea

- Zyvox: linezolid injection, linezolid tablets, linezolid for oral suspension package insert. Kalamazoo, MI: Pharmacia & Upjohn Company; 2002.

Meropenem (Mpm)

DRUG CLASS: BETA-LACTAM – CARBAPENEM (IT IS RELATED TO THE PENICILLIN/ CEPHALOSPORIN FAMILY OF ANTIBIOTICS BUT IS CLASSIFIED AS BELONGING TO THE CARBAPENEM CLASS).

Activity against TB, mechanism of action, and metabolism	In vitro activity – very limited clinical experience (meropenem is stable to renal dipeptidases and requires no cilastatin).
Dose	Adults: No oral absorption. Recent case–controlled study used 1000 mg IV every 8 hours. ⁶ Must be given with clavulanate (available as amoxicillin/clavulanate), 125 mg every 8–12 hours. Children: Not established for TB however for other bacterial infections in children: 20 mg/kg/dose and 40 mg/kg/dose for meningitis or particularly severe infections. Given IV every 8 hours up to 2 grams per dose. Renal failure/dialysis: Adjustment required – 750 mg every 12 hours for creatinine clearance of 20–40 ml/min; 500 mg every 12 hours for creatinine clearance <20 ml/min.
Route of administration	IV only; No oral absorption.
Preparation	Crystalline powder. Product is available in 500 mg, or 1 gram vials.
Storage	Powder should be kept at room temperature (15–25 °C); suspended product should be kept no more than 4 hours at room temperature or no more than 24 hours refrigerated.
CSF penetration	Adequate CSF penetration.

Special circumstances	Use during pregnancy/breastfeeding: There is little information regarding use during pregnancy; unknown safety during breastfeeding. Use in renal disease: Dose adjustment required (see above); dose after dialysis. Use in hepatic disease: Liver disease does not alter the pharmacodynamics of meropenem. Adjustment in dose and interval are based on severity of renal failure and body weight – e.g. 750 mg every 12 hours for creatinine clearance of 20–40 ml/min, 500 mg every 12 hours for creatinine clearance <20 ml/min.
Adverse reactions	Diarrhoea, nausea or vomiting. Seizure (noted with CNS infection), but rare compared to imipenem. Rarely elevated LFTs, haematologic toxicity, hypersensitivity
Contraindications	Carbapenem intolerance.
Monitoring	Symptomatic monitoring.
Patient instructions and alerting symptoms trouble breathing.	Make sure your doctor knows if you are also taking valproic acid or have allergy to penicillins or cephalosporins. Instruct patients to inform their health care provider right away if any of the following occurs: • Severe diarrhoea (watery or bloody) • Skin rash, hives or itching • Swelling in the face, throat or lips • Wheezing or

- De Lorenzo S, Alffenaar JW, Sotgiu G, Centis R, D’Ambrosio L, Tiberi S, et al. Efficacy and safety of meropenem/ clavulanate added to linezolid containing regimens in the treatment of MDR-/XDR-TB. European Respiratory Journal 2013;41(6):1386-1392.

Moxifloxacin (Mfx)

DRUG CLASS: FLUOROQUINOLONE

Activity against TB, mechanism of action, and metabolism	Bactericidal; inhibits DNA gyrase; cross-resistance with other fluoroquinolones, but may be more active based on in vitro data.
Dose	Adults: 400 mg daily (oral or IV). Children: No established dose. Renal failure/dialysis: No dose adjustment required.
Route of administration	Oral or IV.
Preparation	Tablets (400 mg); aqueous solution (400 mg/250 ml) for IV injection.
Storage	Store oral and IV products at room temperature (15–25 °C). Do not refrigerate.
Oral absorption (didanosine, sucralfate).	Good oral absorption (90% bioavailable). Moxifloxacin is an anion and taking with divalent cations will result in bonding and not being absorbed: Administrate 2 hours before or 4 hours after ingestion of milk-based products, antacids, or other medications containing divalent cations (iron, magnesium, calcium, zinc, vitamins,
CSF penetration	Good penetration in animal model studies.

Special circumstances	Use during pregnancy/breastfeeding: Fluoroquinolones are generally avoided during pregnancy and breastfeeding due to observation of arthropathy in animal models. However, there are a few case reports of fluoroquinolones being used safely during pregnancy. Use in renal disease: Excretion unchanged during renal failure; no data on effect of dialysis. Use in hepatic disease: Rarely associated with hepatotoxicity; use with caution. No dose adjustment required for mild or moderate liver disease.
Adverse reactions	Nausea and diarrhea. Headache and dizziness. Rare tendon rupture; arthralgias. Rare hepatotoxicity. QTc prolongation, hypo/hyperglycaemia.
Contraindications	Fluoroquinolone intolerance, prolonged QTc.
Monitoring	Symptomatic monitoring.
Patient instructions and alerting symptoms or dizziness.	Moxifloxacin can be taken with food, but do not take milk-based products, antacids (especially aluminum-coating), vitamin supplements, or sucralfate within 2 hours of this medication or 4 hours after. Instruct patients to inform their health care provider right away if any of the following occurs: • Pain, swelling or tearing of a tendon (such as the back of your ankle, elbow), or muscle or joint pain • Rashes, hives, bruising or blistering, trouble breathing, or tightness in the chest • Diarrhoea • Yellow skin or eyes • Anxiety, confusion

Para-aminosalicylic acid (PAS)

DRUG CLASS: SALICYLIC ACID – ANTI-FOLATE

Activity against TB, mechanism of action, and metabolism	Bacteriostatic.
Dose	Adults: 8–12 grams per day divided 2–3 times per day Children: 200–300 mg/kg/day divided 2–4 times per day Renal failure/dialysis: No change
Route of administration	Oral; should be given sprinkled on or stirred into yogurt or similar food. Not available parenterally in the US
Preparation	4 grams per packet
Storage	Packets should be kept in the refrigerator or freezer
Oral absorption	Incomplete absorption – sometimes requires increased doses to achieve therapeutic concentrations
CSF penetration	Poorly penetrates the meninges (somewhat better with inflammation)

Special circumstances	Use during pregnancy/breastfeeding: Not studied, but no teratogenicity known. There is little data regarding use during breastfeeding. In one patient, the milk concentration was 1 mcg/ml compared to a serum concentration of 70 mcg/ml Use in renal disease: Inactive metabolite is cleared by the kidneys. The package insert says to avoid with severe renal failure. Other authorities believe it can be used with caution (toxicity of metabolite not known) Use in hepatic disease: Use with caution; 0.5% incidence of hepatotoxicity
Adverse reactions	Gastrointestinal distress (less with the PASER® formulation than with older preparations) Rare hepatotoxicity and coagulopathy Reversible hypothyroidism (increased risk with concomitant use of ethionamide); treat with thyroid replacement
Contraindications	Pregnancy (relative).
Monitoring	Monitor TSH, electrolytes, blood counts and liver function tests.
Patient instructions and alerting symptoms	Keep the PASER® product in the refrigerator or freezer. Sprinkle granules over apple-sauce or yogurt or swirl in acidic juices (tomato, grape, grapefruit, cranberry, apple or orange). Do not chew the granules. Take with food if desired. Do not use the packet if it is puffed up or if the granules are discoloured. Gastrointestinal discomfort and diarrhoea usually improve over time. The shells of the granules may be seen in the stool, which is normal. Instruct patients to inform their health care provider right away if any of the following occurs: • Skin rash, severe itching or hives • Severe abdominal pain, nausea or vomiting • Unusual tiredness or loss of appetite • Black stools or bleeding.

Pyrazinamide (Pza)

DRUG CLASS: SYNTHETIC DERIVATIVE OF NICOTINAMIDE.

Activity against TB, mechanism of action, and metabolism	Bactericidal for semi-dormant M. tuberculosis. Mechanism unclear.
Dose	Adults: 25 mg/kg/day (max dose 2 grams). Intermittent dosing at twice or thrice weekly up to 50 mg/kg can be given. Children: 30–40 mg/kg/dose. Renal failure/dialysis: 25 mg/kg/dose, 3 times per week (not daily). Obesity: Use adjusted weight as follows: Ideal body weight + 40% of excess weight Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft
Route of administration	Oral; not available parenterally.
Preparation	500 mg scored or unscored tablet.

Storage	Store the tablets at room temperature (15–25 °C).
Oral absorption	Well absorbed from the gastrointestinal tract.
CSF penetration	Concentrations equivalent to serum.
Special circumstances	Use during pregnancy/breastfeeding: In the United States, pyrazinamide is avoided during pregnancy for drug-susceptible disease due to lack of data regarding teratogenicity, but should be used for drug-resistant TB when the isolate is sensitive to pyrazinamide (no known teratogenicity). Can be used while breastfeeding. Use in renal disease: Cleared by the kidneys; dose 3 times a week and after dialysis. Use in hepatic disease: Use with caution; pyrazinamide is associated with hepatotoxicity in about 1% of patients. It can be quite severe and worsen treatment progress.
Adverse reactions	Gout (hyperuricaemia) and arthralgias. Hepatotoxicity. Rash. Photosensitivity. Gastrointestinal upset.
Contraindications	Allergy to pyrazinamide; severe gout.
Monitoring	Monitor transaminases and uric acid.
Patient instructions and alerting symptoms loss of appetite.	May be taken with or without food; this medicine may cause a rash after sun exposure, so limit sun exposure. Instruct patients to inform their health care provider right away if any of the following occurs: • Skin rash, severe itching or hives • Pain or swelling in the joints • Yellowing of the skin or eyes or dark urine • Nausea or vomiting • Unusual tiredness or

Rifabutin (Rfb)

DRUG CLASS: RIFAMYCIN

Activity against TB, mechanism of action, and metabolism	Bactericidal: same mechanism of activity as rifampin (inhibits RNA polymerase). Less than 20% of rifampin-resistant strains are susceptible to rifabutin.
Dose	Adults: 5 mg/kg/dose (max dose 300 mg, though doses up to 450 mg are sometimes used). Dose adjustments sometimes required when dosing with interacting drugs. Children: The paediatric dose is not established, but doses of 5–10 mg/kg/day have been used (higher doses have been recommended for children <1 year of age). Caution is advised when used in very young children in whom visual changes might not be obvious. Renal failure/dialysis: No dose adjustment in mild renal insufficiency. For creatinine clearance of <30 ml/minute, the usual dose may be used, but monitor drug concentrations to avoid toxicity. Concomitant medications: Dosage adjustment may be required, particularly with antiretroviral therapy is being given. See Tables 15 a-e in http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

Route of administration	Oral; not available parenterally.
Preparation	150 mg capsule.
Storage	Capsules should be kept at room temperature (15–25 °C).
Oral absorption	Well absorbed from the gastrointestinal tract.
CSF penetration	Penetrates inflamed meninges.
Special circumstances	Use during pregnancy/breastfeeding: Insufficient data about use during pregnancy. Unknown effects from breastfeeding. Use in renal disease: Used without dose adjustment in mild renal insufficiency. For creatinine clearance <30 ml/minute, the usual dose may be used, but monitor drug concentrations to avoid toxicity. Use in hepatic disease: Use with caution and additional monitoring in liver disease. Dose adjustments are necessary for drug interactions, especially HIV drugs.
Adverse reactions	Leukopenia (dose dependent); thrombocytopenia. Rashes and skin discolouration (bronzing or pseudojaundice). Anterior uveitis and other eye toxicities. Hepatotoxicity similar to that of rifampin. Drug interactions with many other drugs—but only 40% of that is seen with rifampin. Rifabutin concentrations may be affected by other drugs. Arthralgias.
Contraindications	Rifamycin hypersensitivity. Data are lacking on cross-sensitivity to rifabutin in patients with hypersensitivity. If used, use with caution, with careful monitoring of patient for development of hypersensitivity. Should not be used for patients with MDR-TB.
Monitoring	Increased liver function monitoring; monitor drug concentrations of interacting medications; blood counts and vision screening.
Patient instructions and alerting symptoms or loss of appetite.	May be taken with or without food; if it irritates the stomach, try taking it with food. It is normal for urine, tears and other secretions to turn a brownish-orange color when taking this medicine. Sometimes the skin becomes discoloured. Soft contact lenses may become discoloured while on this medicine. Make sure your doctor knows all the medicines you take, as there are many drugs that interfere with this one. Avoid the use of oral hormone-based birth control methods because rifabutin may decrease their effectiveness. Instruct patients to inform their health care provider right away if any of the following occurs: • Any eye pain, change in vision or sensitivity to light • Fever, chills or sore throat • Pain or swelling in the joints • Yellowing of the skin or eyes or dark urine • Nausea or vomiting • Unusual tiredness

Rifampin (Rif)

DRUG CLASS: RIFAMYCIN

Activity against TB, mechanism of action, and metabolism	Bactericidal; inhibits protein synthesis; cross-resistance with other rifamycins.
Dose	Adults: 10 mg/kg/dose up to 600 mg (oral or IV). Children: 10-20 mg/kg/dose up to 600 mg (oral or IV). Renal failure/dialysis: No adjustment required. Concomitant medications: Dosage adjustment may be required for concurrent medications, including warfarin. After stopping rifampin, warfarin dosage may require downward adjustment to prevent toxicity. Concurrent treatment with most antiretroviral drugs is not recommended, as antiretroviral drug concentrations are substantially reduced. Rifampin plasma concentrations are not affected by most other drugs (based on current data).
Route of administration	Oral or IV.
Preparation	150 and 300 mg capsules; lyophilized powder for injection: 600 mg/vial; contents of capsules can be mixed with liquid or semi-soft vehicles. Extemporaneously prepared oral solutions have unproven homogeneity and shelf life. Immediate administration of the dose after mixing capsular contents in a vehicle is ideal.
Storage	Capsules and powder should be kept at room temperature (15–25 °C); powder suspended in saline is stable for 24 hours; powder suspended in dextrose solutions is stable for 4 hours.
Oral absorption	Usually absorption is rapid but may be delayed or decreased by high-fat meals.
CSF penetration	Rifampin CSF penetration is variable and typically achieves only 10–20% of serum concentrations in CSF (may be better in the face of inflamed meninges), but this may still be an important contribution to the regimen. Some authors recommend increased doses of rifampin in patients with TB meningitis.
Special circumstances	Use during pregnancy/breastfeeding: Recommended for use during pregnancy; can be used while breastfeeding. Use in renal disease: Can be used without dose adjustment. Use in hepatic disease: Use with caution as it can be associated with hepatotoxicity.
Adverse reactions	Many drug interactions. Orange staining of body fluids Rash and pruritus Gastrointestinal upsets, flu-like syndrome (usually only with intermittent administration). Hepatotoxicity. Haematologic abnormalities (thrombocytopenia, haemolytic anaemia).
Contraindications	Rifamycin allergy; due to drug interactions, may be contraindicated with concurrent use of certain drugs.

Monitoring	Liver function monitoring if appropriate (if given with other hepatotoxic medications or if there are symptoms of hepatotoxicity); monitor drug concentrations of interacting medications.
Patient instructions and alerting symptoms B upset • Fever or chills.	est taken without food; if it irritates the stomach, try taking it with a small amount of food. It is normal for urine, tears and other secretions to turn an orange color when taking this medicine. Soft contact lenses may become discolored while on this medicine. Make sure your doctor knows all the medicines you take because many drugs can interfere with this one. Avoid the use of oral hormone-based birth control methods because rifampin may decrease their effectiveness. Instruct patients to inform their health care provider right away if any of the following occurs: • Unusual tiredness or loss of appetite • Severe abdominal

Rifapentine (Rpt)

DRUG CLASS: RIFAMYCIN

Activity against TB	Bactericidal; same mechanism of action as rifampin, inhibits RNA polymerase. 100% cross-resistant with rifampin.
Dose Tuberculosis Disease	Adults: 600 mg once weekly during the continuation phase of treatment. (Not recommended in the US for the initial treatment phase.) Higher daily doses are being studied. Children: (12 years and older), 600 mg once weekly if >45 kg. 450 mg once weekly if <45 kg.
Dose for LTBI Adults: on current data).	900 mg once weekly for 12 doses given with isoniazid 900 mg. Children: (12 years and older), once weekly dose for 12 weeks based on weight (10.0–14.0 kg = 300 mg; 14.1–25.0 kg = 450 mg; 25.1–32.0 kg = 600 mg; 32.1–49.9 kg = 760 mg; >50 kg = 900 mg) given with isoniazid 15 mg/kg weekly. Renal failure/dialysis: No adjustment required. Only 17% of ingested dose is excreted renally. Concomitant medications: Dosage adjustment may be required for concurrent medications. Concurrent treatment with most antiretroviral drugs is not recommended, as antiretroviral drug concentrations are substantially reduced, as with rifampin. However, rifapentine plasma concentrations are not affected by most other drugs (based
Route of administration	Oral
Preparation	150 mg tablets.
Storage	Tablets should be stored at room temperature (15–25 °C).
Pharmacokinetics	Time to peak concentration after an oral dose is 5–6 hours. Peak concentrations after a 600 mg dose are expected to be 8–30 mcg/ml. The half-life is approximately 13 hours.

Oral absorption	Oral bioavailability is 70%. Peak concentration and area under the curve (AUC) are increased if given with a meal.
CSF penetration	No information available
Special circumstances	Use during pregnancy: Pregnancy category C. Use only if potential benefit outweighs possible risk. Use in renal disease: Insufficient data, but likely to be safe since only minimally excreted by the kidneys. Use in hepatic disease: Pharmacokinetics are very similar to normal volunteers in persons with mild to severe liver impairment. Dose adjustments: Not necessary to adjust rifapentine dosage due to drug interactions but may be needed for concurrent drugs, as for rifampin.
Adverse reactions	Many drug interactions. Red–orange staining of body fluids Rash and pruritis Hypersensitivity reaction Hepatotoxicity Haematologic abnormalities.
Contraindications	History of hypersensitivity to any of the rifamycins (i.e. rifampin or rifabutin)
Monitoring	Liver function monitoring if appropriate (if given with other hepatotoxic medications or if there are symptoms of hepatotoxicity); monitor drug concentrations of interacting medications.
Patient instructions and alerting symptoms	Rifapentine may cause reddish coloration of your urine, sweat, sputum, tears, and breast milk – be aware that your contact lenses or dentures may be permanently stained. The reliability of oral or other systemic hormonal contraceptives may be affected; consider using alternative contraceptive measures. If you are prone to nausea, vomiting, or gastrointestinal upsets, taking rifapentine with food may be useful. Instruct patients to inform their health care provider right away if any of the following occurs: • Fever • Loss of appetite • Malaise • Nausea and vomiting • Darkened urine • Yellowish discoloration of the skin and eyes • Pain or swelling of the joints.

Streptomycin (Sm)

DRUG CLASS: AMINOGLYCOSIDE

Activity against TB, mechanism of action, and metabolism	Bactericidal; inhibits protein synthesis; no significant cross-resistance with other aminoglycosides.
Dose	Adults: 15 mg/kg/day in a single daily dose, 5–7 days per week (maximum dose is generally 1 gram) >59 years of age: 10 mg/kg/dose (max 750 mg) 5–7 times per week or 2–3 times per week after the initial period. Alternatively, 15 mg/kg/dose, 3 times per week. Children: 20–40 mg/kg/day (max 1 gram), 5–7 days per week. Renal failure/dialysis: 12–15 mg/kg/dose, 2–3 times weekly (not daily). Markedly obese individuals should have an adjusted dose due to the decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations. For dosing, use adjusted weight as follows: Ideal body weight + 40% of excess weight. Ideal body weight (men): 50 kg plus 2.3 kg/inch over 5 ft Ideal body weight (women): 45 kg plus 2.3 kg/inch over 5 ft If possible concentrations should be followed closely.
Route of administration	IV or IM (has been used intrathecally and intraperitoneally). Not absorbed orally.
Preparation	1 gram vial for injection.
Storage	Store in the refrigerator.
Oral absorption	There is no significant oral absorption. Intramuscular absorption might be delayed if the same site is used consistently.
CSF penetration	Variable penetration; appears to penetrate inflamed meninges better.
Special circumstances risk of ototoxicity.	Use during pregnancy/breastfeeding: Avoided during pregnancy due to documented cases of congenital deafness. Can be used while breastfeeding. Use in renal disease: Use with caution. Concentrations should be monitored for patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis. See section above for dosage under renal disease or dialysis. The drug is variably cleared by haemodialysis. Use in hepatic disease: Drug concentrations are not affected by hepatic disease (expect a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution as patients with severe liver disease may progress rapidly to hepatorenal syndrome. Diuretic use: Coadministration of loop diuretics and aminoglycoside antibiotics carries an increased

Adverse reactions	Nephrotoxicity: Less nephrotoxic than amikacin. Ototoxicity (hearing loss): Increased with advanced age and prolonged use. Vestibular toxicity. Local pain with IM injections. Electrolyte abnormalities, including hypokalaemia, hypocalcaemia, and hypomagnesaemia.
Contraindications	Pregnancy (congenital deafness seen with streptomycin and kanamycin use during pregnancy); Hypersensitivity to aminoglycosides; caution with renal, vestibular or auditory impairment.
Monitoring	Monitor renal function by documenting creatinine at least monthly (more frequently if renal or hepatic impairment); document creatinine clearance if there is baseline renal impairment or any concerns; document baseline and monthly audiology exam. Question patient regularly about vestibular complaints and perform serial vestibular exams. Document peak and trough concentrations at baseline if there is any question about renal function. Some experts monitor aminoglycoside concentrations routinely, regardless of renal function. Monitor concentrations serially for patients with impaired renal function.
Patient instructions and alerting symptoms	Instruct patients to inform their health care provider right away if any of the following occurs: • Problems with hearing, dizziness or balance • Rash or swelling of your face • Trouble breathing • Decreased urination • Watery or bloody diarrhoea • Swelling, pain or redness at your IV site • Muscle twitching or weakness.

Drug interaction sheets

AMIKACIN (Am)

DRUG CLASS: AMINOGLYCOSIDE

Drug interactions

Loop diuretics (bumetanide, furosemide, etacrynic acid, tora-semide). Co-administration of aminoglycosides with loop diuretics may have an additive or synergistic auditory ototoxicity. Ototoxicity appears to be dose-dependent and may be increased with renal dysfunction. Irreversible ototoxicity has been reported. Avoid concomitant administration; if used together, careful dose adjustments in patients with renal failure and close monitoring for ototoxicity are required.

Non-depolarizing muscle relaxants (atracurium, pancuronium, tubocurarine, gallamine triethiodide): possible enhanced action of non-depolarizing muscle relaxants resulting in possible respiratory depression. Nephrotoxic agents (amphotericin B, foscar-net, cidofovir): additive nephrotoxicity.

Penicillins: in vitro inactivation (possible). Do not mix together before administration.

CAPREOMYCIN (Cm)

CLASS: CYCLIC POLYPEPTIDE

Drug interaction

Avoid co-administration of non-depolarizing muscle relaxants. If concurrent administration is needed, titrate the non-depolarizing muscle relaxant slowly and monitor neuromuscular function closely. Though not reported with capreomycin, neuromuscular blockade has been reported with other polypeptide antibiotics when administered with non-depolarizing muscle relaxants. Avoid use with other nephro- or ototoxic agents because of the additive effect.

CIPROFLOXACIN

CLASS: FLUOROQUINOLONE

Drug interactions

Sucralfate: decreased absorption of fluoroquinolones caused by chelation by aluminium ions contained in the sucralfate. Antacids (magnesium, aluminium, calcium, Al-Mg buffer found in didanosine): binding to fluoroquinolone antibiotics resulting in decreased absorption and loss of therapeutic efficacy. Probenecid: interferes with renal tubular secretion of cipro-floxacin; this may result in 50% increase in serum level of cipro-floxacin.

Milk or dairy products: decrease the gastrointestinal absorption of ciprofloxacin by 36–47%. Vitamins and minerals containing divalent and trivalent cations such as zinc and iron: formation of fluoroquinolone-ion complex results in decreased absorption of fluoroquinolones.

CLOFAZIMINE (Cfz)

DRUG CLASS: PHENAZINE DERIVATIVE

Drug Interactions

May decrease absorption rate of rifampicin. Isoniazid increased lofazimine serum and urine concentrations and decreases skin concentrations. Ingestion of clofazimine with orange juice resulted in a modest reduction in clofazimine bioavailability.

Annexure-III

CYCLOSERINE (Cs)

DRUG CLASS: ANALOG OF D-ALANINE

Drug Interactions

Ethionamide: additive nervous system side-effects. Isoniazid: additive nervous system side-effects. Phenytoin: may increase phenytoin levels. Toxic effect if combined with alcohol, increases risk of seizures. Vitamin B₆ decreases CNS effect.

Ethionamide & Prothionamide

DRUG CLASS: CARBOTHIONAMIDES GROUP, DERIVATIVES OF ISONICOTINIC ACID

Drug Interactions

Cycloserine: potential increase incidence of Neurotoxicity. Ethionamide has been found to temporarily raise serum concentrations of isoniazid. Thionamides may potentiate the adverse effects of other antituberculosis drugs administered concomitantly. In particular, convulsions have been reported when ethionamide is administered with cycloserine. Excessive ethanol ingestion should be avoided because of possible psychotic reaction. PAS: possible increase in liver toxicity, monitor liver enzymes; hypothyroidism in case of combined administration.

GATIFLOXACIN (Gfx)

DRUG CLASS: FLUOROQUINOLONE

Drug Interactions

Mexiletine: fluoroquinolones may inhibit cytochrome P450 1A2, resulting in increased mexiletine concentration. Warfarin: case reports of gatifloxacin enhancing anticoagulation effect of warfarin.

KANAMYCIN (Km)

DRUG CLASS: AMINOGLYCOSIDE

Drug Interaction

Non-depolarizing muscle relaxants (atracurium, pancuronium, tubocurarine, gallamine triethiodide): possible enhanced action of non-depolarizing muscle relaxant resulting in possible respiratory depression. Avoid co-administration; if concurrent administration is needed, titrate the non-depolarizing muscle relaxant slowly and monitor neuromuscular function closely. Nephrotoxic agents (amphotericin B, foscarnet, cidofovir): additive nephrotoxicity. Avoid co-administration; if used together, monitor renal function closely and discontinue if warranted. Penicillins: in vitro inactivation (possible). Do not mix together before administration.

LEVOFLOXACIN (Lfx)**DRUG CLASS: FLUOROQUINOLONE****Drug Interactions:**

Should not be given to patients receiving class Ia antiarrhythmic drugs (such as quinidine and procainamide) or Class III anti-arrhythmics (such as amiodarone and sotalol). Sucralfate: decreased absorption of fluoroquinolones caused by the chelation by aluminium ions contained in the sucralfate. Antacids (magnesium, aluminium, calcium, Al-Mg buffer found in didanosine): antacid binding to fluoroquinolone antibiotics resulting in decreased absorption and loss of therapeutic efficacy. Probenecid: probenecid interferes with renal tubular secretion of fluoroquinolones, which may result in 50% increase in serum level of levofloxacin. Vitamins and minerals containing divalent and trivalent cat ions such as zinc and iron. Formation of fluoroquinolone-ion complex results in decreased absorption of fluoroquinolones. Mexiletine: fluoroquinolones may inhibit cytochrome P450 1A2 resulting in increased mexiletine concentration.

MOXIFLOXACIN (Mfx)**DRUG CLASS: FLUOROQUINOLONE****Drug Interactions:**

Should not be given to patients receiving class Ia antiarrhythmic drugs (such as quinidine and procainamide) or class III anti-arrhythmics (such as amiodarone and sotalol). Sucralfate: decreased absorption of fluoroquinolones caused by the chelation by aluminium ions contained in the sucralfate. Antacids (magnesium, aluminium, calcium, Al-Mg buffer found in didanosine): antacid binding to fluoroquinolone antibiotics resulting in decreased absorption and loss of therapeutic efficacy. Vitamins and minerals containing divalent and trivalent cat ions such as zinc and iron: formation of fluoroquinolone-ion complex results in decreased absorption of fluoroquinolones

OFLOXACIN (Ofx)**DRUG CLASS: FLUOROQUINOLONES****Drug Interactions**

Fluoroquinolones are known to inhibit hepatic drug metabolism and may interfere with the clearance of drugs such as theophylline and caffeine that are metabolized by the liver. Cations such as aluminium, magnesium or iron reduce the absorption of ofloxacin and related drugs when given concomitantly. Changes in the pharmacokinetics of fluoroquinolones have been reported when given with histamine H₂ antagonists, possibly due to changes in gastric pH, but do not seem to be of much clinical significance. The urinary excretion of ofloxacin and some other fluoroquinolones is reduced by probenecid; plasma concentrations are not necessarily increased.

P-AMINOSALICYLIC ACID (PAS)**DRUG CLASS: SALICYLIC ACID; ANTI-FOLATE****Drug Interactions**

Digoxin: possible decrease in digoxin absorption; monitor digoxin level – may need to be increased. Ethionamide: possible increase in liver toxicity, monitor liver enzymes;

hypothyroidism in case of combined administration. Isoniazid: decreased acetylation of isoniazid resulting in increased isoniazid level. Dose may need to be decreased.

MDR-TB INDICATORS

A minimum set of indicators for the programmatic management of MDRTB in national tuberculosis control programmes

The indicators are grouped into four classes:

1. Detection
2. Enrolment
3. Interim results
4. Final outcomes

Abbreviations:

ART :	antiretroviral therapy
DST :	drug susceptibility testing
HIV :	human immune deficiency virus
MDR/MDR-TB :	multidrug-resistant tuberculosis; resistance to at least isoniazid and rifampicin
TB :	tuberculosis
XDR/XDR-TB :	extensively drug-resistant tuberculosis; MDR with additional resistance to a fluoroquinolone and a second-line injectable (amikacin, kanamycin, or capreomycin) anti-TB medication

1. Detection

Rationale

Drug susceptibility tests (DST) for rifampicin and isoniazid are indicated in patients suspected to harbour drug-resistant TB strains. Early detection of resistance is intended to ensure an appropriate drug regimen from the start and presumably increase likelihood of success and allay amplification of resistance patterns. Limited resources usually mean that DST is reserved for patients considered at increased risk of drug resistance. Groups to be targeted for DST vary by national policy but usually include patients who have been previously treated but failed a first or a subsequent course of TB medication. Contacts of confirmed MDR-TB patients, and in some settings patients with HIV-associated TB, are also often tested. DST for fluoroquinolones and second-line injectable anti-TB medication is important in MDR case management. The four indicators for detection measure the access of TB patients to DST. The delay in testing and the frequency of MDR among individuals in different risk categories is also evaluated. The importance of these parameters for the programme manager is that they calculate how the targeting and timeliness of DST, as well as the yield of MDR cases, vary by the risk category of the patient targeted.

The period of assessment is six calendar months. This is usually counted from January to end June and July to end December. Indicators are measured three months after the end of the six-month period. All data can be extracted from the basic TB register and treatment card and the laboratory register for culture and DST. **Calculation**

1) TB patients with result for isoniazid and rifampicin DST

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

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

2) Confirmed MDR-TB cases detected among TB patients tested for isoniazid and rifampicin DST

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

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

These two indicators are to be calculated for all cases tested and as many risk categories as exist in the national policy.

3) Confirmed MDR-TB cases tested for susceptibility to fluoroquinolone and second-line injectable

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

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

4) Delay in diagnosis of MDR-TB

Definition: The duration in days between the date when the TB patient was identified as being in a risk category as per the national policy and the date of the DST results for isoniazid and rifampicin as recorded in the laboratory register. The first date is determined by type of risk category. It may correspond to when TB is diagnosed if universal DST is practised, or when a laboratory result indicates treatment failure or persistent sputum smear positivity during a course of TB treatment, or when HIV-associated TB is detected, or, in the case of a contact with TB, when the laboratory confirms MDR in the index case.

The calculation is done on all cases with DST results for isoniazid and rifampicin (sensitive or resistant) entered in the laboratory register during the six-month period of assessment. The indicator is expressed as the arithmetic mean number of days with the minimum and maximum ranges for all episodes included in the calculation. The number of episodes included in the calculation should be indicated.

2. Enrolment

Rationale

The programme manager is responsible to ensure that all patients in whom MDR-TB is suspected or detected are placed on appropriate treatment in the shortest time possible. Early detection of resistance is intended to ensure a correct drug regimen from the start and lower risks of further amplification of drug resistance. Four minimum indicators have been identified to assess the pattern of enrolment of TB patients on second-line drug treatment, including that among children and females. An additional stratification for HIV-positive MDR-TB patients assesses the proportion of them on antiretroviral treatment (ART). Confirmed XDR-TB patients should be put on adequate medication. A comparison of enrolled to identified MDR-TB cases gives an indication of access to care albeit that patients started on treatment may have been detected prior to the period of assessment.

This period is six calendar months, usually counted from January to end June and July to end December. Indicators are measured in the month following the end of the six-month period. All data can be extracted from the MDR-TB treatment register and the laboratory register for culture and DST.

Calculation

1) MDR-TB cases (suspected or confirmed) enrolled on MDR-TB treatment

Definition:	Number of MDR-TB cases (suspected or confirmed) registered and started on a prescribed MDR-TB treatment regimen during the period of assessment.
Comparator:	Number of MDR-TB cases (suspected or confirmed) eligible for second line drugs treatment during the period of assessment.

This indicator is computed for (i) all cases, (ii) cases aged < 15 y, and (iii) females.

2) Confirmed MDR-TB cases enrolled on MDR-TB treatment regimen

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

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

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

3) Confirmed XDR-TB cases enrolled on XDR-TB treatment regimen

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

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

4) Delay in start of MDR-TB treatment

Definition: The duration in days between the date of MDR confirmation (DST results showing resistance to both isoniazid and rifampicin in the MDR-treatment register) and the date when the patient started a prescribed second-line drug regimen as per the MDR-treatment register.

The calculation is done on all confirmed MDR-TB cases recorded on the MDR-treatment register during the six-month period of assessment. The indicator is expressed as the arithmetic mean number of days with the minimum and maximum ranges for all episodes included in the calculation. If treatment was started before the confirmatory DST was reported then the delay is marked as zero days. The number of episodes included in the calculation should be indicated.

4. Interim results

Rationale

Treatment for MDR-TB typically takes two years or more. The programme manager often needs an indication of how patients are faring well before final outcomes can be assessed, typically two to three years after the start of enrolment. This is particularly important when a drug-resistant TB treatment programme starts. Assessing culture conversion (for confirmed pulmonary cases) and death by six months is widely used as a proxy of final outcomes. Information on defaulting by 6 months is helpful. It is also useful to know how many patients started on second-line drugs for MDR turned out not to be MDR. And likewise for XDR. This evaluates the effectiveness of the treatment algorithm in reserving treatment for patients who really need it and avoiding a potentially toxic regimen in patients who do not.

The period of assessment is three calendar months (quarter), usually counted from January to end March, April to end June, July to end September and October to end December. All patients registered and starting treatment during the period of assessment are included in the calculation. Indicators are measured nine months after the end of the quarter of assessment. This gives sufficient time for culture results at month 6 to be issued and retrieved. All data can be extracted from the MDR-TB treatment register.

Calculation

1) MDR-TB cases on MDR-TB treatment regimen with negative culture by six months

Numerator: Number of confirmed pulmonary MDR-TB cases registered and started on a prescribed MDR-TB treatment with negative results for culture during month 6 of their treatment.

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

2) MDR-TB cases on MDR-TB treatment regimen who died by six months

Numerator: Number of confirmed MDR-TB cases registered and started on a prescribed MDR-TB treatment who died of any cause by the end of month 6 of their treatment.

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

3) MDR-TB cases on MDR-TB treatment regimen who defaulted by six months

Numerator: Number of confirmed MDR-TB cases registered and started on a prescribed MDR-TB treatment who defaulted by the end of month 6 of their treatment

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

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

4) Patients on MDR-TB treatment regimen found not to have MDR

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

5) Patients on XDR-TB treatment regimen found not to have XDR

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

4. Final outcomes

Rationale

For the manager, the final outcome is the most important direct measurement of the effectiveness of the MDR-TB control programme in terms of patient care. All confirmed MDR-TB patients entered on the treatment register should be assigned one of six mutually exclusive outcomes at the end of their therapy. The outcome categories are aligned to the ones in use for treatment of drug-susceptible TB, and the definitions are the same with the exception of cured and failed (WHO/HTM/TB/2008.402). Cases who are not evaluated due to transfer, treatment still not completed at the time of final assessment or missing information are grouped together. All patients should be assigned the first outcome they experience for the treatment being evaluated. Success (cure and completion) and death should be measured separately for HIV-positive individuals in high prevalence situations.

The period of assessment is 12 calendar months, usually counted from January to end December, and referred to as an annual cohort. All patients starting treatment during this period are included in the calculation. Indicators are measured 24 months after the end of the year of assessment. This gives sufficient time for most patients to complete their

treatment and for the final culture results to be issued and retrieved. All data can be extracted from the MDR-TB treatment register.

Calculation

MDR-TB cases on MDR-TB treatment regimen with an outcome :

- 1 -cured
- 2 -completed
- 3 -died
- 4 -failed
- 5 -defaulted

6 -MDR-TB cases on MDR-TB treatment regimen with no outcome assigned (transferred, still on treatment or unknown).

Numerator: In the above, the numerator is the number of confirmed MDR-TB cases registered for MDR-TB treatment during the period of assessment with an outcome as noted from 1 -6.

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

Programmes having the capacity to differentiate XDR-TB from other MDR-TB cases and in which >5% of MDR-TB cases have XDR should report outcomes for non-XDR MDR-TB and XDR-TB cases separately. MDRTB patients found to have XDR anytime in the course of their MDR treatment would be taken out of the non-XDR MDR-TB cohort and put in the XDR cohort.

The outcome "cured" is restricted to pulmonary cases only. The first three indicators (cured, completed, and died) should be computed separately for cases with positive HIV status in countries where HIV prevalence is 1% in pregnant women or 5% in TB patients (WHO/HTM/TB/2007.379). When these indicators are used at sub-national level, stratification by HIV-status may also be warranted depending on the local HIV epidemiology and the magnitude of HIV-associated TB in the particular setting.

Variables for reporting

The following tables are intended for illustrative purposes only and countries may wish to adapt the format of their reporting templates as is necessary for their specific programmes.

1. Detection

Six-month period
of assessment:

Risk category (list as many as exist)	Number of TB cases			
	Total	With results for isoniazid & rifampicin	Resistant to both isoniazid & rifampicin (MDR)	With MDR and tested for a fluoroquinolone & a 2 nd line injectable
Risk category 1 (specify)				
Risk category 2 (specify) ...				
Total				

Number of MDR-TB cases with information on interval	Interval between MDR suspicion and DST results (in days)		
	Mean	Minimum	Maximum

2. Enrolment

Six-month period of assessment:

TB patient type	Identified during assessment period	Enrolled on M(X)DR-TB treatment during period of assessment
All patients eligible for treatment*		
< 15 y		
Female		

Confirmed MDR		
Confirmed MDR, HIV+ on ART		
Confirmed MDR, HIV+ not on ART		
Confirmed XDR		

Number of MDR-TB cases with information on interval	Interval between DST results and start of treatment (in days)		
	Mean	Minimum	Maximum

* suspected or confirmed MDR

3. Interim results

Three-month period of assessment:

Number of confirmed MDR-TB cases started on MDR-TB treatment	Culture negative at six months		Died by six months		Defaulted by six months	
	N	%	N	%	N	%

Number of patients started on MDR-TB treatment found not to have MDR	
Number of patients started on XDR-TB treatment found not to have XDR	

4. Final outcomes

Twelve-month period of assessment:

TB patient type	Number of cases started on treatment	Cured		Completed		Died		Failed		Defaulted		No outcome assigned	
		N	%	N	%	N	%	N	%	N	%	N	%
All confirmed MDR-TB cases													
All confirmed XDRTB cases *													
MDR-TB HIV+ *													

See note in text above for the conditions under which these separate strata are indicated

Annexure IVA: Laboratory safety requirements for persons who manipulate *Mycobacterium tuberculosis* complex species

ATS Level	BSL	Activity	Facility	Safety equipment	Practices and procedures
1	2	<ul style="list-style-type: none">) Collecting clinical specimens (including aerosol-induced sputa).) Transporting specimens to a higher level laboratory for isolation and identification. 	BSL-2 and/or BSL-3 requirements including the availability of: <ul style="list-style-type: none"> ■ a hand washing sink. ■ an autoclave. 	All specimens from patients suspected of having tuberculosis must be handled in a Class I or Class II BSC.	Standard microbiological practices including: <ul style="list-style-type: none">) Limited access to the laboratory) Biosafety manual available describing procedures for waste decontamination,

		<ul style="list-style-type: none">) Preparing and examining smears of killed tubercle bacilli for presumptive diagnosis and or following the progress of tuberculosis patients on chemotherapy.* 	<ul style="list-style-type: none"> ■ an eyewash facility 	<p>Personal protective equipment must be used as indicated (see *Personal Protective Equipment).</p>	<p>emergency responses, and medical surveillance policies</p> <ul style="list-style-type: none">) Adherence to "sharps" precautions.) Annual tuberculin skin test for all laboratories.
II	3	<p>Performing functions of ATS Level 1 laboratory and processing specimens as necessary for microscopy and culture on standard egg- or agar-based media.</p> <ul style="list-style-type: none">) Identifying <i>M. tuberculosis</i>.) Performing optional drug susceptibility studies against <i>M. tuberculosis</i>.) Retaining mycobacterial cultures for additional or repeat tests (for up to 6 months). 	<p>BSL-3 facility requirements including:</p> <p>Physical separation from access corridors</p> <ul style="list-style-type: none">) Access via two self-closing doors (e.g., through an anteroom, or a BSL-2 area).) Single-pass air system; exhaust air not recirculated.) Directional air flow through the laboratory following a negative pressure gradient. 	<p>Class II or III BSCs must be used for all manipulations of specimens and cultures that may contain <i>M. tuberculosis</i>. Personal protective equipment required includes gloves gown/lab coat, and respirator; eye protection required for persons who wear contact-lenses.</p>	<p>BSL-3 practices and procedures including:</p> <ul style="list-style-type: none"> • Controlled access to laboratory. • Decontamination of all waste before removal from the laboratory. • Personal protective equipment removed before leaving the laboratory. • Decontamination of laboratory clothing before laundering or disposal. • Baseline serum stored (for blood borne-pathogen surveillance procedures).
III	3	<p>Performing functions of ATS level I and II laboratories including:</p> <ul style="list-style-type: none">) Identifying all <i>Mycobacterium</i> species from clinical specimens) Performing required drug susceptibility studies against mycobacteria.) Conducting research and providing training to other laboratorians 	<p>Same as for ATS Level II.</p>	<p>Same as for ATS Level II.</p>	<p>Same as for ATS Level II.</p>

*Proficiency in reading smears may be maintained by examination of 10-15 specimens per week.

#These precautions include a) no recapping of needles, and b) use of puncture- and leak-proof waste containers.

§Proficiency in culture and identification of *M. tuberculosis* may be maintained by digestion and culture of 20 specimens per week.

NOTE:ATS=American Thoracic Society; **BSL**=Biosafety Level; **BSC**=Biosafety Cabinet.

Annexure IV B: Technical Specification of Transport Box for Sputum Samples transportation in Cold Chain

A: Gujarat Model: Total capacity up to 4 Falcon Tubes (from peripheral DMCs)

Thermacol Box: Outer dimension (Cm): 18.5 X 12.5 X 13 Inner dimension (Cm): 14.25 X 8.25 X 10.25

No. of gel packs required: 2

Weight of fully packed consignment box: 400 grams.

Approximate cost of courier charge: 60-70 Rupee per box



Gel packs maintain a temperature between 12 - 20 Deg Celsius for up to approximately +48 hours in tightly packed thermacol boxes (average outside temperature 35°C)

If conditioned in the deep freezer (temperature between -20 to C to -15 o C) for a minimum of 48 hours to a maximum of 72 hours before use

{This is a onetime use box. Thermacol boxes and gel packs are not reused.}

B: Andhra Pradesh Model: Total capacity up to 8 Falcon Tubes (from high burden TU/DTC DMCs)

Thermacol Box: Outer dimension (inches): 11 X 9 X 9 Inner dimension (inches): 8 X 6.5 X 6.5

A cardboard /thermocool sheet also to hold the falcon tubes upright

No. of gel packs required: 2

Weight of fully packed consignment box: 1.5 kg.

Approximate cost of courier charge: 200-300 Rupee per box



Gel packs maintain a temperature between 12 - 20 Deg Celsius for up to approximately +48 hours in tightly packed thermocol boxes (average outside temperature 35°C)

If conditioned in the deep freezer (temperature between -20 to C to -15 o C) for a minimum of 48 hours to a maximum of 72 hours before use

{This is a onetime use box. Thermocol boxes and gel packs are not reused.}

