2023

NATIONAL GUIDELINES ON

Drug Resistant Tuberculosis Management



Government of Nepal
Ministry of Health and Population
Department of Health Services
National Tuberculosis Control Centre
Thimi, Bhakatapur

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PREFACE

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PREFACE

The National Tuberculosis Program (NTP) has envisioned a TB Free Nepal in line with WHO END TB Strategy and Sustainable Development Goals (SDGs). Nepal has made notable progress in increasing universal access to the drug-susceptibility testing for all diagnosed TB patients and expanding the scope of people-centered care for DR-TB patients. However, Tuberculosis (TB) still remains a major public health problem in Nepal. Especially, the emergence of drug resistance among TB patients has been a significant threat.

To address this growing public health threat, the former National Guideline on Drug-resistant Tuberculosis (DR-TB) Management, 2019 has been updated, aligning with the recent WHO Guidelines for Tuberculosis, to uptake the newer, safer, shorter, all-oral, and people-friendly treatment regimens in the country. This document serves as a guide to healthcare workers at all levels who are involved in the management of DR-TB. Further, implementing these guidelines requires strong commitment and collaborative effort from all stakeholders including policymakers, program managers, clinicians, public health professionals, paramedics, and caregivers, along with investments in improving access to quality services and enabling effective surveillance systems for programmatic management of the DR-TB in Nepal.

I congratulate the director and the team of National Tuberculosis Control Center (NTCC) along with other relevant stakeholders for developing this comprehensive guideline. I adjure all program managers, clinicians, and health care providers for upright implementation of these guidelines at all levels. Additionally, with unwavering effort from civil society, and community members, I truly believe we can win this battle against DR-TB together.

Dr. Roshan Pokhrel
Secretary

PREFACE

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PREFACE

Drug-resistant Tuberculosis (DR-TB) poses a significant challenge in TB care and control in Nepal. In 2021, World Health Organization (WHO) listed Nepal as one of the top 30 high burden countries for DR-TB in the world. The National TB Prevalence survey conducted in 2018 has estimated an annual 2200 incident cases of DR-TB in Nepal. The national Drug-resistance survey (DRS) conducted in 2011 observed 2.2% multidrug resistant/rifampicin resistant tuberculosis (MDR/RR-TB) among new patients and 15.4% among retreatment patients.

In the past few years, the National Tuberculosis Program (NTP) has made major progress in the diagnosis and treatment of DR-TB. The rapid molecular diagnostic facilities were expanded to cover the whole country, treatment centers were upgraded to improve the quality treatment and community based directly observed treatment (CB-DOT) for DR-TB patients were initiated.

In this updated guideline, the major changes are the uptake of all-oral, shorter, and safer people friendly regimens for DR-TB treatment aligned with latest WHO recommendations. This guideline works as a comprehensive national reference document intended for use by healthcare professionals, including clinicians, chest specialists, physicians, medical officers, public health decision makers, program managers, technical and implementing partners involved in the prevention, diagnosis, care, and treatment of DR-TB. Effective management of DR-TB necessitates the collective efforts of all stakeholders across various levels.

I would like to express my sincere appreciation for the invaluable contributions made by my team at NTCC during the preparation of this guideline. I want to extend special gratitude to the WHO country office in Nepal for their robust technical support in aligning this guideline with the latest WHO recommendations. Additionally, I am deeply thankful to the clinicians, pulmonologists, pediatricians, physicians, chest specialists and endocrinologists whom we frequently consulted during the guideline development phase. Finally, I extend my heartfelt thanks to all the individuals, experts, partners, civil society that actively participated in shaping this guideline into its final form.

Dr. Prajowl Shrestha
Director

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ABBREVIATIONS

aDSM	Active Tuberculosis Drug Safety Monitoring and Management
ANC	Antenatal Care
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
BAL	Bronchoalveolar Lavage
BMI	Body Mass Index
BPaL	A Regimen of Bedaquiline, Pretomanid and Linezolid
BPaLM	A Regimen of Bedaquiline, Pretomanid, Linezolid and Moxifloxacin
CBC	Complete Blood Count
CNS	Central Nervous System
CSF	Cerebrospinal fluid
CXR	Chest X-ray
DNA.	Deoxyribonucleic Acid
DOT	Directly Observed Treatment
DR	Drug Resistant
DR-TB	Drug-Resistant Tuberculosis
DRS	Drug-Resistance Surveillance
DS	Drug Susceptible
DS-TB	Drug Susceptible Tuberculosis
DST	Drug Susceptibility Testing
ECG	Electrocardiography
FDC	Fixed-Dose Combination (Of medicines)
GDF	Global Drug Facility
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development And Evaluation
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HMIS	Health Management Information System
HR	Isoniazid-Rifampicin
Hr-TB	Rifampicin-Susceptible, Isoniazid-Resistant Tuberculosis
HRZE	Isoniazid-Rifampicin-Ethambutol-Pyrazinamide
IPD	Individual Patient Data (Or dataset)
IV	Intravenous
LPA	Line Probe Assay
MDR/RR-TB	Multidrug- Or Rifampicin-Resistant Tuberculosis
MDR-TB	Multidrug-Resistant Tuberculosis
MGIT	Mycobacterial Growth Indicator Tube
MIC	Minimum Inhibitory Concentration
NAAT	Nucleic Acid Amplification Test
NTP	National Tuberculosis Program

PLHIV	People Living With HIV
PMDT	Programmatic Management of Drug Resistance Tuberculosis
Pre-XDR-TB	Pre-Extensively Drug-Resistant Tuberculosis
RCT	Randomized Controlled Trial
RGLC	Regional Green Light Committee
RR-TB	Rifampicin-Resistant Tuberculosis
SOC	Standard of Care
TB	Tuberculosis
TDM	Therapeutic Drug Monitoring
WHO	World Health Organization
WHO/GTB	World Health Organization Global Tuberculosis Program
XDR-TB	Extensively Drug-Resistant Tuberculosis

ABBREVIATIONS FOR TB MEDICINES

Am	Amikacin
B or Bdq	Bedaquiline
C or Cfz	Clofazimine
Cs	Cycloserine
Dlm	Delamanid
E	Ethambutol
Eto	Ethionamide
H	Isoniazid
Hh	Isoniazid high dose
Ipm-Cln	Imipenem-Cilastatin
L or Lzd	Linezolid
Lfx	Levofloxacin
M or Mfx	Moxifloxacin
Mpm	Meropenem
P or Rpt	Rifapentine
Pa	Pretomanid
PAS	P-Aminosalicylic acid
Pto	Prothionamide
R	Rifampicin
S	Streptomycin
Z	Pyrazinamide

THE MAIN CHANGES IN THIS GUIDELINE

The main changes in this guideline is based on the key recommendations outlined in the World Health Organization, 2022 guidelines for the treatment of drug-resistant tuberculosis. The following points summarizes the key updates and changes made to the National Guidelines on DR TB Management, 2019:

1. **Use of the 6-month oral treatment regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM/BPaL) in most patients with MDR/RR-TB and with Pre-XDR TB.**
2. **A nine-month all-oral regimen (Oral Standardized Shorter Treatment Regimen, OSSTR) in selected patients with MDR/RR-TB in whom fluoroquinolone susceptibility is confirmed. This regimen will also be used by patients who are otherwise not eligible for BPaLM or if any of its component drugs is not available.**
3. **The previously used injectable based standardized shorter treatment regimen (SSTR) will be phased out. All oral longer regimens (18 months) remain valid options if shorter regimens cannot be implemented.**

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

National Tuberculosis program is moving forward with the vision of TB Free Nepal by 2050 and ending TB epidemic by 2030, in alignment with United Nation Sustainable Development Goals (UN SDGs) and National Health Policy 2014 under the direction of the Global End TB Strategy.

BOX 1.1: Goal and Objectives of National Strategic Plan 2021/22 - 2025/26

Goal

- Decrease the Incidence rate from 238 in 2020/21 to 181 per 100,000 population by 2025/26
- Decrease mortality rate from 58 in 2020/21 to 23 per 100,000 by 2025/26
- End TB epidemic by 2035
- Eliminate TB by 2050; and
- Reduce the catastrophic cost to zero.

Objectives

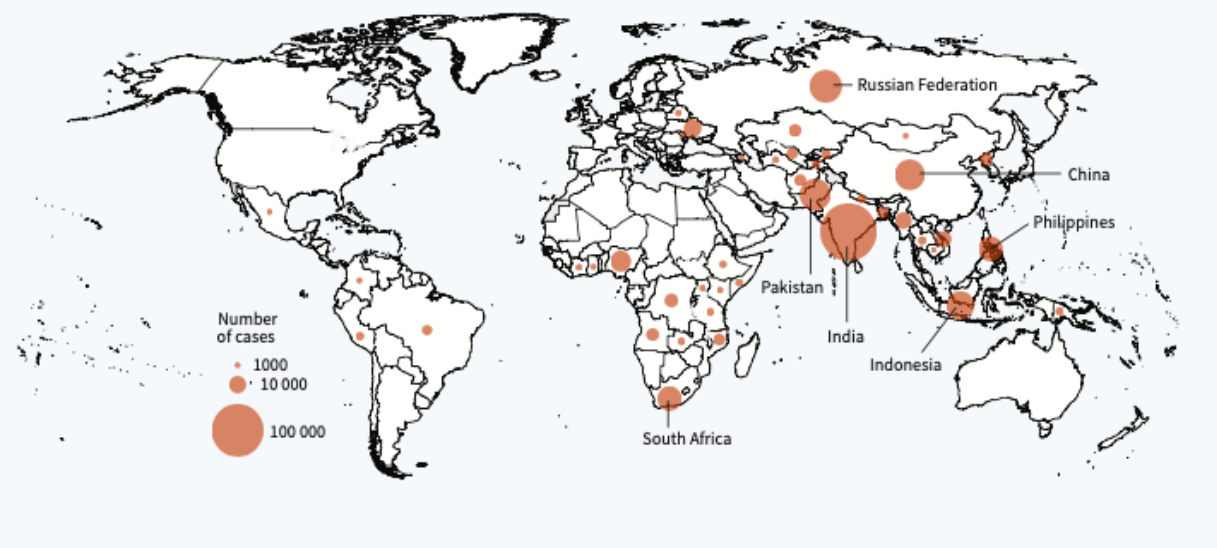
- **Objective 1:** To build and strengthen political commitment, sustainability, and patient-friendly health system to end TB.
- **Objective 2:** To ensure the identification of TB, diagnosis, quality treatment and prevention.

1.1.1 Multi Drug Resistant/Rifampicin Resistant Tuberculosis (MDR/RR-TB) in the world

- There were an estimated 450,000 incident drug-resistant TB (DR-TB) patients globally in 2021.
- The three countries with the highest number of DR-TB patients were India (26%), the Russian Federation (8.5%), and Pakistan (7.9%).
- Treatment success for DR-TB remained low, at 60% globally. Some high burden countries, such as Bangladesh, Ethiopia, Kazakhstan, Myanmar, and Vietnam, achieved better treatment success rates above 70%.
- Nepal is listed among 30 high burden MDR/RR-TB countries in the world by WHO in 2021

FIGURE 1.1: DR-TB Burden

Estimated incidence of MDR/RR-TB in 2021, for countries with at least 1000 incident patients



Source: Global TB Report, 2022

1.1.2 MDR/RR-TB in South East Asia Region (SEAR)

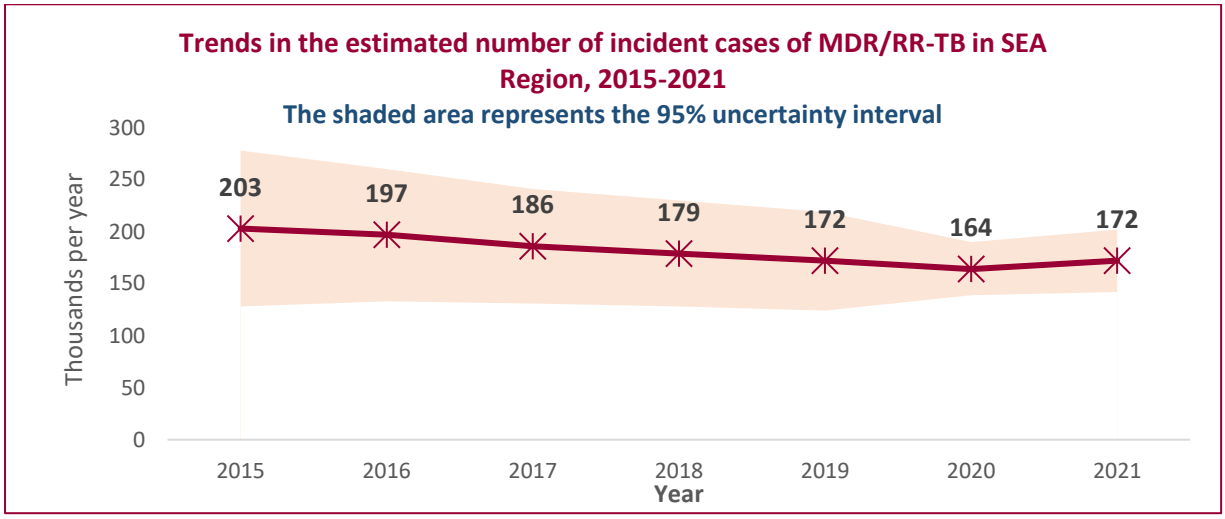
- The estimated number of MDR/RR-TB patients in 2021 was 172,000 (with a range of 142,000 to 202,000), and the incidence rate was 8.4 per 100,000 population.
- Among the countries with a high burden of TB worldwide, six of them are in the Southeast Asia (SEA) Region: Bangladesh, Democratic People's Republic of Korea, India, Indonesia, Myanmar, and Thailand. However, when considering the burden of MDR/RR-TB, Nepal replaces Thailand in the list of high-burden countries for the region.

TABLE 1.1: Estimated proportion of TB patients with MDR/RR-TB in SEAR, 2021

New Patients	2.9% (1.7-4.1)
Previously treated patients	14% (4.1-23)

Source: Tuberculosis profile: WHO South-East Asia Region: https://tinyurl.com/4exm4cvn

FIGURE 1.2: Trends in the estimated number of incident patients of MDR/RR-TB in SEA Region, 2015-2021



Source: Global TB Report, 2022

1.1.3 MDR/RR-TB in Nepal

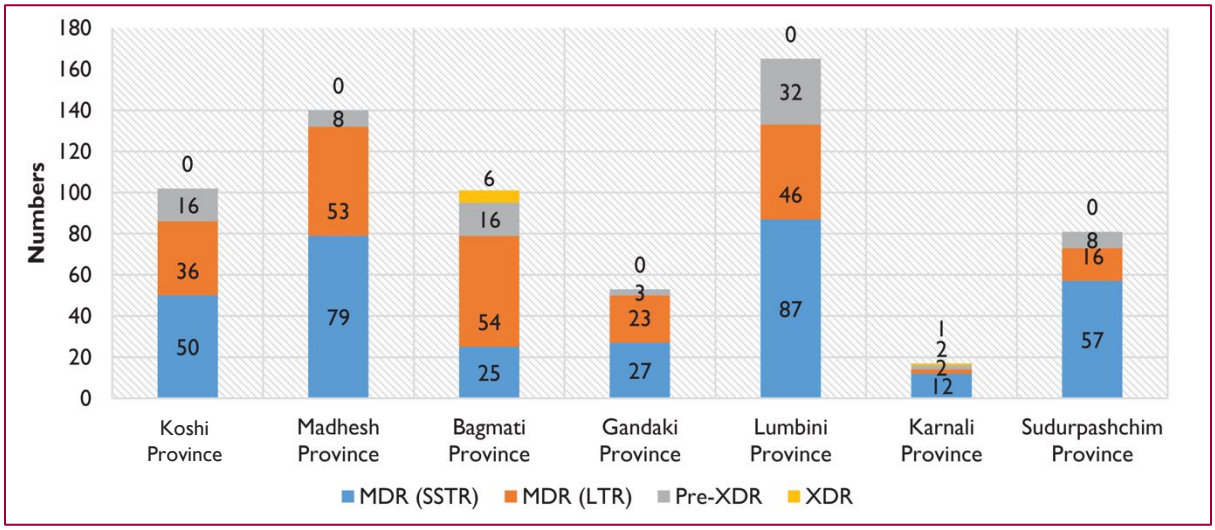
- Prior to the National TB Prevalence Survey (NTPS) 2018/19, annual DR-TB incident patients were estimated to be around 1400. Following the NTPS and current epidemiological data, the burden of MDR/RR-TB was estimated to be 2200 annual incident patients.
- In FY 2078/79 BS (2022 AD), 942 MDR/RR-TB patients were laboratory confirmed and notified in the National TB Program (NTP).
- Out of the notified patients, 681 MDR/RR-TB patients were enrolled in treatment at different provinces: 15% of these in Koshi Province, 21% in Madhesh Province, 15% in Bagmati Province, 8% in Gandaki Province, 25% in Lumbini Province, 3% in Karnali Province, and 12% in Sudurpaschim Province.
- Among the reported MDR/RR-TB patients, 51% were registered as MDR (SSTR), 35% as MDR (LTR), 13% as Pre-XDR, and 1% as XDR (as per the definition prior to 2021)
- The estimated gap in patient notification for DR-TB was 57% when compared to the estimated annual incident DR-TB patients of 2200.
- The overall treatment success rate for DR-TB was 74% in 2021/22.

TABLE 1.2: Revised TB estimates including DR-TB from NTPS

Fiscal Year	TB Incidence for all forms (Rate per 100,000)	TB Prevalence for all forms (Rate per 100,000)	Mortality (Annual)	DR-TB (Total Estimates) (Annual)
2017/18 Incidence	69,000 (245)	117,000 (416)	17,003 (9,000-26,000)	2,200
2017/18 Prior estimates	42,000 (151)	60,000 (215)	5,500 (3,900-7400)	1400
Revised burden, higher by	1.6 Times	1.8 Times	3.1 Times	1.57 times

Source: National TB Strategic Plan (2021/22-2025/26)

FIGURE 1.3: DR-TB patients enrollment by provinces (2021/2022)



Source: Annual Health Report, DOHS, FY 2078/79

Five drug resistance surveys were conducted between 1996/1997 and 2011/2012 (TABLE 1.3). National drug resistance survey (2023) is ongoing and the results are awaited.

TABLE 1.3: Findings of the drug resistance survey conducted in Nepal between 1996-2011

Year	MDR/RR-TB in new TB patients	MDR/RR-TB in retreatment TB patients
1996/1997	1.1%	Not available
1998/1999	3.7%	12.5%
2001/2002	1.3%	20.5%
2006/2007	2.9%	11.7%
2010/2011	2.2%	15.4%

1.2 ORGANISATION OF DR-TB CONTROL IN NEPAL

The management of DR-TB falls under the purview of the national tuberculosis programme and is organized as below:

- Ministry of Health and Population approves the policies, strategies and allocates the budgets to the program
- National Tuberculosis Control Center (NTCC) develops and recommends the strategies and guidelines and manages federal budget for the program.
- Technical Working Groups (TWGs) at National TB Program (NTP) provides inputs and technical advice on policies, strategies, and guidelines, plans for DR-TB management, and provides technical inputs to the partners and stakeholders.
- DR-TB Treatment section at NTCC, manages, monitors, and evaluates of the DR-TB activities and provide inputs to the DR-TB program
- Dedicated human resources for DR-TB Treatment Section will manage under NTCC and support to manage the Procurement and Supplies of drugs and logistics.
- Provincial Health Directorate supports to implement the DR-TB activities; manage to supply anti-TB drugs and other logistics, reporting, monitoring, supervision, and evaluation of the DR-TB.
- Treatment and Sub-Center will provide treatment, care, and support, refer for management of adverse drug reaction to the DR-TB patients, record, and report, manage sputum transport for culture and DST and screening of presumptive DR-TB patients.

1.3 ROLES AND RESPONSIBILITIES

A. National Level (NTCC)

- Develop the policies, strategies, and guideline for DR-TB
- Support planning, coordination, monitoring and evaluation of TB control activities with concerned stakeholders.
- Support monitoring and supervision of all personnel involved in tuberculosis work.
- Manage and advise on procurement and distribution of TB drugs and supplies.
- Prepare forms, registers, health education and teaching materials for DR-TB
- Compile reports on patient-finding and treatment with feedback to lower levels
- Monitor and provide supportive supervision to the provincial level
- Advise and carry out capacity enhancement activities at all levels on DR-TB management
- Coordinate with partner agencies.
- Manage budget for implementation of the program.
- Promote TB and HIV Collaboration and MDR/RR-TB management.
- Promote research and development in DR-TB

B. Provincial Level [Ministry for Health/Provincial Health (Service) Directorate)]

- Develop plans and strategies for DR-TB program in line with NTP
- Carry out capacity enhancement activities at provincial and local levels health care workers on DR-TB management
- Implement, coordinate, and supervise tuberculosis control activities.

- Review, validate, compile, and send quarterly reports on patient-finding and treatment to NTP on time (end of the month following the quarter that just ended)
- Coordinate with partner agencies at the province level
- Request, receive, distribute, and manage TB drugs, diagnostics and other supplies for the diagnosis and management of TB
- Monitor and provide supportive supervision to the provincial level
- Establish provincial TB, TB and HIV and PMDT committees and coordinate implementation of their respective activities in their provinces
- Provide feedback to the health facilities on the quality of the reports
- Conduct and ensure quality assurance for sputum microscopy services (EQA) for the facilities
- Coordinate with partners and mobilize community-based organizations to support implementation of DR-TB activities
- Monitor, evaluate and review DR-TB activities in their respective provinces

District Level (Health Offices)

- Develop the plan at the district level
- Manage, organize and facilitating TB training to health workers
- Monitoring, supervision, and evaluation of the program
- Implement the program following the national policies and guideline
- Manage drugs, reagents and required logistics for the program
- Coordinate with different stakeholders at district level
- Organize awareness and education program to increase knowledge on TB in the community
- Update recording and reporting forms and registers and submit timely

C. Local Level (Palikas)

- Support to implement the program following the national policies and guidelines
- Manage drugs, reagents and required logistics for the program
- Organize supportive supervision at the treatment and sub-center to enhance the performance of the program
- Organize workshops to review the performance of treatment and diagnostic center
- Coordinate with different stakeholders at palikas
- Organize awareness and education program to increase knowledge on DR-TB in the community
- Enhance capacity of health workers on DR-TB management

D. Treatment/Sub Center Levels

- Provide directly observed Treatment (DOT) to all DR-TB patients
- Collaborate with local level to implement community-based DOTS
- Monitor TB treatment through follow up sputum examinations and reviews.
- Trace and retrieve lost to follow up and or patients missing treatment or poor compliant patients.
- Complete and update all recording and reporting forms including TB treatment cards and registers and submit quarterly reports on time

- Provide health education and counseling to the patients and to the community.
- Educate community on DR-TB.
- Cooperate with the microscopy/diagnostic services, for examination of sputum.
- Coordinate referral of DR-TB patients from hospitals to peripheral centers.
- Promote and implement TB/HIV activities and referral of presumptive MDR/RR-TB
- Organize contact tracing activities in the community
- Manage necessary drugs, reagent, and necessary logistics for the program
- Update patients' records and ensure submission on time

E. DOT Providers/Treatment Supporters

- Provide daily DOT to the patient and maintain duplicate treatment card
- Inform the condition and the treatment being given to the patient and care providers
- Recognize adverse events and and make referrals to the treating physician at DR-TB treatment centers
- Assess the patient's adherence to the regimen and address poor adherence when it occurs.
- Complete appropriate documentations.
- Collaborate with the local public health services.
- Ensure that the patient accepts the proposed care and support.
- Report patients' treatment status to the Treatment center
- Maintain confidentiality of the patients
- If DOT provider/treatment supporters will be absent for providing DOT due to their personal reasons, manage alternate DOT provider/treatment supporter for that duration.
- Provide referrals for psychological, socio-economic and legal support and other services including substance abuse treatment; Provide joint (integrated) support for DR-TB patients with addictive behaviors.

F. Patient and Community Level

- DR-TB patients should comply with drugs under supervision and complete treatment.
- The community should supervise and support DR-TB patients to ensure the treatment compliance and completion.
- Attend regular follow ups with the health facility staff for monitoring of treatment, submit sputum, follow up on results and report side effects.
- Support all DR-TB patients in their communities for necessary support
- Mobilize patient and peer support groups toreduce stigma and help them adapt well in the community

1.4 KEY DEFINITIONS

Pulmonary tuberculosis (PTB) refers to any bacteriologically confirmed or clinically diagnosed patient of TB involving the lung parenchyma or the tracheobronchial tree.

Bacteriologically confirmed TB is when a biological specimen is positive by smear microscopy, culture, or a WHO-recommended rapid molecular diagnostic test (such as Xpert MTB/RIF). All such patient should be notified, regardless of whether TB treatment has started.

Drug susceptibility testing (DST): In vitro testing using either: 1) molecular, genotypic techniques to detect resistance-conferring mutations; or 2) phenotypic methods to determine susceptibility to a medicine.

Drug-resistant TB (DR-TB): TB disease caused by a strain of *Mycobacterium tuberculosis* complex that is resistant to any TB medicines.

BOX 1.2: Type of DR TB

Based on drug susceptibility testing (DST) of clinical isolates confirmed to be *M. tuberculosis,* DR TB is classified into below category:

- **Monoresistance:** resistance to one first-line anti-TB drug only.
- **Polydrug resistance:** resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).
- **Isoniazid Resistant TB (Hr-TB):** TB disease caused by a strain of *M. tuberculosis* complex that is resistant to isoniazid but susceptible to Rifampicin
- **Rifampicin resistant (RR TB):** TB caused by *M. tuberculosis* strains that is resistant to Rifampicin. Refers to either multidrug-resistant TB (MDR TB) or rifampicin resistant TB (RR-TB).
- **Multidrug resistant (MDR TB):** resistance to at least both isoniazid and rifampicin.
- **Pre-Extensively Drug-Resistant TB (Pre-XDR TB):** TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin)
- **Extensively Drug-Resistant TB (XDR TB):** TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other "Group A" drug (Bedaquiline or Linezolid).

Drug-susceptible TB (DS-TB): A bacteriologically confirmed or clinically diagnosed TB without evidence of infection with strains resistant to rifampicin and isoniazid.

Extensive (or advanced) pulmonary tuberculosis (TB) disease: Presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.

Extrapulmonary tuberculosis (EPTB) refers to any bacteriologically confirmed or clinically diagnosed patient of TB involving organs other than the lungs (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges).

Severe extrapulmonary TB: presence of miliary TB, TB meningitis, osteoarticular TB or pericardial TB. In children aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) is considered severe.

New patient: a newly registered episode of TB in a patient who has never been treated for TB or who has taken anti-TB medicines for less than 1 month.

Previously treated patients: Patients who have received 1 month or more of anti-TB drugs in the past.

Serious adverse event: an adverse event that leads to death or a life-threatening experience, to hospitalization or prolongation of hospitalization, to persistent or significant disability, or to a congenital anomaly. Adverse events that do not immediately result in one of these outcomes but that require an intervention to prevent such an outcome from happening are included. Serious adverse events may require a drastic intervention, such as termination of the drug suspected of having caused the event.

TB case: the occurrence of TB disease in a person.

TB disease: a disease in humans caused by the M. tuberculosis complex, which comprises eight distinct but closely related organisms – *M. bovis, M. caprae, M. africanum, M. microti, M. pinnipedii, M. mungi, M. orygis* and *M. canetti*. The most common and important agent of human disease is *M. tuberculosis*.

TB patient: a person who is in care for TB disease.

1.5 DRUG RESISTANCE IN TUBERCULOSIS

1.5.1 Causes of Drug Resistance

1.5.1.1 Drug Resistance by naturally occurring mutants

In an untreated smear positive pulmonary tuberculosis patient, there are naturally occurring drug resistant mutants of tuberculosis bacilli to different drugs at different frequencies. The larger the bacterial population higher is the probability that resistant mutant strains are present.

TABLE 1.4: Frequency occurrence of DR mutants

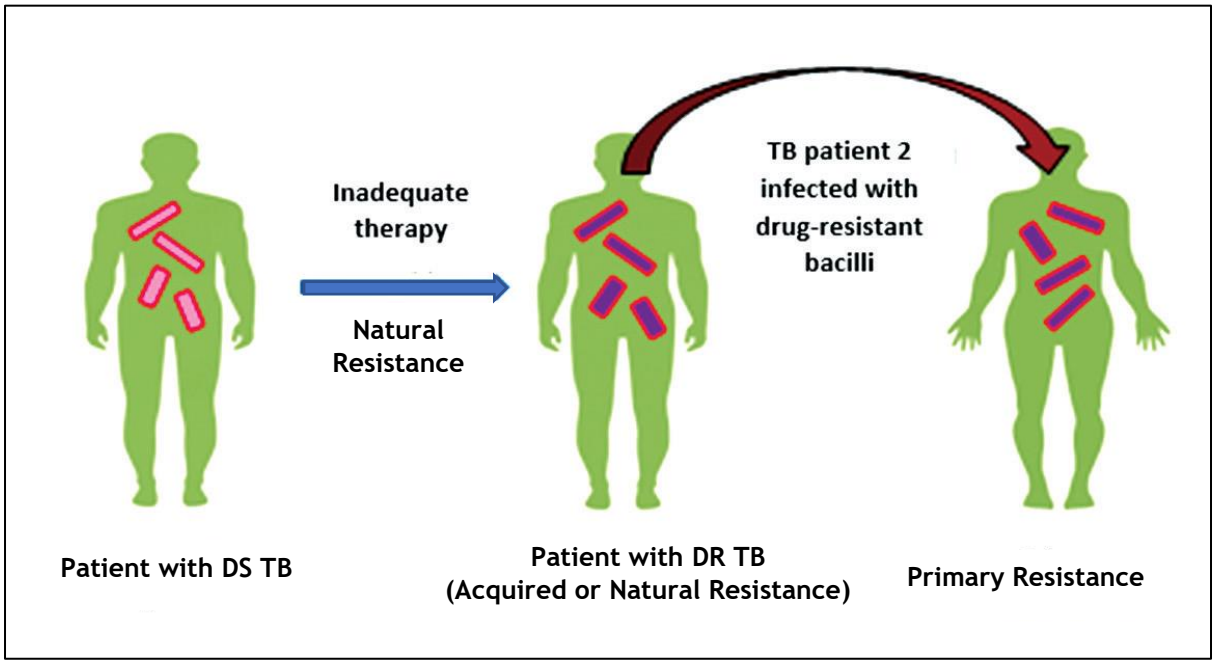
Name of the drugs	Frequency occurrence of DR mutants
Isoniazid (H)	1×10^5-10^6 Bacilli
Rifampicin (R)	1×10^7-10^8 Bacilli
Ethambutol (E)	1×10^5-10^6 Bacilli
Pyrazinamide (Z)	1×10^2-10^4 Bacilli
Quinolones	1×10^5-10^6 Bacilli

A very small portion (around 1 in a million or $1/10^6$) of the tuberculosis bacilli are spontaneously resistant to INH (these bacilli are called: drug resistant mutants). A TB patient with smear positive pulmonary TB will be infected with 10^8 to 10^9 bacilli. If a TB patient is treated with only INH, most bacilli will be killed, and the patient may improve clinically and bacteriologically, but 1 out of every million bacilli will not be killed. These resistant bacilli will continue to multiply, and soon the patient will again be infected with 10^8 bacilli, but this time all bacilli will be resistant to INH. This phenomenon is called: selection of drug-resistant mutants. Additionally, even smaller, portion (around 1 in 100 million or $1/10^8$) of the bacilli are spontaneously resistant to Rifampicin (R). If a patient is treated with only R, almost all bacilli will be killed, but those few that are resistant to R will not be killed and will multiply. The end result is a patient who is resistant to R. Multi-drug anti-tubercular therapy, early patient-finding, and treatment of DR-TB helps prevent transmission of MDR/RR-TB.

1.5.1.2 Drug resistance by evolution

- Primary drug resistance: Drug resistance caused by person-to-person transmission of drug resistant organisms.
- Acquired drug resistance: Drug resistance developed during TB treatment, either because the patient was not treated with the appropriate treatment regimen or because the patient did not follow the treatment regimen as prescribed.

FIGURE 1.4: Type of resistance by evolution



Source: Drug Resistant TB, technical manual, NTCC, 2017

1.5.2 Factors related to Drug Resistance

TABLE 1.4: Factors related to Drug Resistance

Health care providers: Inappropriate treatment	Drugs: inadequate supply/ quality	Patients: inadequate drug intake or treatment response
Inappropriate guidelines	Poor quality	Lack of information
Non-adherence to guidelines	Unavailability of some drugs (stock outs)	Lack of means to adhere to treatment (transportation, food, etc.)
Absence of guidelines	Poor storage conditions	Social barriers
Poor training	Inappropriate dosage or combination	Adverse events (AEs)
Lack of treatment monitoring	Poor regulation of medicines	Inadequate directly observed treatment (DOT)
Poor management of adverse drug reactions		Poor absorption of drugs
Poorly organized or funded TB control programs		Substance abuse/dependence

Source: Companion Handbook to the WHO Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2014.11. Geneva, Switzerland: World Health Organization, 2014

1.5.3 How to prevent drug resistance

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

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

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

CHAPTER 2

DIAGNOSIS OF DR-TB

The effective management of TB relies on the rapid diagnosis of TB, rapid detection of drug resistance and prompt initiation of an effective treatment regimen. Thus, there is a need for access to fast and accurate detection tests and rapid and accurate drug-susceptibility testing (DST) for all TB patients.

2.1 IDENTIFICATION OF PRESUMPTIVE DR-TB

Any person who presents with symptoms or signs suggestive of TB is at risk of having drug resistance and is a potential presumptive DR-TB. Thus, all presumptive TB should be offered DST services wherever feasible.

As per the current national TB programme, the following categories of TB patients are prioritized and screened for drug resistance until the DST services are universally accessible.

1. *Close contact of DR-TB patient*
2. *Previously treated patients* who either:
   - failed
   - relapsed
   - returned after loss to follow-up

   The proportion of R resistance is very high among people who fail treatment, and among people who relapse and in those who return to treatment after loss to follow-up.
3. *A new smear-positive TB patient*
   - who shows positive sputum after intensive phase of DS TB treatment.
   - who shows high bacillary load in sputum (3+) or cavities in the CXR during diagnosis
   - who is not getting better/getting worse during continuation phase of the first-line treatment.
   - who is with frequent interruptions and irregular first line drugs.
4. *TB patients on treatment at private sector* not complying with the standards of TB treatment and those with inadequate or no information on past TB treatment history.
5. *PLHIV, Diabetes, immunocompromised*
6. *Health workers with symptoms*
7. *Belonging to vulnerable groups* such as migrants' slums, prisons, refugees, and those residing in congregate settings.

Most patients with presumptive DR-TB will be bacteriologically confirmed pulmonary disease, but clinically confirmed pulmonary or extrapulmonary TB may also present with presumptive DR-TB if they show a clinically unfavorable evolution.

2.2 DIAGNOSTIC TEST OF TUBERCULOSIS

All TB patients are initially be tested with molecular WHO recommended Rapid Diagnostic Tests (mWRDs), wherever feasible and accessible. Sputum microscopy and culture is used to monitor a patient's response to treatment. Culture is important in the diagnosis of pediatric and extrapulmonary TB from paucibacillary samples, and in the differential diagnosis of non-tuberculous mycobacteria (NTM) infection.

- Molecular WHO-recommended Rapid Diagnostics (mWRDs)
- Mycobacterial culture and DST
- Sputum smear microscopy

2.2.1 Molecular WHO-recommended Rapid Diagnostics (mWRDs)

Xpert MTB/RIF or Xpert MTB/RIF Ultra

- The Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, USA), developed by Cepheid, as a more sensitive next-generation assay, uses the same GeneXpert® platform as the Xpert MTB/RIF.
- It detects the presence of DNA from the tubercle bacillus as well as the occurrence of mutations in the DNA that cause rifampicin resistance.

Xpert MTB/XDR

- It performs broader spectrum of genetic targets in a single assay.
- It is an automated in vitro diagnostic test for detection of MTB DNA and resistance to isoniazid (target genes: inhA promoter, katG, fabG1, oxyR-aphC intergenic region), ethionamide (inhA promoter), fluoroquinolones (gyrA and gyrB), and second line injectables such as Amikacin (rrs and eis promoter) and their associated mutations.

TABLE 2.1: Detection limit, run time and detection of drug resistance for mWRDs

S.N.	Cartridge	Resistance Detection	Detection Limit	Run Time
1	Xpert MTB/RIF	Rifampicin	131 CFU/ml	<2 hr
2	Xpert MTB/RIF Ultra	Rifampicin	16 CFU/ml	<80 mins
3	Xpert MTB/XDR	Fluoroquinolones, Isoniazid, Ethionamide, Amikacin	131 CFU/ml	<90 mins

Point to remember:

- mWRDs such as Xpert MTB/RIF, Xpert MTB/RIF-Ultra, Xpert MTB/XDR and LPA is not recommended for monitoring the treatment of the patient because it does not differentiate between viable and non-viable bacilli.
- An Xpert result "MTB detected, rifampicin resistant/sensitive/ indeterminate (whichever)" in a previously successfully treated patient does not confirm recurrent TB in the absence of clinical signs and symptoms and/or positive culture.
- Xpert testing is also recommended for the diagnosis of extra-pulmonary TB. Samples from cerebrospinal fluid, lymph nodes, stool, N/G aspirate and other tissues are suitable. The test has low sensitivity for pleural fluid, and data on its sensitivity in urine samples are limited.

TABLE 2.2: Interpretation of Xpert MTB/RIF or Xpert MTB/RIF/Ultra results

Label	Result and Interpretation	Action to be taken
T	MTB detected; rifampicin resistance not detected	Diagnosis of TB confirmed. Treat with first-line TB regimen in new patients.
RR	MTB detected; rifampicin resistance detected	Refer to DR-TB treatment Center.
TI	MTB detected; rifampicin resistance indeterminate	Diagnosis of TB is confirmed. Start treatment with first-line TB regimen and send new sputum specimen to repeat the test. Pay special attention to quality of sputum sample, conditions of storage and transportation and speed of shipment. If the result of the repeat test is RR, refer to DR-TB treatment Center.
N	MTB not detected	Additional investigations are required to exclude TB.
I	Invalid/no result/error	Send a new sputum specimen to repeat the test. Pay special attention to quality of sputum sample, conditions of storage and transportation and speed of shipment
TTI	MTB trace detected; rifampicin resistance indeterminate/unknown (In Xpert MTB/RIF Ultra)	Start first line treatment: • PLHIV • Children • Extra pulmonary TB • Adults being evaluated for pulmonary TB who are - not at risk of HIV and - who do not have a history of prior TB or TB treatment within the past 5 years. Otherwise, reevaluate clinically, need to do additional tests* to assess rifampicin resistance. Review treatment based on DST result.

Once RR is detected, the first thing is to inform and refer the patient to the DR-TB treatment center for treatment enrollment.

* In patients with a prior history of TB within the past 5 years or whose TB treatment was completed less than 5 years ago, Xpert Ultra trace results (and occasionally Xpert MTB/RIF " MTBC detected low or very low") may be positive, not because of active TB but because of the presence of non-viable bacilli. Clinical decisions must be made based on all available information and clinical judgement.

BOX 2.1 What needs to be done at the DR-TB Center?

- **The patient must be registered in the DR-TB Treatment Center.**
- **All the baseline examinations (CBC, LFT, TFT, RFT, Serum Glucose, HIV, Hep-B, Hep-C, and pregnancy test in case of female of reproductive age etc) should be done before DR TB treatment.**
- **One early morning sputum sample or other specimen (for EP TB, if feasible) should be collected and sent to nearest center for Xpert XDR testing for second-line DST (Quinolone, Amikacin).**
- **In addition, two sputum samples (morning-morning or morning-spot) or other specimens (for EP TB, if feasible) should be collected before starting the treatment and sent to the reference TB culture lab without delay for second-line DST.**
- **If the result of Xpert MTB/XDR (or LPA) from direct sample shows no result or invalid, then repeat the test from another sample and/or second LPA will be tested from culture positive. The result of the LPA should be available at the DR TB Center sooner the possible, after sending the specimens.**
- **Before Xpert MTB/XDR (or LPA) result is available, MDR/RR-TB treatment should be started.**

Line Probe Assay (LPA)

LPA is a DNA strip-based molecular tests that is used to detect resistance to INH, rifampicin, fluoroquinolones drugs and second line injectables. In those patients who has been recently diagnosed with MDR/RR-TB, resistance to fluoroquinolones drugs and second line injectables are tested.

- **The first-line LPA** detects mutations in the *rpoB* gene (resistance to R) and the *katG* and *inhA* genes (resistance to H).
  - A *katG* mutation signifies high level H resistance, a *inhA* mutation without accompanying *katG* mutation indicates low level H resistance.
  - It is not necessary to perform this test if the Xpert MTB/RIF/Ultra test has already detected rifampicin resistance.
  - Whether or not additional isoniazid resistance is present in these conditions, it will not have any influence on the therapeutic decision making.
  - In case of Xpert MTB/RIF/Ultra test not detecting RIF Resistance, the result of 1st line LPA is important to make therapeutic decision.

- **The second line LPA** detects mutations in the *gyrA* and *gyrB* genes (resistance to the fluoroquinolones) and *rrs and eis* genes (for resistance to second line injectables).
  - The results of the LPA should arrive at the DR-TB treatment Center as soon as possible (preferably within 2 week). The result of 2nd line LPA will be used to guide the therapeutic decision.

Note: LPA needs higher bacterial load in samples than Xpert for a positive result and hence smear positive samples and cultures are preferred. Xpert MTB/XDR can be used for early detection of FQ resistance wherever accessible.

Table 2.3: Interpretation of DST results by LPA and treatment decision

	Mutation*	Meaning and resistance caused	Treatment regimen
First-line LPA result	*InhA*	Low level H resistance and confers resistance to Eto	Treat with the regimen for H-resistant TB
	KatG	High level H resistance and confers resistance to Hh	Treat with the regimen for H-resistant TB
	Dual (InhA and KatG)	High level H resistance and confers resistance to both Hh and Eto	Avoid Eto containing regimen
	RpoB	Rifampicin resistance with and without H resistance	Treat with MDR/RR-TB regimen
Second line LPA result (all RR-TB casepatients)	*GyrA, GyrB*	FQ resistance (Ofx, Lfx, Mfx)	Treat with FQ Resistant MDR/RR-TB Regimen (BPaL or longer regimen).
	rrs, eis	Resistance to Second-line injectables	Any regimen (Shorter/Longer Regimen)

Note: This is not provided in the official result but can be requested by the Laboratory to assist physicians in designing individualized regimens for DR-TB when standard regimen can't be used.

Collection of Sputum Specimen for mWRDs

A single sputum sample is collected. It must be of the high quality to ensure a correct reading by mWRDs:

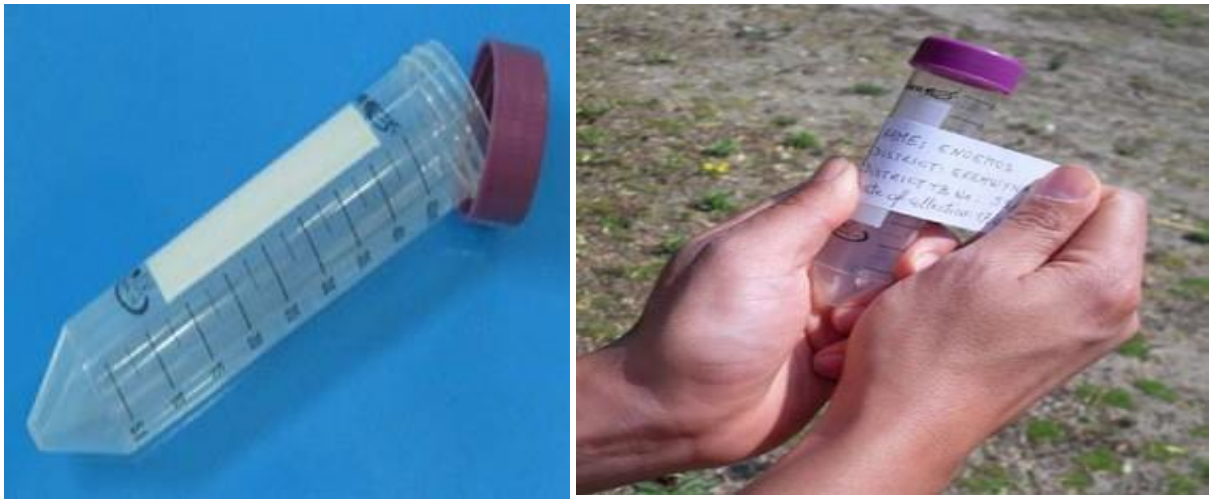
- One early morning sample is preferable (supervised spot sample is also acceptable if it is of good quality).
- Explain why the sputum is needed and demonstrate how to cough up sputum.
- Before coughing up the sputum, the patient should rinse the mouth
- Collect sputum in a well-ventilated area, preferably outdoors, and away from other people.
- Expectoration should be from deep inside the chest
- Minimum quantity should be 2-3 ml.
- Good-quality specimens are those that are free from blood and food particles. The quality of sputum holds significant importance, so it is crucial to verify if the sample contains enough mucopurulent sputum rather than just saliva. In cases where it lacks sufficient sputum, request the individual to produce more by coughing.

FIGURE 2.1 Steps of sputum specimen sample collection method



- The patient may be asked to take lukewarm water a few minutes before taking sample to increase sputum production. A few deep breaths, thumping of the upper back of patient or resting in supine position also may elicit a productive cough.
- If it is not possible to collect the recommended minimum quantity, the available sample should still be sent to the laboratory. Avoid sending tissue sample/biopsy in formaldehyde. Tissue sample should be sent in normal saline.

FIGURE 2.2 Falcon tube and proper identification of falcon tube



Falcon tube | Proper identification of Falcon tube

- Sputum samples for Xpert MTB/RIF/Ultra should be collected in Falcon tubes.
- There is no need to add any reagent to the specimen.
- The tubes must be properly identified with a self-adhesive sticker.
- Label the containers (not the lids) before collecting the sputum samples
- On the sticker, the name of the patient, the registration number of the patient, the lab number and the date of specimen collection must be written with an indelible marker. The tubes must be tightly closed.
- After collecting the sputum, be sure that the lid is closed tightly. Wipe off the outside of the container if needed.
- Wash your hands thoroughly with soap and water.
- Fill out the laboratory request form
- Send the samples with the request form from health facility to the laboratory.
- Sputum should be sent to the laboratory within 24-48 hrs but no later than 72 hrs after collection.
- Sputum samples should be stored in refrigerator (4–8 degrees Celsius; avoid deep-freeze) if there is a delay of more than 24 hrs, till then, store in cool dry place away from direct sunlight.
- Clinicians should fill one lab request form completely per patient and submit with the specimen for Xpert MTB/RIF/Ultra, Xpert MTB/XDR, LPA or culture. It is very important that clinicians fill the form correctly and indicate by ticking the specific investigation requested.

Other specimens for Xpert MTB/RIF/Ultra testing in case of presumptive extrapulmonary (EP) DR-TB

- Xpert MTB/RIF/Ultra testing on urine is usually not recommended except for PLHIV and children but testing of an appropriate specimen can be helpful in certain types of presumptive EP DR-TB (see TABLE 2.4).
- The test will not perform well as on sputum, but it can be particularly useful when testing cerebrospinal fluid or lymph node tissue or aspirate.
- In case of children who cannot produce sputum, stool sample may be considered for Xpert. Xpert MTB/RIF/Ultra also performs well on gastric aspirate, nasopharyngeal aspirate and BAL.
- The test is not very sensitive on pleural fluid or other specimens such as intra-articular fluid, for which few data are available at present. Nevertheless, it is preferable to do the test because some cases might be positive.
- It must be borne in mind that a negative Xpert MTB/RIF/Ultra result on an EP specimen is not the final answer. For every case of presumptive EP DR-TB, send a specimen for culture and DST.

TABLE 2.4: Specimens collected for Xpert MTB/RIF/Ultra testing in presumptive EP DR-TB

Type of EP TB	Specimen	Quantity* to be collected	Type of container
Tuberculous pleuritis	Pleural Fluid	10-15 ml	Sterile containers
Tuberculous meningitis	cerebrospinal fluid (CSF)	Minimum 2 ml	
TB of the peripheral lymph adenitis	Pus and/or excision biopsy	Minimum 2 ml	
Musculoskeletal TB, Osteo-articular TB	Intra-articular Fluid Biopsy samples	Minimum 2 ml	
TB pericarditis	Pericardial Fluid	Minimum 2 ml	
TB peritonitis	Ascitic Fluid	10-15 ml	
TB of other organs	Other tissue samples e.g., Endometrial Biopsy, Stool, Gastric Lavage, BAL	As appropriate	

**The tissue specimens should be sent in normal saline.*

Transportation of sputum (or other) sample to the Xpert Center

- In health facilities where the Xpert MTB/RIF/Ultra tests are available, the specimen together with the request form should be sent for the test.
- If, Xpert MTB/RIF/Ultra testing is not available, samples should be transported to the Xpert Center.
- Triple layer packaging must be ensured for the transportation of the samples.
- The health facility must ensure that the specimens are delivered to the Xpert Center as early as possible (preferably within 72 hrs).

2.2.2 Culture and drug susceptibility testing

2.2.2.1 Culture

Culture is a growth-based gold-standard test for detection of viable TB bacilli, which is also considered the most sensitive method for diagnosis of TB. It detects up to 10-100 TB bacilli per ml sputum. Minimum biosafety level 2 (BSL-2) is required to perform TB culture.

Types of culture media

- **Automated Liquid culture systems e.g.,** BACTEC MGIT 960. The MGIT system can take 1-6 weeks for detection of bacterial growth while it may take additional 1-2 weeks for DST. MGIT DST can provide drug susceptibility testing for more than 10 drugs including new drugs such as Bedaquiline, and Delamanid.
- **Solid media,** such as Lowenstein Jensen (LJ):3 – 8 weeks for growth and another 4 weeks for DST. However, DST in solid media is no more used in TB reference lab.

Liquid Culture

Mycobacteria multiply in a nutrient-rich medium, while contaminating bacteria are inhibited by the addition of a cocktail of antibiotics. Growth of bacteria, including mycobacteria, is indicated by fluorescence, which increases proportionally as oxygen decreases in the tube. The instrument detects this fluorescence in the medium using a UV light and complex computer algorithms.

At the culture labs, sample should be inoculated onto MGIT (liquid culture). If no growth appears till 6 weeks, then the culture is considered negative. If bacilli are present in the sample, colonies start to grow on the medium 1-6 weeks in liquid culture.

FIGURE 2.3 BACTEC MGIT 960



Interpretation of Liquid Culture

- Positive for Mycobacterium tuberculosis complex
- Negative for Mycobacterium tuberculosis complex.
- Positive for Non-TB Mycobacterium (NTM)- in such case, report and refer to the treating physician

Note: For treatment monitoring of DR-TB patients, liquid culture is recommended over solid culture.

Solid Culture

- At the culture labs, sample will be inoculated into solid culture medium (Löwenstein-Jensen). If no growth appears till 8 weeks, then the culture is considered negative. If bacilli are present in the sample, colonies start to grow on the medium after 3 to 8 weeks in solid culture.
- For solid culture, the colony growth will be graded according to the number of colonies observed:

Number of colonies	No colonies after 8 weeks	Exact number	10-100	101-200	>200
Result	NEGATIVE	1-9	1+	2+	3+

2.2.2.2 Drug Susceptibility Testing (DST)

When samples are received in TB reference laboratory, along with Xpert MTB/XDR (or LPA), in parallel culture is also performed for:

a. Identifying viable Mycobacterium tuberculosis complex (MTBC)
b. Carrying out phenotypic DST.

When DST is performed as per the diagnostic algorithm, the following drugs listed below are tested for susceptibility.

TABLE 2.5: List of drugs tested for susceptibility (liquid media)

DST in Liquid Media	
FIRST LINE DRUGS	**SECOND LINE DRUGS**
- Isoniazid - Rifampicin - Ethambutol - Pyrazinamide	- Levofloxacin - Moxifloxacin - Bedaquiline - Linezolid - Clofazimine - Amikacin - Delamanid

BOX 2.2: Sputum specimen collection for culture and DST

- Two samples (good quality) are necessary to provide the best possible conditions for the culture to grow.
- If possible, both specimens should be early morning samples.
- If morning samples are not possible to collect, then good quality sample taken at spot can also be considered.

How to send the specimens for culture and DST?

- Two samples along with culture and DST request form must be sent to the TB reference labs without delay maintaining the cold chain. The time between sputum collection and initiation of culture should not exceed 72 hours.
- Triple layer packaging must be ensured for the transportation of the samples.

FIGURE 2.4: Cold Box with Ice



2.2.3 Sputum microscopy

Direct examination following proper staining of a sputum smear or other specimen by light microscopy or fluorescence microscopy is useful to detect TB. However, it does not differentiate the viable/non-viable bacteria, MTBC, or NTM. Smear microscopy will be needed, however, to monitor treatment progress. Sputum microscopy is comparatively less sensitive than molecular diagnostic tests.

2.3 DIAGNOSIS OF EXTRAPULMONARY DR-TB IN THE ABSENCE OF DST

Often, the diagnosis will be based solely on clinical criteria (when it is difficult to obtain bacteriological confirmation of the EP TB diagnosis, it will be even more difficult to obtain bacteriological proof of drug resistance. Whenever a presumption of EP DR-TB is made, all possible efforts should be made to obtain a suitable specimen for Xpert MTB/RIF/Ultra, culture and DST.

In the absence of culture and DST results, only a presumptive diagnosis of EP DR-TB can be made. The most likely instances when EP DR-TB will come to mind are:

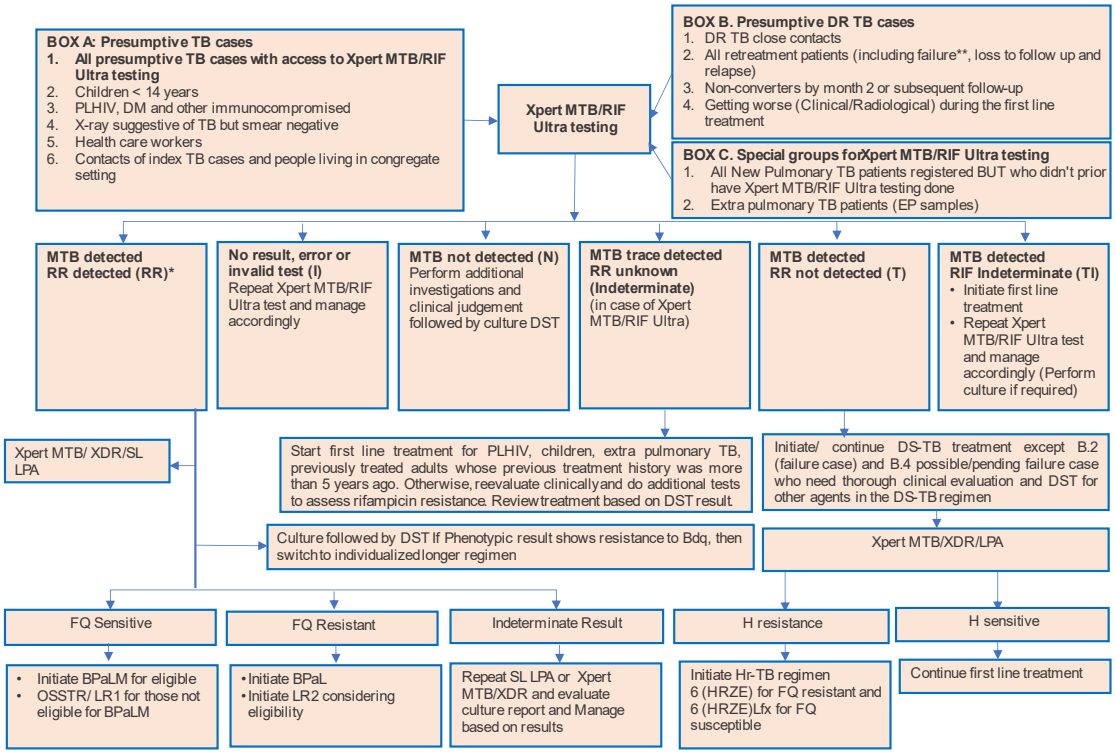
- an EP TB patient who is a contact of a known TB patient with drug resistance.
- a correctly treated EP TB patient who presents a clinically unfavorable evolution.

Patients with presumptive EP DR-TB should be sent to the DR-TB Center. The diagnosis of EP DR- TB must be made in consultation with the expert team constituted under the Technical Working Group (TWG) of the NTCC.

2.4 DIAGNOSTIC PATHWAY

The diagnostic pathway to arrive at a proper diagnosis of DR-TB (and the subsequent prescription of the appropriate treatment) based on the procedures explained in the algorithm **FIGURE 2.5**.

FIGURE 2.5: Diagnostic algorithm for DR-TB and Decisions for DR-TB Treatment



*For new cases with low risk of MDR/RR TB, clinician may consider to repeat the Xpert MTB/RIF/Ultra testing
** In failure cases, if H resistant diagnosed, consider to refer to the Tb specialists (NTCC)

BOX 2.3: Preferred regimen of DR-TB treatment

The regimens for DR-TB treatment are preferred as below:

- **The initial preferred regimen for eligible MDR/RR TB patients should be 6 months BPaLM regimen.**
- **For children below 14 years, both variations of Nine month OSSTR can be used while for pregnant women, linezolid variation OSSTR can be applied.**
- **For those not eligible for BPaLM regimen, longer regimen can be used.**
- **For XDR TB patients treatment, consult with TB specialists at referral centers and longer regimen based on DST profile.**

2.5 DIAGNOSIS OF DR-TB IN SPECIAL GROUPS

2.5.1 Diagnosis of DR-TB in children

The term "children" incorporates a broad range as, 2-year-old child requires a different approach to a 12-year-old, and the treatment of children with MDR/RR-TB will never be a "one size fits all" approach.

Children and young adolescents aged under 15 years represent about 11% of all TB patients globally. However, there is a large case detection gap of children who are not diagnosed and/or not reported. The gap is largest in children aged under 5 years. This is because the diagnosis of TB in children is difficult, and more so for DR-TB.

TB in children may have non-specific symptoms such as:

- cough, especially if persistent and not resolving
- prolonged fever with or without night sweats
- not eating well or anorexia
- weight loss or failure to thrive
- unusual fatigue, reduced playfulness, or decreased activity.

Diagnostic approaches for TB in children

Children who screen positive during contact investigation or who are identified as having presumptive TB by any health facilities must be evaluated further for TB disease. Diagnosing TB in children relies on a combination of

- Careful history, including any TB contact (especially in the past 12 months), previous TB treatment, and signs and symptoms consistent with TB.
- Clinical examination, including growth assessment (weight-for-age,height-for-age and height-for-weight curves, mid upper arm circumference, signs of malnutrition such as oedema or severe wasting).
- HIV testing if status unknown.
- Bacteriological confirmation should always be attempted; at least two good quality specimens should be collected and sent for Xpert MTB/ RIF/Ultra and mycobacterial culture and DST. Many children will not have bacteriological confirmation due to paucibacillary disease or some forms of extra-pulmonary disease. In children, stool specimen should be considered for Xpert testing.
- CXR (preferably anteroposterior and lateral in children aged under 5 years and posteroanterior in older children and adolescents).
- TB infection testing (TST or IGRA).
- Tests to diagnose EPTB, such as appropriate imaging and collection of specimens (such as fine needle aspirates, biopsies, different bodily fluids and CSF) for bacteriological confirmation and DST, should be performed, where possible. Peripheral lymph node disease is the most common form of EPTB in children, and fine needle aspiration is minimally invasive and has high yield of bacteriological confirmation.

Clinical Diagnosis of TB/ MDR/RR-TB in children

- All TB tests, including the microbiological reference standard (usually culture or Xpert Ultra on respiratory samples) have suboptimal sensitivity in children, due to the paucibacillary nature of TB disease in this age group.
- Therefore, a positive test accurately determines a patient of TB disease, but a negative test does not exclude TB disease.
- Hence, clinical diagnosis continues to play an important role in the management of childhood TB.
- Physical examination, clinical history, contact history, radiography, response to treatment, and other assessments together can lead to a confident, empirical diagnosis of TB in young children and should be paired with available laboratory diagnostic testing to support and confirm a TB diagnosis where feasible.
- However, it is important to consider that the drug resistance pattern of a child patient will be similar to the index patient and similar drug regimen can be considered.

Presumptive DR-TB
DR-TB in a child should be suspected when:

- there is contact with a person with confirmed DR-TB;
- there is contact with a person with presumed DR-TB (source patient did not respond to treatment (failed treatment) or is currently retreated for TB or recently died from TB);
- a child with TB is not responding to first-line treatment after 2–3 months despite good adherence (and IRIS is not considered likely in a child living with HIV on ART);
- a child previously treated for TB (especially within the past 12 months) presents with recurrence of disease (either a true relapse or reinfection).

Diagnostic tools for DR-TB in Children

Children, particularly young ones, do not cough up sputum, hence, nasopharyngeal aspirate, gastric aspirate or stool sample should be considered. Sputum induction could be a safe and effective alternative in children of all ages. However, training, and specialized equipment are required to perform this procedure properly.

Collect the specimen at optimal times (e.g., early morning fasting gastric aspirate or nasopharyngeal aspirate; induced sputum after fasting 2-4 hours; expectorated sputum early morning). Always try to collect an optimal quantity of sample, which varies by specimen type; larger volumes generally provide higher bacteriological yields.

Children often have a paucibacillary form of the disease. Direct microscopy of sputum or other specimens (such as gastric aspirates) often will be negative, and even cultures will not always show growth. Nevertheless, every effort should be made to obtain a bacteriological confirmation of diagnosis to avoid exposing children to toxic drugs. If a specimen can be obtained, Xpert testing must always be done (the test also performs well on gastric aspirates and stool samples) and culture (with subsequent DST) must be attempted.

For presumptive TB patients where the specimens mentioned above are negative, other samples such as BAL, FNAC or biopsy from the affected sites can be considered in setting

with appropriate facilities and technical expertise. Xpert MTB/RIF/Ultra and culture in liquid media should be prioritized in children.

Following should always be considered for DR-TB in Children to move forward with diagnosis and decision for treatment.

1. Bacteriologically confirmed MDR/RR-TB is based on identification of *M.tuberculosis* from a specimen from the child by molecular or culture-based methods, along with demonstration of at least rifampicin resistance with a genotypic or phenotypic DST.
2. Clinically diagnosed MDR/RR-TB can be made based on a clinical diagnosis of TB (TB disease without bacteriological confirmation) and either exposure to a known patient of MDR/RR-TB or presence of other risk factors for MDR/RR-TB (child treated previously for TB or exposed to a source patient who died from TB or failed TB treatment).

Testing for TB infection

Testing for *M. tuberculosis* infection using TST or IGRA is useful to support a diagnosis of TB in children with suggestive clinical features who are sputum smear-negative or who cannot produce sputum. A positive test for TB infection indicates prior or current infection with M. tuberculosis and can be particularly useful in the absence of known TB exposure (no positive contact history), as it confirms the child has been infected at some point in time.

2.5.2 Diagnosis of DR-TB in PLHIV

The association of TB and HIV/AIDS is well known and MDR/RR-TB outbreaks among PLHIV have been reported in situations where MDR/RR-TB is common. MDR/RR-TB in PLHIV is more difficult to treat and will have a higher mortality than in HIV-negative people. Therefore, all TB/HIV co-infected patients and all PLHIV with presumptive TB should be tested by mWRDs such as Xpert.

Diagnosing MDR/RR-TB will be even more difficult because many TB/HIV co-infected patients will be paucibacillary, resulting in negative sputum smears and cultures that may not show any growth, which makes it impossible to perform DST. Even the Xpert test will often be negative.

If the presumption of MDR/RR-TB is present in the absence of clear clinical or bacteriological evidence and both Xpert and culture are negative, it is recommended that the diagnosis of MDR/RR-TB in PLHIV be made by a team of experts at the DR-TB Treatment Center.

Note: **Xpert MTB/RIF Ultra is preferred for HIV infected people to diagnose MDR/RR -TB.**

CHAPTER 3

REGISTRATION CATEGORY OF DR-TB

3.1 REGISTRATION CATEGORY

Classification based on history of previous TB treatment (patient registration group):
(Reference: WHO Companion handbook for programmatic management of DR-TB- 2014)

Registration group: Patients are assigned to a registration group based on the most recent treatment history at the time of initiating DR-TB treatment.

1. **New:** A patient who has received NO or LESS than one month of anti-TB treatment.
2. **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).
3. **Failure:** A previously treated TB patient who has received an anti-tubercular treatment whom the treatment has failed.
    - 3.1 After failure of first line Treatment with FLD (TAF New_FLD)
    - 3.2 After failure of Re-Treatment with FLD (TAF Retreatment)
    - 3.3 After failure of Treatment with Hr TB Regimen (TAF Ret_Hr TB)
    - 3.4 After failure of Treatment with SLD (TAF 2nd Line)
4. **Treatment after loss to follow-up (TALF):** 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.
5. **Other previously treated patients (OPT):** A previously treated TB patient whose outcome after the most recent course of treatment is unknown or undocumented.
6. **Patients with unknown previous TB treatment history (UPTH):** who do not fit into any of the categories listed above.

CHAPTER 4

TREATMENT OF DR-TB

It is challenging to treat and manage DR-TB. Since the bacilli are resistant to the most effective first-line drugs, the treatment must include second-line drugs. These drugs are limited in number, less effective than the first-line drugs, poorly tolerated, some side effects can be very severe and difficult to recognize, and drugs are very expensive. Complicated patients with extensive drug resistance patterns are even more difficult to treat.

However, recent evidences suggest that all oral MDR/RR-TB regimens including "BPaLM/BPaL" and bedaquiline-containing shorter regimens are found to be more efficacious as compared to injectable-based regimens. BPaLM/BPaL regimen is very promising as the interim analysis of ongoing operational research (BPaL) in SEAR show 91-95% treatment success rate. The side effects are relatively recognizable; the duration of treatment is 6 months same as DS-TB and drug prices for oral MDR/RR-TB regimen are reduced to an extent.

Following is strongly recommended before the treatment initiation is considered:

- Ahead of enrolment on DR-TB treatment, all patients should receive appropriate counseling to enable informed and participatory decision-making.
- Ensure that patients are appropriately informed about their treatment options.
- Ensure patient-centered approach to the delivery of care including social and psychological support.
- Active TB drug safety monitoring and management (aDSM) is essential for all patients enrolled on DR-TB treatment.
- Baseline and follow-up investigations are mandatory as per guideline.

4.1 PATIENT EDUCATION

- Patient education is an essential component of any DR-TB control program and is possible when there is trusting interpersonal communication between patients and medical personnel.
- Provision of emotional & social support to DR-TB patients may increase the likelihood of adherence.
- The organization of patient education should be considered equally with the other components of the DR-TB program (such as detection and diagnostics, drug supply, etc.)
- The patient's knowledge and understanding of his/her role in achieving a successful treatment outcome is an essential component for treatment selection.

TABLE 4.1: Components of health education and deliverable messages

S. N.	Component	Deliverable messages for education of patient and treatment supporter
1	Patient knowledge and understanding of Disease	What is TB and DR-TB, difference between TB & DR-TB, treatment for DR-TB, monthly follow ups and routine investigations, benefits of regular treatment and harms of interruption of treatment.
2	Prevention of Spread of DR-TB	What measures are to be taken to prevent spread of DR-TB at household and community level, close contact screening, importance of regular intake of medicine
3	Information about possible side effects and drug interactions	What most common side effects patient may experience and how to report side effects for management, appropriate ways of drug intake. Antacids (especially those containing aluminum), mineral supplements (e.g., iron or magnesium) or multivitamins should be taken more than 2 hours before or after of medication. There are no major interactions with milk or dairy products in third-generation fluoroquinolones. PAS should be swallowed with acidic liquid. The constituted Injectable (if applicable) dosages should be used within 24 hrs and kept refrigerated.
4	Patients' Rights and Responsibilities	Explain patients' role in treatment completion, what are patient rights and responsibilities during whole period of treatment.
5	Role & Responsibilities of Treatment Supporter	Clearly explain the role and responsibility of Treatment Supporter, daily supervised DOT provision, identifying side effects, emotional support to patient and family, accompanying patient on monthly follow ups to DR TB Treatment center and on weekly basis to nearest DOTS center, support in contact tracing, benefits of supervised treatment and benefits of successful treatment completion, and incentives where feasible such as communication cost for treatment supporter)
6	Psycho-Social support throughout Treatment	Patients should be supported by the counsellors to provide counseling, support and refer where necessary to psychologists, explain that all drugs and investigations related to DR-TB treatment are free of cost and delivery of social support in terms of travel allowances and food baskets where possible.
7	Maintaining confidentiality	The PMDT health team should explore the need of the patient to maintain strict confidentiality regarding their disease and all aspects of ethical consideration should be applied.

BOX 4.1: Patient Instructions

The following instructions should be given to the patient:

- **Avoid meeting with other people in closed spaces. Apply appropriate precautions such as wearing face masks when going to markets, festivals, gatherings, while having group meetings or when taking a public transportation.**
- **The same precautionary measures when meeting with family members or other people at home. Family members should use N95 masks whenever they are together.**
- **If it is possible, stay at home in a separate room. If you can have a room that is well ventilated and has windows that let in sunlight, it is even better.**
- **Eat separately, either in the room or outside.**
- **If other people come to the house, only meet them outside for a short time and stay at a safe distance.**
- **Avoid contact with children because they are extremely vulnerable. If this is difficult, conssider letting the children stay with friends or family.**

Note: In situations in which patients are isolated, de-isolation should be based on the likely infectivity of the individual case, clinical improvement, culture and smear conversion and the availability of other supportive systems. The infectivity in individual depends on bacillary burden and choice of regimen used.

4.2 REGIMEN OPTIONS IN THE TREATMENT OF DR-TB

In patients with MDR/RR-TB, there are several regimens that can be used based on current WHO policy. The key factors that define treatment regimen choice include drug-resistance profile, prior exposure to TB medicines and patient history, drug-resistance profile of close contacts, the patient's age, extent of pulmonary TB disease and localization of extrapulmonary TB lesions.

After reviewing the current evidence and treatment options available, three types of treatment regimen are to be used for management of MDR/RR-TB in Nepal (Box 4.2). All are largely standardized.

Box 4.2: MDR/RR TB treatment regimen of Nepal

- Shorter Regimen
  - BPaLM/BPaL regimen: 6 months
  - All-oral standardized shorter treatment regimen (OSSTR): 9 months
- Longer regimen (LR): 18 months

TABLE 4.2: MDR/RR TB treatment regimen for Nepal

Regimen	MDR/RR TB fluoroquinolone susceptible	Pre-XDR-TB	XDR-TB	Extensive pulmonary TB	Extrapulmonary TB	Age <14 years
6-month BPaLM/BPaL	Yes (BPaLM)	Yes (BPaL)	No	Yes	Yes - except TB involving CNS/meningitis, miliary TB, osteoarticular TB and pericardial TB	No
9-month all-oral regimen (OSSTR)	Yes	No	No	No	Yes - except TB involving CNS/meningitis, miliary TB, osteoarticular TB and pericardial TB	Yes
18 months Longer Regimen	Yes*/No	Yes*/No	Yes	Yes	Yes	Yes
Additional factors to be considered if several regimens are possible	Drug intolerance or adverse events					
	Treatment history, previous exposure to regimen component drugs or likelihood of drug effectiveness					
	Patient or family preference					
	Access to and cost of regimen component drugs					

BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin, CNS: central nervous system; MDR/RR-TB: multidrug- or rifampicin-resistant TB; TB: tuberculosis; XDR-TB: extensively drug- resistant TB.
* When 6-month BPaLM/BPaL and 9-month regimens could not be used
Source: *WHO Operational Handbook on Tuberculosis; Module 4: Treatment (Drug-resistant tuberculosis treatment), 2022 update*

4.2.1 Shorter Regimen

4.2.1.1 BPaLM regimen (6 Bdq-Pa-Lzd-Mfx)

The 6-month BPaLM regimen, comprising bedaquiline, pretomanid, linezolid and moxifloxacin is the initial choice for all eligible patients diagnosed with MDR/RR-TB. This regimen may also be used without moxifloxacin (BPaL) in patient of documented or indeterminate resistance to fluoroquinolones (in patients with pre-XDR-TB). The duration of BPaLM regimen is largely standardized for 6 months (26 weeks), whereas BPaL can be extended to a total of 9 months (39 weeks) in selected patients.

Box 4.3: BPaLM regimen

In May 2022, WHO released a rapid communication which was subsequently updated and incorporated in the consolidated guideline, stating that the 6-month all-oral regimen of bedaquiline, pretomanid, linezolid with or without moxifloxacin (BPaLM/BPaL) may be used programmatically for patients (aged ≥14 years) with MDR/RR TB who are not yet exposed to the former three drugs. This new recommendation was based upon data from multiple trials, notably TB-PRACTECAL which showed significantly high treatment success rates with the BPaLM regimen (89%) compared with the usual regimens (52%). Data from ZeNix trial also suggest fewer adverse events with lower linezolid dose of 600 mg while maintaining high efficacy. It was judged that implementing this regimen was feasible and acceptable, with cost-effectiveness and equity probably improved in selected patients. Similarly, the injectable based shorter regimen (SSTR) will be completely phased out where the injectable drug will be replaced by bedaquiline.

Indications

- Adults and adolescents aged 14 years and older
- People with MDR/RR TB or pre- XDR-TB
- People with confirmed pulmonary TB and non-severe EPTB
- All people regardless of HIV status
- Patients with less than 1- month previous exposure to its component drugs e.g., bedaquiline, linezolid, pretomanid or delamanid or if resistance is ruled out

Contraindications

- Severe EPTB such as TB involving CNS/meningitis, miliary TB, and osteoarticular TB and pericardial TB.
- One month or more previous exposure to bedaquiline, linezolid, pretomanid or delamanid unless resistance to those drugs has been ruled out
- Pregnant and breastfeeding women
- XDR-TB
- Patients having allergy to any of the BPaLM component drugs

4.2.1.2 BPaL (without moxifloxacin) regimen (6 Bdq-Pa-Lzd)

- The BPaL regimen is provided for those who have proven fluoroquinolone resistance from DST.
- The BPaL regimen uses the same doses of pretomanid, bedaquiline and linezolid as the BPaLM regimen
- If fluoroquinolone resistance is detected while an individual is on the BPaLM regimen, moxifloxacin is omitted from the regimen and BPaL is continued.
- Individuals who switch from BPaLM to BPaL should consider their treatment start date the same as the date BPaLM was initiated.
- The treatment duration of BPaL regimen is 6 months.
- The duration of the treatment can be extended to 9 months (39 weeks) continuing from the start of the therapy with BPaLM or BPaL.

- The extension of the BPaL regimen to 9 months can occur where there is lack of culture conversion or clinical response (based on the clinical judgement of the treating physician) between 4 and 6 months.

TABLE 4.3: Drug dosing for BPaLM/BPaL regimen (26weeks)

Drug	Formulation	Daily dose
Bedaquiline	**100 mg tab**	**200 mg daily for 8 weeks; then 100 mg daily(18weeks)**
Pretomanid	**200 mg tab**	**200 mg once daily**
Linezolid	**600 mg tab**	**600 mg once daily**
Moxifloxacin	**400 mg tab**	**400 mg once daily**

Points to remember:

- Dose modifications for bedaquiline, moxifloxacin and pretomanid are not allowed.
- If either bedaquiline or pretomanid needs to be permanently discontinued, the entire BPaLM/BPaL regimen should also be discontinued
- Given the lack of evidence for the use of other fluoroquinolones, substitution of moxifloxacin with levofloxacin is not recommended.
- In case of drug intolerance or adverse events, temporary cessation of the full regimen for no more than 14 days is allowed and missed doses need to be made up and added to the treatment regimen.
- Dose modification of linezolid should be avoided in the first 9 weeks of therapy.
- Linezolid is by far the most toxic drug in the BPaLM and BPaL regimens. Linezolid should be continued at the full recommended dose (600mg once daily); however, the dose of linezolid can be reduced to 300 mg or discontinued after first 9 weeks of therapy.
    - Myelosuppression (even of Grade 3 or 4) – This can be life threatening and even fatal. Most patients of anaemia occur in the first 2 months and is often reversible with a short 1-to-2-week drug holiday followed by reducing the dose of linezolid to 300 mg per day; severe anaemia may need to be treated with transfusions or erythropoietin.
    - Peripheral neuropathy (Grade 2)- reduce the dose of linezolid to 300 mg per day with a possible drug holiday for 1–2 weeks before dose reduction
    - Peripheral neuropathy (Grade 3 or 4)- in most patients permanent suspension of linezolid will be needed
    - Optic neuritis (diagnosed at any grade)- permanent discontinuation of linezolid is indicated.
- If linezolid is permanently discontinued during the initial 9 consecutive weeks of treatment, the entire regimen should be discontinued and switched to Ethionamide containing all oral regimen (OSSTR).
- If linezolid is withheld in the later weeks of the regimen, with the total remaining duration of the regimen not exceeding 8 weeks, the regimen can be completed with the remaining component drugs.

Box 4.4: Linezolid induced toxicity

Anemia

Anaemia in TB patients is common. It is often due to TB itself, a normocytic normochromic anemia. Treating the TB treats the anemia. There may be other contributing factors including nutritional deficiencies, blood loss from hemoptysis or other sources and HIV co-infection. TB patients are vulnerable to drops in Haemoglobin (Hb) and may decompensate easily.

Prior to starting treatment: Ideally a full blood count with a differential white cell count and platelets needs to be done prior to starting treatment. However, from a practical point of view, health care providers can use a point of care Hb test. If the Hb is above 8 g/dl, then BPaLM/BPaL can be started. If the Hb is below 8 g/dl, the treatment may need to be delayed until the anaemia is corrected. Patients with severe anaemia and MDR/RR-TB should be admitted to the hospital. If possible and acceptable, a blood transfusion can be considered.

There is no evidence for initiating this regimen without Linezolid and introducing it later. As the patient's bacillary load is high at this time, an inadequate regimen may result in the amplification of resistance. If there is FQ sensitivity, the short oral regimen (OSSTR) with ethionamide can be considered. If there is FQ resistance, then a longer individualized regimen must be given.

For weeks 9 to 26: full blood count with a differential white cell count and platelets needs to be done every four weeks. If the Hb drops below 8g/l, Linezolid can be stopped temporarily and restarted later with reduced dose (300 mg) provided there has been a clinical response. This would include a reduction of symptoms, increase in weight, reduction in smear positivity, and if available, culture conversion.

Peripheral Neuropathy (PN)

This adverse event tends to occur later in treatment, the peak time of onset usually around 16 weeks. The patients' experience is often subjective.

The key to detection and management of this condition is patient and health care provider education and counselling. As with most adverse events, pre-treatment counselling needs to include the common symptoms to watch out for: pins and needles, pain, and numbness. The Brief Peripheral NeuropathyScore (BPNS) is a useful and more objective guide to any worsening.

If the clinician and the patient decide that the PN has requires alteration in the Linezolid,then the severity of the TB, clinical response and mycobacterial response need to be considered. Linezolid remains a key drug in the regimen even in RR/MDR TB, withdrawal too early may compromise the efficacy of the regimen.

Table 4.4: Management of peripheral neuropathy

Duration	MDR/RR-TB (BPaLM)	Pre-XDR TB (BPaL)
Weeks 1 to 9	Change to OSSTR or an individualized longer regimen without Linezolid	Change to an individualized longer regimen without Linezolid
Weeks 10 to 18	Reduce dose of Linezolid (300 mg) or consider temporary discontinuation	Reduce dose of Linezolid (300 mg) or consider temporary discontinuation
Weeks 18+	Permanent discontinuation of Linezolid if clinical response and culture conversion has occurred.	Permanent discontinuation of Linezolid if clinical response and culture conversion has occurred.

Optic Neuritis

This is an uncommon adverse event but if left can cause permanent disability. Optic neuritis is usually bilateral.

It is important to establish a baseline for all patients about to start the regimen. An ophthalmology history should be taken. Prior visual problems including trauma, near-or shorted-sightedness, infections and cataracts should be recorded. Poor visual acuity prior to treatment is not a reason to withhold Linezolid. A full slit lamp examination is not necessary. Visual acuity should be measured using a Snellen test. It should be noted if the patients wear spectacles The visual acuity for each eye should be recorded as -/6 (20) R and -/6 (20) L.

The Ishihara charts can be used for color vision if available. It is important that visual acuity be checked at every visit when the patient is on LINEZOLID. At each visit, the patient should be asked if there are any changes in visual acuity. If there is more than a two line drop in visual acuity, this requires action. If possible, the patient should be referred for (ophthalmology) assessment with a full examination of the optic nerve. If this cannot be done, then Linezolid should be permanently discontinued.

Box 4.5: Some examples of changes in Linezolid dosing within the BPaLM/BPaL Regimen

- ☑ **A patient diagnosed with MDR/RR-TB (based on Xpert results) completes 4 weeks of treatment with BPaLM, with 600 mg of linezolid, when they experience symptoms of severe paresthesia in the feet preventing them from completing their daily life activities. This adverse event necessitates the cessation of linezolid within the first 9 weeks of therapy. Because permanent discontinuation of linezolid was needed, the entire regimen must be discontinued, and a new regimen started.**

- ☑ **A patient completing treatment with BPaL, with 600 mg of linezolid, for MDR/RR-TB with fluoroquinolone resistance, experiences Grade 3 optic neuritis in week 20 of therapy. Linezolid must be ceased permanently; however, because there is less than 8 weeks of treatment remaining, the patient completes a further 6 weeks of therapy with bedaquiline and pretomanid and has a negative sputum culture at the end of 26 weeks, achieving a successful treatment outcome on BPaL therapy. The optic neuritis improves slowly after cessation of linezolid.**

4.2.2 Nine months all-oral standardized shorter treatment regimen (OSSTR)

The regimen consists of an initial phase of 4 months that may be extended up to 6 months and a continuation phase of 5 months, giving a total duration of 9-11 months. Bdq is used for a duration of 6 months.

4.2.2.1 Composition and duration of the regimen

i. **The Linezolid variation**

This is the preferred regimen and it is summarized as:

4–6 $Bdq_{(6\,m)}$-$Lzd_{(2\,m)}$-Lfx/Mfx-Cfz-Z-E-Hh / 5 Lfx/Mfx-Cfz-Z-E

ii. **The Ethionamide variation**

The regimen is summarized as:

4–6 $Bdq_{(6\,m)}$-Lfx/Mfx-Cfz-Z-E-Hh-Eto / 5 Lfx/Mfx-Cfz-Z-E

Note: **In view of higher risk of QT prolongation with moxifloxacin, when used along with other drugs (Bdq and Cfz), levofloxacin is preferred for OSSTR.**

Indications

- Patients with no documented resistance or suspected ineffectiveness or less than 1-month previous exposure to its component drugs i.e., bedaquiline, fluoroquinolones, INH, clofazimine, or ethionamide or linezolid.
- Children (less than 14 years)
- Women who are pregnant or breastfeeding are eligible for the linezolid containing OSSTR.
- Linezolid containing regimen is also preferred in patients with (WHO 2022):
  - serum haemoglobin above 8 g/dL
  - neutrophils above 0.75×10^9/L
  - platelets above 150×10^9/L (at the start of treatment)
  - no evidence of severe peripheral neuropathy, or any sign or suspicion of optic neuritis, at the start of treatment.
- Ethionamide containing regimen is preferred in patients with pre-existing hematological abnormalities (as above) and severe peripheral neuropathy.
- If pretomanid (in BPaLM regimen) is not available for some reason, OSSTR may be used, if eligible.
- In case of mutation to both InhA and KatG, ethionamide based regimen cannot be used. Thus, linezolid variation should be used in these patients.

Contraindications

- MDR/RR-TB Patients with FQ resistance.
- Severe EPTB such as TB meningitis, miliary TB, osteoarticular TB and pericardial TB.
- Extensive pulmonary TB disease.

Points to remember:

The nine month all-oral shorter (OSSTR) regimen should be implemented as a standardized package. It is not advisable to change the composition of the regimen or the duration of either the initial or continuation phase, with a few exceptions, as follows:

- Bedaquiline is usually given for 6 months but may be extended to 9 months if the initial phase of the regimen is extended from 4 to 6 months because of positive sputum smears at month 4 of treatment.
- Linezolid is only given for initial 2 months (instead of 4–6 months of ethionamide). If occasional doses of linezolid are missed during that time, the missed doses can be added on to the end of the 2-month period if the patient is tolerating the drug well, however, once fluoroquinolone resistance has been definitively ruled out, it may not be strictly necessary to make up the missed doses.
- The linezolid dose should not be reduced to less than the recommended dose to reduce the severity of adverse effects. If the full dose of linezolid (600 mg in adults) is not tolerated for the first full 2 months of treatment (apart from occasionally missed doses, which can be added to the end of the 2-month period), then the patient must either switch to an ethionamide-containing OSSTR regimen (provided fluoroquinolone susceptibility is confirmed and the patient is not pregnant) or to an individualized longer regimen without linezolid.
- If, for any reason, a patient is unable to tolerate pyrazinamide or ethambutol within the OSSTR, then one (but only one) of these drugs may be dropped during the continuation phase without necessitating a switch to a longer regimen.
- If two or more of these drugs are not tolerated within the OSSTR, the treatment will have to switch to a longer regimen. If any of the other drugs within the 9-month regimen (bedaquiline, levofloxacin/moxifloxacin, linezolid/ethionamide or clofazimine) are stopped early because of toxicity or intolerance then the patient will also have to switch to a new regimen. Patients switching to a new regimen due to toxicity or intolerance need to be reported as “treatment failed”.
- At the fourth month of treatment on the OSSTR, the decision to extend the initial phase from 4 to 6 months is based on the sputum smear status and clinical response. If the specimen is smear negative at month 4 (regardless of smear status at the start of treatment), the patient may move to the continuation phase of treatment. If the specimen is smear positive at month 4, the initial phase is prolonged to 6 months.The duration of the continuation phase remains fixed at 5 months.
- At the sixth month of treatment, the culture result from the specimen taken at month 4 and possibly month 5 should be available
  - POSITIVE CULTURE AT 4 MONTHS: The clinician should undertake a full work-up to assess for treatment failure
    - Comprehensive clinical assessment
    - Review of treatment adherence to address specific challenges
    - Radiological assessment

- Collection of another respiratory sample for bacteriological assessment, as well as repeat DST of the most recent positive culture to test for emerging resistance to second-line TB drugs

- POSITIVE CULTURE AT 5 & 6 MONTHS (if extended)
  - Treatment failure should be suspected, particularly if the patient has had suboptimal adherence to treatment or shows other signs of poor clinical or radiological response to treatment.
  - These patients must switch to a different regimen.

4.2.2.2 Drugs, dosages, frequency, and duration of administration

The OSSTR consists of an initial phase of 4 months with 7 drugs, followed by a continuation phase of 5 months with 4 drugs. If Eto is used, it should be introduced gradually. On day 1, treatment will start with all drugs except Eto. If there is no major adverse event on day 1, Eto 250 mg will be added on day 2. The dosage of Eto will be escalated to 500mg on day 5 if patient can tolerate Eto 250 mg, and further escalated to 750mg (250mg in the morning, 500mg in the evening) on day 8 if necessary, depending on patients' body weight. An antiemetic drug may be used if there is gastrointestinal disturbance.

TABLE 4.5: Medicines used in OSSTR

Month	1	2	3	4	5	6	7	8	9	10	11
Bedaquiline											
High-dose isoniazid											
Ethionamide/ prothionamide							Ethionamide Variation				
Moxifloxacin/Levofloxacin											
Clofazimine											
Pyrazinamide											
Ethambutol											
Linezolid			Linezolid Variation								

Orange	OSSTR Regimen
Blue	Added months if still smear positive after 4 months of treatment
Green	added, if necessary
Pink	Only if Linezolid variation is used

TABLE 4.6: Adult dosages of the drugs used in the OSSTR

Drug	Dosage	Weight group (Kg)				
		30-35	36-45	46-55	56-70	>70
Bedaquiline tablet (tablet 100 mg)	Fixed	400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks				
Ethionamide1 (tablet 250mg)	15-20mg/kg/d	500mg (2 tab)	500mg (2 tab)	750mg (3 tab)	750mg (3 tab)	1gm (4 tab)
Isoniazid high dose (tablet 300mg)	10mg/kg/d	300mg (1 tab)	450mg (1.5 tab)	600mg (2 tab)	600mg (2 tab)	600mg (2 tab)
Moxifloxacin high dose (tablet 400mg)	10-15mg/kg/d	600mg (1.5 tab)	600mg (1.5 tab)	600-800mg (1.5-2 tab)	800mg (2 Tab)	800mg (2 tab)
Levofloxacin (tablet 250 mg)	15-20 mg/kg/d	750mg (3 tab)	750 mg (3 tab)	1000 mg (4 tab)	1000 mg (4 tab)	1000 mg (4 tab)
Clofazimine (capsule 100mg)	Fixed dose	100mg (1 tab)	100mg (1 tab)	100mg (1 tab)	100mg (1 tab)	100mg (1 tab)
Pyrazinamide (tablet 400mg)	20-30mg/kg/d	1000mg (2.5 tab)	1200mg (3 tab)	1600mg (4 tab)	2000mg (5 tab)	2000mg (5 tab)
Ethambutol (tablet 400mg)	15-25mg/kg/d	800mg (2 tab)	1200mg (3 tab)	1200mg (3 tab)	1200mg	1200mg
Linezolid (tablet 600 mg, 150mgdt, 20mg/ml syp)	10-12 mg/kg/d	300 mg	450mg	600mg	600mg	-

[1] 250mg once daily on days 2 to 4; 2 x 250mg/day on days 5 to 7; 250mg in the morning, 500mg in the evening from day 8 onwards if patient >50kg.

For pediatric dosing of drugs used in the OSSTR, refer to Table 4.8 under the Longer Regimen.

4.2.3 Longer Regimen (LR)

The use of longer regimens is reserved for patients with MDR/RR-TB who are not eligible for BPaLM/BPaL regimen and OSSTR, and for patients in whom these regimens failed or not tolerated.

Indications

- Severe extrapulmonary TB
- Additional resistance to key medicines of the BPaLM/BPaL regimen (except moxifloxacin) or the OSSTR.
- Lack of response to shorter treatment regimens (e.g., treatment failure due to no bacteriological conversion, no clinical response, emerging resistance, or loss to follow-up).
- Drug intolerance to the component medicines of the BPaLM/BPaL regimen (except moxifloxacin) or 9 months all-oral treatment regimen; and
- Pregnant and lactating women who could not benefit from the 9-months shorter all-oral regimen owing to certain clinical conditions.
- A longer regimen could also be considered as an option for patients with low BMI (<18 kg/m2).

4.2.3.1 Composition and duration of longer regimen

- The composition of longer regimens is guided by the selection of individual medicines considered to be effective and by a need to combine sufficient medicines to maximize the likelihood of relapse-free cure without increasing toxicity.
- Regimens may be of standardized (fixed) composition or may be individualized to the patient's needs.
- Apart from the ranking by balance of effectiveness and harms, choice is also determined by- a preference for composition of agents; the results of drug-susceptibility testing (DST); the reliability of existing DST methods; population drug resistance levels; history of previous use of the medicine in a patient; drug tolerability; and potential drug-drug interactions.
- In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped.
- If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.
- In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy.
- In MDR/RR-TB patients on longer regimens, a treatment duration of 15–17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy.

Based on the WHO drug grouping recommendations, the regimen is designed by adding medicines sequentially going down from group A to group C, as outlined in the TABLE 4.7.

TABLE 4.7: Grouping of Medicines recommended for use in longer MDR/RR-TB regimens

Groups	Steps	Medicines	Abbreviations
A	Include all three medicines in the regimen, if no contraindication	Levofloxacin OR Moxifloxacin	Lfx Mfx
		Bed aquiline	Bdq
		Linezolid	Lzd
B	Add one or both Medicine	Clofazimine	Cfz
		Cycloserine OR Terizidone	Cs Trd
C	Add to Complete regimen and when medicines from Group A and Group B cannot be used	Ethambutol	E
		Delamanid	Dlm
		Pyrazinamide	Z
		Imipenem-cilastatin OR Meropenem	Imp,Cln Mpm
		Amikacin or Streptomycin	Am S
		Ethionamide OR prothionamide	Eto Pto
		P-aminosalicylic acid	PAS

Source: WHO consolidated guidelines on drug-resistant tuberculosis treatment,2019

BOX 4.6: Additional Notes

- **Drugs that should be included in treatment of MDR/RR-TB patients on longer regimens**
  - Levofloxacin or moxifloxacin
  - Bedaquiline
  - Linezolid
- **Drugs that may be included in treatment of MDR/RR-TB patients on longer regimens**
  - Clofazimine and cycloserine or terizidone
  - Ethambutol
  - Delamanid
  - Pyrazinamide
  - Imipenem-cilastatin or meropenem
  - Amikacin- more than 18 years
- **Use these drugs only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible**
  - Ethionamide or prothionamide
  - P-aminosalicylic acid
- **Drugs that should not be included**
  - Kanamycin and capreomycin

Basic Principles for construction of Individualized Longer Regimen

- It is recommended by WHO that treatment should start with at least four effective medicines
- It is imperative that all diagnosed MDR/RR-TB should be placed on DST regardless of choice of regimen and current availability of rapid molecular DST (Xpert-XDR or LPAs) make the results availability quicker.
- The DST result to FQ should be known as soon as possible and regimen to be adjusted accordingly.
- However, as implementation consideration there might be delays in result availability and treatment initiation with best empirical regimen should not be delayed.
- The basic principle of having at least 4 effective drugs on board in the beginning and at least 3 drugs to be continued after 6 months (or when Bdq/Dlm is stopped). It is important that at least one strong bactericidal drug should be on board throughout.
- Possibly all three Group A agents (Lfx/Mfx, Bdq,Lzd) and at least one Group B agent(Cfz or Cs) should be part of regimen and if only one or two Group A agents are used, then both Group B agents are to be included in regimen.
- If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.
- Starting treatment with five effective agents rather than four may also be a practice and this provision is expected to apply to those with additional resistance or **suspected** resistance to fluoroquinolones or other medicines.
- Bdq and Dlm can be used together to complete the regimen in patients who have limited other treatment options.
- The use of three cardiotoxic drugs (Bdq, Dlm and Cfz) in combination should be with caution and with close monitoring. However, recent data shows that combined use of Bdq and Dlm is safe and QTcF interval with co administration of both drugs is clinically modest (Dooley et al, 2019)
- The use of Lzd for whole duration is associated with better treatment outcomes and lower mortality but is expected to cause toxic effects in significant number of patients. The neurological toxicity is associated with duration, while hematological toxicity/ myelosuppression is dose related.
- For Lzd use in the regimen, baseline assessment by blood picture and neuropathy screening should be done and if contraindicated, should not be part of regimen or if possible, with lower dose of 300 mg daily or 600 mg alternative days.
- Imipenem should be used with Amoxiclav Every dose of imipenem-cilastatin or meropenem should be preceded by the oral administration of oral clavulanic acid 30-60 minutes beforehand; oral clavulanic acid is only available in formulations combined with amoxicillin. Amoxicillin-clavulanic acid is not counted as an additional effective TB agent and should not be used without imipenem-cilastatin or meropenem
- Injectable, Amikacin should only be used in regimen if there is documented no other options or documented susceptibility to it and appropriate monitoring for hearing loss is available. WHO also recommends to use Am only in those 18 years of age or above.
- If the longer regimen fails, treatment options will be very limited. The patient must be referred to the DR-TB Referral Center.

TABLE 4.8: MDR/RR-TB -Longer Regimen in Nepal

Resistance pattern and background history		Regimen	Comments
LR1	Standard longer MDR/RR-TB Regimen for adults and children Non-eligible for BPaLM /BPaL and OSSTR and for those whose FQ results are susceptible Patient on household contact with FQ resistant patients are not eligible	Bdq(6),18Lfx, Lzd, Cfz	1. In of toxicity or need to decrease or substitute Lzd with Cs, Refer to aDSM relevant section 2. If Lzd is well-tolerated, should be continued throughout the treatment duration 3. If Lzd is not tolerated for the whole treatment duration and if Cs cannot be used, consider another drug from Group C in the place of Lzd
LR2	RR TB with FQ resistance at baseline Non-eligible for BPaL	Bdq(12),18Lzd, Cfz, Cs	1. High dose Lfx or Mfx can be added once resistance level to FQs is known 2. In patients with intolerance/toxicity to Lzd, stopping Lzd, replacing with Dlm can may be a suitable option. If Dlm cannot be added, then Eto. can be used instead 3. Close and careful monitoring with combination of three cardiotoxic drugs (Bdq, Cfz, Dlm)
LR3	Failed by MDR/RR-TB standard treatment (LR1) /Relapse or recurrence of MDR/RR-TB	Am (6), Dlm (12), 18Eto, PAS (Cs), Cfz (Mfx or Lfx)	1. DST to FLD and SLDs should guide further modification where necessary 2. Use Am if documented susceptibility to it, design regimen based on previous exposure to SLDs and likely effective drugs. 3. If susceptible to FQ, high dose Lfx or Mfx can be used, if resistance to FQ then FQ can be used in line with level of resistance reported 4. Extending use of Dlm for whole duration could be an option 5. If Cs was used as a part of LR1 then use PAS instead 6. Imp Clv can be used when injection (Am) cannot be used, or after Am stopped by 6-8 months

TABLE 4.9: Weight based dosing of medicines used in multidrug resistant TB regimens, adults, and children

Medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	Weight-based daily dose	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
GROUP A MEDICINES														
Levofloxacin (Lfx)	100 mg dt (10 mg/mL)	15-20 mg/kg	5 mL (0.5 dt)	1	1.5	2	3	-	-					
	250 mg tab (25 mg/mL)		2 mL[b]	5 mL (0.5 tab)[b]		1	1.5	2	3		4			
	500 mg tab		-					1	1.5		2			
	750 mg tab		-						1		1.5			
Moxifloxacin (Mfx	100 mg dt (10 mg/mL)	(10-15 mg/ standard dose)	4 mL	8 mL	1.5	2	3	4	4		-			
	400 mg tab (40 mg/mL) Standard dose		1 mL[b]	2 mL[b]	3 mL[b]	5 mL (0.5 tab)[b]	7.5 mL (0.75 tab)[b]	1	1					
	400 mg tab high dose[c]		-		-	-	-		1 or 1.5	1.5	1.5 or 2	2		
Bedaquiline (Bdq)	20 mg dt		0 to <3 months: 1.5 od (2 weeks); then 0.5 od M/W/F (22 weeks) ≥ 3 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks		0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F 3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F ≥6 months: 4 od for 2 weeks; then 2 od M/W/F	3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F ≥ 6 months: 6 od for 2 weeks; then 3 od M/W/F	10 od for 2 weeks; then 5 od M/W/F		20 od for 2 weeks; then 10 od M/W/F		-			

Medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	Weight-based daily dose	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Bedaquiline (Bdq)	100 mg tab (10 mg/mL)[d]		0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F[b] ≥ 3 months: 6 mL od for 2 weeks; then 2 mL od M/W/F[b]		0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F[b] 3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F[b] ≥ 6 months: 8 mL od for 2 weeks; then 4 mL od M/W/F[b]	3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F[b] ≥ 6 months: 12 mL od for 2 weeks; then 6 mL od M/W/F[b]	2 od for 2 weeks; then 1 od M/W/F		4 od for 2 weeks; then 2 od M/W/F				
	100 mg tab (10 mg/mL)		-								200 mg daily (od) for 8 weeks; then 100 mg dose daily (od)			Dosing scheme is for BPaLM/BPaL regimen (>14 years).
Linezolid (Lzd)	20 mg /mL susp	15 mg/kg od in 1–15 kg;	2 mL	4 mL	6 mL	8 mL	11 mL	14 mL	15 mL	20 mL	-			
	150 mg dt (15 mg/mL)		2.5 mL	5 mL (0.5 dt)	1		2[e]		2	3	-			

Medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	Weight-based daily dose	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
	600 mg tab (60 mg/mL)	10–12 mg/kg od in ≥ 15 kg	-	1.25 mL[b]	2.5 mL[b]		5 mL (0.5 tab)[b, e]		5 mL (0.5 tab)[b]	7.5 mL (0.75 tab)[b]	1	1		
GROUP B MEDICINES														
Clofazimine (Cfz)	50 mg cap or tab[f]	2–5 mg/kg (when dose daily	1 M/F	1 M/W/F		1		2	2					For children <24 kg, the use of the 50 mg tab is preferred.
	100 mg cap or tab[f]		-	1 M/F		1 M/W/F		1	1					
Cycloserine or terizidone (Cs/Tz)	125 mg mini cap (Cs) (12.5 mg/mL)	15–20 mg/kg in 7 to<30 kg	2 mL[b, g]	4 mL [b]	1	2	3	4	4		-			
	250 mg cap (25 mg/mL)	10–15 mg/kg in a 30 kg and above	1 mL[b, g]	2 mL[b]	5 mL[b]	1	2	2	2		3			
GROUP C MEDICINES														
Ethambutol (E or EMB)	100 mg dt (10 mg/ mL)	15-20 mg/kg	5 mL (0.5 dt)	1	2	3	4	-	-					-
	400 mg tab (40 mg/mL)		1.5 mL[b]	3 mL[b]	4 mL[b]	6 mL	1	1.5	2		3		4	
Delamanid (Dlm)	25 mg dt		1 od	<3 months: 1 od ≥3 months: 1 bd		1 bd	2 mornings 1 evening		2 bd		-			
	50 mg tab[h] (5 mg/ mL)		5 mL (0.5 tab) od[b]	<3 months: 5 mL (0.5 tab) od[b] ≥3 months: 5 mL (0.5 tab) bd[b]		5 mL (0.5 tab) bd[b]	10 mL (1 tab) morning 5 mL (0.5 tab) evening		1 bd		2 b d			

Medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	Weight-based daily dose	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Pyrazinamide (Z or PZA)	150 mg dt (15 mg/ mL)	30-40 mg/kg	5 mL (0.5 dt)	1	2	3	5	-	-					-
	400 mg tab (40 mg/mL)		2.5 mL[b]	5 mL (0.5 tab)[b]	7.5 mL (0.75 tab)[b]	1	2	2.5	3	4			5	
	500 mg tab (50 mg/mL)		2 mL[b]	5 mL (5 mL)[b]		1	1.5	2	2.5	3			4	
Imipenem-cilastatin (Ipm/Cln)	500 mg + 500 mg powder for injection, vial (10 mL)		Not used in patients aged <15 years (use meropenem)						2 vials (1 g + 1 g) bd					Only to be used with clavulanic acid.
Meropenem (Mpm)	1 g powder for injection, vial (20 mL)	20-40 mg/kg in every 8 hours	1 mL tid	2 mL tid	4 mL tid	6 mL tid	9 mL tid	11 mL tid	1 vial tid or 2 vials bd					Only to be used with clavulanic acid.
Amikacin (Am)	500 mg/2 mL solution for injection, ampoule		- i								3-4 mL	4 mL	4 mL	Recommended only in adults aged >18 years.
Streptomycin (Sm)	1 g powder for injection, vial		- i								Calculate according to the dilution used			Recommended only in adults aged >18 years.
Ethionamide or Prothion-amide (Eto/ Pto)	125 mg dt (Eto) (12.5 mg/mL)	15-20 mg/kg	3 mL[b]	7 mL[b]	1	2	3	4	4		-			Although once daily dose advised, two divided doses can be also given to improve tolerance.
	250 mg tab (25 mg/mL)		-	3 mL[b]	5 mL (0.5 tab)[b]	1	2		2		3		4	
P-aminosal-icylic acid (PAS)	PAS sodium salt (equivalent to 4 g PAS acid) sachet	200-300mg/kg in 2 divided doses	0.3 g bd	0.75 g bd	1 g bd	2 g bd	3 g bd	3.5 g bd	4 g bd				4-6 g bd	Usually given in divided doses.

Medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	Weight-based daily dose	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
OTHER MEDICINES														
Isoniazid [j] (INH or H) (high dose)	50 mg/5 mL soln	15-20 mg/kg (high dose)	5 mL	9 mL	15 mL	20 mL	-	-	-					Pyridoxine is always given with high-dose isoniazid in children (1-2 mg/kg) and in people at risk of side- effects (e.g., those with HIV or malnutrition). In infants, pyridoxine may be given as part of a multi-vitamin syrup.
	100 mg dt or tab (10 mg/mL)		5 mL (0.5 dt)	1	1.5	2	3	4	4	4.5	-			
	300 mg tab		-				1	1.5	1.5		2			
Clavulanic acid [j] (as amoxicillin/ clavulanate) (Amx/clav)	62.5 mg clavulanic acid as amoxicillin/ clavulanate (250/62.5 mg), powder for oral solution, 5 mL		1.5 mL tid	2 mL tid	3 mL tid	5 mL tid	8 mL tid	10 mL tid	10 mL bd or tid		-			Only available in combination with amoxicillin. To be given with each dose of imipenem/cilastatin (bd) or meropenem (tid).
	125 mg clavulanic acid as amoxicillin/ clavulanate (500/125 mg) tab		-					1 tid	1 bd or tid					
Pretomanid (Pa)	200 mg tab		-						1					Currently only used as part of the BPaLM/ BPaL regimens.

bd: two times a day; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; cap: capsule; DR-TB: drug-resistant TB; dt: dispersible tablet; g: gram; GDG: Guideline Development Group; HIV: human immunodeficiency virus; kg: kilogram; MDR/RR-TB: multidrug-resistant TB; MDR/RR-TB: multidrug or rifampicin-resistant TB; mg: milligram; mL: millilitre; M/F: Monday and Friday; M/W/F: Monday, Wednesday and Friday; od: once daily; soln: solution; susp: suspension; tab: tablet, TB: tuberculosis; tid: three times a day; WHO: World Health Organization.

[a] Dosing guidance is based 2022 WHO operational handbook on tuberculosis.

[b] Dissolving of crushed adult tablets or capsule content in 10 mL of water is required for administering this dose. The number of mL in the table reflects the dose to provide. This avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (use of dispersible tablets is preferred).

[c] The higher dose may be used except when there is risk of toxicity; levels are expected to be lowered because of pharmacokinetic interactions, malabsorption or other reasons; or the strain has low-level drug resistance

[d] Bedaquiline adult tablets (100 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole. Vigorous stirring/shaking is needed prior to administering the 100 mg tablet crushed and suspended in water.

[e] When using the 600 mg tab and the 150 mg dt to dose children weighing 16 to <24 kg, the dose in mg/kg will exceed 10-12 mg/kg and clinicians may opt to administer 1.5 dt or 4 mL of the 600 mg tab dispersed in 10 mL water.

[f] Clofazimine tablets are technically not dispersible, but they do slowly (this takes approximately 5 minutes) dissolve in water (5 mL and 10 mL for the 50 mg and 100 mg tablets, respectively). The suspension should be stirred prior to administration. The 100 mg soft gel capsule is difficult to swallow for young children and therefore countries are strongly encouraged to make the 50 mg tablet formulation available.

[g] In children weighing 3 to <7 kg doses are lower than previously recommended. This is because of relatively high exposures associated with risk of neuropsychiatric adverse events, which is especially concerning when co-administering cycloserine with delamanid.

[h] Delamanid adult tablets (50 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole.

[i] Amikacin and streptomycin may be used in adults aged 18 years or more, in situations where an effective regimen cannot otherwise be designed using oral agents, when susceptibility is demonstrated and when adequate measures are in place to monitor for adverse events. Given the profound impact that hearing loss can have on the acquisition of language and the ability to learn at school, the use of injectable agents in children should be exceptional and limited to salvage therapy, and the treatment needs to be provided under strict monitoring to ensure early detection of ototoxicity. If used, the weight-based daily dose for amikacin is 15-20 mg/kg and for streptomycin it is 20-40 mg/kg for children aged 2 years and older. To determine the dosing for infants and children aged below 2 years, a paediatric DR-TB expert should be consulted and a lower mg/kg dose used to compensate for immature clearance. Co-administration with lidocaine is advised to reduce pain at the injection site (156).

[j] These medicines are only recommended as a companion agent (amoxicillin/clavulanic acid) or are not included in Groups A, B and C, because of a lack of data from the latest analysis on longer MDR/RR-TB regimens in adults (isoniazid).

Specific comments on dosing children with medicines used in second line MDR/RR-TB regimens:

- For dosing of premature and low birth weight infants weighing <3 kg, advice should be sought from a pediatric DR-TB expert.
- For dosing of infants weighing 3 to <5 kg, a pediatric DR-TB expert should be consulted whenever possible.
- The use of child-friendly, dispersible tablets in infants and young children is preferred over manipulating adult tablets or administering or manipulating capsules. Where applicable, the dosing provided is based on dissolving the dispersible formulation in 10 mL of water and administering the number of mL (aliquots). The number of mL in the table reflects the dose to provide. The dissolved solution should be used immediately and the remainder of the 10 mL should be discarded.
- For some weight bands, dosing is indicated with both child-friendly, dispersible formulations and adult formulations. If adult formulations are used, the table provides the dose using aliquots in mL and tablet fractions where applicable (if the fraction is 0.5 or more). Aliquots refer to the volume to administer after crushing and dissolving the tablet in 10 mL of water.

Contraindications and Drug-Drug Interactions

Contraindications

In line with WHO guidelines in longer regimen regrouping of medicine, Bdq and Lzd will be part of standard MDR/RR-TB regimen. Therefore, it is important to thoroughly learn about these medicines and their use. In the best judgement of treating physician and specialist advise, these medicines can be used with precautions. It may be needed that patients should be given a card mentioning the name of drugs that should not be prescribed by any doctor while patient is on ambulatory care in community. Therefore, treating physicians should review all the medicines, patients are taking while enrolling on MDR/RR-TB Treatment.

TABLE 4.10: Contraindications and Precautions with Bdq, Dlm and Lzd

Drug name	Relative contraindication	Precautions
Bdq, Dlm	History of syncopal episodes, ventricular arrhythmias, or severe coronary artery disease Baseline ECG with QTcF > 500 ms (repeated)	Use with caution if QTcF > 450/470 ms in male/female patients. Weekly ECG monitoring and serum electrolyte screening should be performed if Bdq or Dlm is being used despite a cardiac contraindication. Dlm is less cardiotoxic than Bdq (data has shown that QTC-F prolongation with combined use of Bdq and Dlm is clinically modest and safe)
Bdq, Lzd, Dlm	Severe renal Failure	Usually, no dose adjustment is required in mild to moderate renal failure With precaution in severe renal failure/impairment
Bdq	Severe hepatic failure	Try not to use if patient has severe liver function impairment ART should be adjusted if used in HIV patients particularly efavirenz containing regimen should be avoided
Lzd	Pre-existing mild to moderate peripheral neuropathy (based on Basic Peripheral Neuropathy Screening (BPNS), subjective sensory neuropathy scoring) Severe Myelosuppression and Anemia, moderate neutropenia	Special precautions when used in combination with Cs, high dose INH and diabetics. In mild to moderate Myelosuppression and Anemia Lzd can be used with lower doses, 300 mg daily or 600 mg alternative days with close monitoring

Drug-Drug Interactions and Overlapping Toxicities with Bdq, Dlm and Lzd

- It is essential to consider the drug-drug interactions with Bdq, Dlm and Lzd as using in concomitant use of many routinely prescribed drugs may have various level impact having either decreased or increased absorption, toxicity, and adverse events.

Drug-Drug Interactions with Delamanid

- Many drugs have overlapping toxicity when used with Bdq and Dlm, such as:
  - Antipsychotic drugs (Haloperidol, Risperidone) Many anti-nausea drugs (Ondansetron, Granisetron, Domperidone, Chlorpromazine), Methadone, Cardiac drugs that may affect the heart rhythm (Amiodarone, Beta-blockers, Digoxin, Quinidine)
  - Linezolid and concomitant medicines that Increase Serotonin Levels: Serotonin re-uptake inhibitors (SSRIs): fluoxetine, paroxetine Tricyclic antidepressants: amitriptyline, nortriptyline
  - Serotonin 5-HT1 receptor agonists MAO inhibitors: phenelzine, isocarboxazid Other serotonergic agents: meperidine, bupropion, or buspirone, quetiapine

More information on drug safety and QT interval prolongation can be obtained at https://crediblemeds.org/

TABLE 4.11: List of the drugs that can be used safely or are to be avoided along with Bdq

Group	Safe to use	Drugs to be avoided
Antiemetics	Metoclopramide	Domperidone, Ondansetron
Analgesics	NSAIDs, Paracetamol	Tramadol
Antacids	Ranitidine, Milk of Magnesia	Pantoprazole, Omeprazole
Anti-histaminics	Pheniramine, Fexofenadine, Cetirizine	Diphenhydramine, Loratadine
Anti-malarials	Artesunate	Chloroquine
Antibiotics	Penicillin, Cephalosporin, Tinidazole	Ciprofloxacin, Norfloxacin, Cotrimoxazole, Metronidazole
Anti-fungals	Terbinafine	
Anti-epileptics	Sodium Valproate	Phenytoin, Carbamazepine, Phenobarbital
Anti-diabetics	Mostly safe	
Anti-hypertensives	Mostly safe(diuretics)	
Lipid lowering agents		Statins Best to avoid
Anti-arrhythmics	Diltiazem, Lignocaine	Amiodarone, Procainamide, Digoxin
Other cardiac drugs	Nitroglycerine, Sorbitrate	Sotalol
Anti-retrovirals	Tenofovir, Zidovudine, Nevirapine, Dolutegravir	Efavirenz, Lopinavir, Ritonavir

Anxiolytics	**Benzodiazepines (Alprazolam)**	**Avoid other sedatives**
Anti-psychotics	**Risperidone, Lurasidone,**	**Haloperidol Clozapine, Quetiapine, Olanzapine**
Anti-depressants	**Best to be avoided, give only if essential with ECG monitoring**	**Citalopram, Fluoxetine, Sertraline**

Source: Guidelines for PMDT, India

4.3 TREATMENT OF ISONIAZID RESISTANT TB (Hr-TB)

Among most potent and effective treatment of TB drugs, Isoniazid (H) plays vital role and because of its strong bactericidal activity, it is one of the most important first-line medicines for the treatment of active tuberculosis (TB) and TB infection (TBI).TB control programs generally focus on MDR/RR-TB because these highly resistant strains are difficult to treat and cause much morbidity and mortality. However, at the same time, the significant number of Hr-TB who remain undiagnosed and inappropriately treated cannot be ignored.

4.3.1. Isoniazid Resistant TB (Hr-TB) Regimen

- The basic regimen for Isoniazid Resistant TB (Hr-TB) is treatment with Rifampicin, Ethambutol, Pyrazinamide, and levofloxacin for a duration of 6 months.
- All medicines in this regimen are to be used daily and continuously for 6 months.
- When fixed-dose combination (FDC) formulations with 4 drugs are used, isoniazid is included only for ease of losgitics but it is not obligatory for the regimen.
- If levofloxacin cannot be used because there is fluoroquinolone resistance or intolerance or other contraindications to the use of fluoroquinolone, then 6(H)RZE may be prescribed daily for 6 months.
- The Hr-TB regimen is recommended once isoniazid resistance has been confirmed and rifampicin resistance is excluded.
- Rifampicin resistance needs to be excluded using rapid molecular tests (e.g., Xpert MTB/ RIF/Ultra) before levofloxacin is used, to avoid the inadvertent treatment of MDR/RR-TB with an inadequate regimen
- The recommendations apply to both adults and children, including PLHIV. Thus, HIV testing and treatment of PLHIV with ART is important, and the aim is to start ART within 8 weeks of TB treatment initiation (regardless of CD4 count), or within the first 2 weeks in patients with profound immunosuppression (e.g., CD4 counts <50 cells/mm3).
- The regimen is also likely to be effective in patients with extrapulmonary Hr-TB; however, consultation with appropriate specialists is advised.
- Total duration of Hr-TB regimen is 6 months, but it can be extended directly to 9 months in certain conditions. In patients with cavitary disease; extensive disease; uncontrolled comorbidity; extra- pulmonary TB; if smear at the end of month 4 is found positive and when regimen is modified, the treatment may be directly extended to 9 months.

- In patients who remain sputum smear positive at the end of month 5 or later, the treatment outcome will be declared as 'treatment failed' and the patient will be re-evaluated as per the diagnostic algorithm as a non-responder
- Failure of first-line anti TB treatment with H resistance will need additional second-line agents (apart from Lfx) such as Lzd, Cs and Eto to avoid adding a single drug "Lfx" to a failed regimen.These patients should be referred to specialists for individualized regimen.
- It is not advisable to give a regimen for Hr-TB unless isoniazid resistance is confirmed or highly suspected (e.g., confirmed TB patient who is the close contact of a documented Hr-TB patient). This will avert the unnecessary use of levofloxacin and prolonged pyrazinamide exposure in TB patients who may be cured with 2HRZE/4HR
- In patients with cavitary disease and with persistent positivity on sputum smear and culture, prolongation of (H)RZE-Lfx beyond 6 months could be considered on a patient-by-patient basis.

The basic regimen can be summarized as: Hr-TB regimen: 6(H)RZE-Lfx

TABLE 4.12: Dosages for drugs used in Hr-TB regimen by weight bands for adults and children

S.N.	Drugs	Weight Categories			
Adults		30-39kg	40-54kg	55-70kg	>70kg
1	Rifampicin (R-150 mg)	2 tabs	3 tabs	4 tabs	5 tabs
2	Ethambutol (E-275 mg)	2 tabs	3 tabs	4 tabs	5 tabs
3	Pyrazinamide (Z-400 mg)	2 tabs	3 tabs	4 tabs	5 tabs
4	Levofloxacin (Lfx-250 mg)	2 tabs	3 tabs	4 tabs	5 tabs
Children		4-7.9 kg	8-11.9 kg	12-15.9kg	16-24.9kg
1	Rifampicin (R-75 mg)	1 tab	2 tabs	3 tabs	4 tabs
2	Ethambutol (E-100 mg)	1 tab	2 tabs	3 tabs	4 tabs
3	Pyrazinamide (Z-150 mg)	1 tab	2 tabs	3 tabs	4 tabs
4	Levofloxacin (Lfx-100 mg)	1 tab	2 tabs	3 tabs	4 tabs

Children weighing more than 25 kg - Use adult dosages and preparations (up to 1.5g/day)

If levofloxacin 100mg dispersible tablet is not available, the 250mg tablet can be used with 6(H) REZ in children aged 0-14 years, based on a slightly different weight band from the above:

TABLE 4.13: Dosages for Levofloxacin 250 mg used in Hr-TB regimen (for children)

Weight	Levofloxacin 250mg
5 - 6 kg	½ tablet / day
7 - 9 kg	¾ tablet / day
10 - 15 kg	1-1.5 tablet / day
16 - 23 kg	1.5.2 tablets / day
24 - 30 kg	2-2.5 tablets / day
31 kg +	Follow adult schedule (up to 1.5g / day)

4.4 TREATMENT OF MDR/RR-TB IN SPECIAL SITUATIONS

4.4.1 TB in Special Situations

Patients who are diagnosed with MDR/RR-TB and other comorbidities or conditions such as pregnancy, HIV coinfection, Diabetes mellitus, breastfeeding, hepatotoxicity, renal insufficiency, psychotic disorder etc. make the treatment of MDR/RR-TB more difficult. These special situations need attention for the proper management of DR-TB treatment along with associated conditions. MDR/RR-TB expects more resources in terms of cost of treatment, duration of treatment, treatment adherence and higher adverse reactions and complications secondary to the coexisting conditions

4.4.1.1 MDR/RR-TB in women of childbearing age

Pregnancy testing and contraception

- Before starting any second-line treatment, all women of childbearing age should have a pregnancy test as most second-line drugs are toxic for the fetus. If the test is negative, contraception must be recommended
- It is prudent to solicit the opinion of an experienced gynecologist/obstetrician while treating such patients. All women of childbearing age who are receiving MDR/RR-TB therapy should be advised to use birth control measures because of the potential risk to both mother and fetus.
- It should be remembered that oral contraceptives might have decreased efficacy due to vomiting and drug interactions with MDR/RR-TB drugs. To avoid this, the contraceptive should be taken at a different time.
- For prevention of pregnancy the use of barrier methods (Condoms/diaphragms), IUDs (CuT) or depot-medroxyprogesterone (Depo-provera) are recommended based on individual preference and eligibility.

Pregnancy and MDR/RR-TB treatment

- The risks and benefits of treatment should be carefully considered, with the primary goal to protect the health of the mother and child, both before and after birth.
- Most pregnant patients should be started on treatment as soon as the diagnosis is made.
- Pregnancy is not a contraindication for the treatment of DR-TB but it poses great risk to both mother and foetus. Due to the limited evidence on the safety of pretomanid, BPaLM/BPaL regimen is not applied for pregnant and breastfeeding women.
- For pregnant and lactating women, it is recommended to use OSSTR (Linezolid variation instead of ethionamide).
- Bedaquiline containing longer regimen can be introduced to pregnant and breastfeeding women with linezolid if Nine month all oral shorter regimen/OSSTR is not applicable for some reasons (Dose of linezolid to be tapered to half after 6-8 months based on bacteriological response). Modify regimen if one or more drugs cannot be used due to the reasons of resistance, tolerability, contraindications, availability etc.
- If patients on BPaLM/BPaL regimen become pregnant during treatment, it is necessary to discontinue the regimen and switch to OSSTR or longer regimen.

- Family members, especially the husband/partner or a guardian may need to be consulted depending on the relevant family, religious, cultural, and social dynamics.
- The termination of pregnancy may be considered if would carry a significant risk to mother's life.

TABLE 4.14: Treatment regimen for MDR/RR-TB in pregnancy

RR/MDR/RR-TB treatment in Pregnancy	**OSSTR** **4-6 Bdq(6 m)-Lzd(2 m)-Lfx/Mfx-Cfz-Z-E-Hh / 5 Lfx/Mfx- Cfz-Z-E**	**1. May be considered eligible for the linezolid containing 9-month regimen but should not receive the 9-month regimen containing ethionamide** **2. After delivery switch the back to the original applicable regimen**
	LR1 **Bdq (6), 18Lfx, Lzd, Cfz**	**1. In of toxicity or need to decrease or substitute Lzd with Cs, Refer to aDSM relevant section** **2. If Lzd is well tolerated, should be continued throughout the treatment duration** **3. If Lzd is not tolerated for the whole treatment duration and if CS cannot be used, consider another drug from Group C in the place of Lzd**

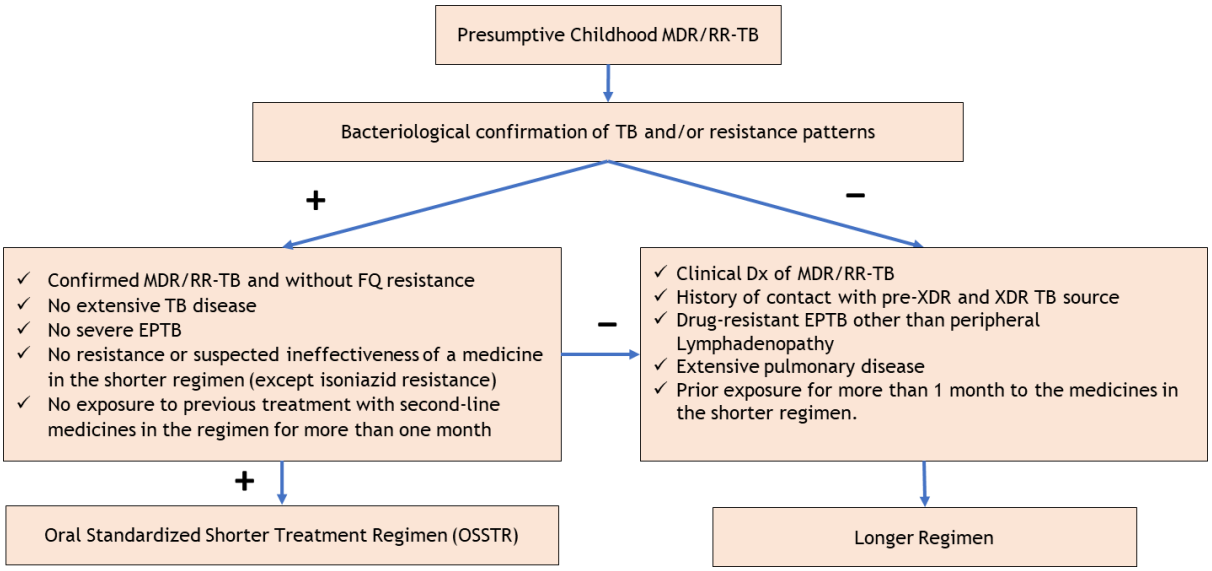
Breastfeeding

- Breastfeeding is no contra-indication for MDR/RR-TB treatment as anti TB drugs excretion through breast milk is in very low concentration that is not harmful for neonate, but the benefit of breastfeeding must be weighed against the risk of exposure to MDR/RR-TB infection of the infant, as well as against the possible risks for the baby associated with the ingestion of second-line drugs with the mother milk.
- Infant formula can only be considered a valid alternative to breastfeeding if all required resources are available and appropriate training has been provided.
- If the infection prevention can be maintained through personal protection like mask to the mother and good environmental control can be achieved, then breast feeding is preferred. If not, option is to keep the baby away from the mother if she is contagious, and to collect the mother's milk using a breast pump and bottle-feed the baby until it is safe to reunite mother and child.

4.4.1.2 MDR/RR-TB in children

Treating MDR/RR-TB in children has been a major challenge because of age-restrictions, and associated drug toxicity. However, most of the drugs used in current DR-TB regimens (except Pretomanid and aminoglycosides) are recommended for all age-groups and are easy to administer because of the availability of child-friendly drug formulations. The principles for treatment of MDR/RR-TB in children is similar to adults and uses the same second-line drugs.

FIGURE 4.1 Flowchart for management of MDR/RR-TB in children



Principles for management of MDR/RR-TB in children

- Always treat in consultation with an expert, preferably pediatrician available/linked to DR-TB Center.
- BPaLM/BPaL should not be used in children below 14 years of age.
- OSSTR may be used in selected children with non-severe PTB and EPTB
- For longer regimen, include at least 4-5 effective medicines from group A and B to which the Mycobacterium tuberculosis strain is known or likely to be susceptible.
- Do not add a single drug to a failing regimen to avoid amplification of resistance.
- Strict monitoring of treatment by clinical examination, radiology, and culture response to be undertaken by pediatrician/ expert available/ linked to DR-TB Center.
- Child-friendly (i.e., dispersible, and palatable) formulations of the medications should be used whenever available. Bdq tablets suspended in water have been shown to have the same bioavailability as tablets swallowed whole and can therefore be used to treat drug-resistant TB in children until a child-friendly formulation becomes available. Child-friendly formulations of most of the component drugs of longer DR-TB regimen are available.

TABLE 4.15: Possible individualized multidrug-resistant and rifampicin-resistant TB treatment regimens for children of all ages and adolescents, by fluoroquinolone resistance and disease severity

Fluoroquinolone susceptibility	Regimen[a]	Additional medicines
Fluoroquinolone-susceptible	Bdq-Lfx-Lzd-Cfz-(Cs)	Cs, Dlm, PAS, Eto[b,c] (E, Z)[d]
Fluoroquinolone-resistant	Bdq-Lzd-Cfz-Cs-(Dlm)[e]	Dlm[e], PAS, Eto[b,c] (E, Z)[d]
Fluoroquinolone-resistant and bedaquiline (±clofazimine)-resistant	Lzd-Cs-Dlm[e]-E-Z[d]	Mpm/Clav, Eto[b,c], PAS[c]

Bdq: bedaquiline; Cfz: clofazimine; Cs: cycloserine; Dlm: delamanid; E: ethambutol; Eto: ethionamide; FQ: fluoroquinolone; Lfx: levofloxacin; Lzd: linezolid; Mpm/Clav: meropenem-clavulanate; PAS: P-aminosalicylic acid; Z: pyrazinamide.

[a] Medicines in parentheses in this column are suggestions for a fifth medicine when there is severe disease.

[b] Use ethionamide only if the child or source does not have a known or suspected inhA mutation.

[c] P-aminosalicylic acid and ethionamide showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and are proposed only when other options to compose a regimen are not possible.

[d] Ethambutol and pyrazinamide should be considered if there is evidence of susceptibility and a regimen with sufficient medicines cannot be composed.

[e] When administering delamanid and cycloserine concurrently, monitoring for neuropsychiatric side-effects is important.

4.4.1.3 DR-TB and Diabetes

Persons with latent TB infection and diabetes have an increased risk of progression to active TB. Also, outcomes for patients who have both TB and diabetes are poorer than for TB patients without diabetes Recent meta-analysis showed a significant association between MDR/RR-TB and DM[1]. New evidence is accumulating that diabetes does increase the risk of drug-resistant TB. One possible mechanism for poorer outcomes and acquired drug resistance could be that blood levels of anti-TB medications may be lower and sub-therapeutic in patients with diabetes. On the other hand, all patients diagnosed with DR TB should be screened for diabetes.

- Patients with newly diagnosed or uncontrolled diabetes mellitus should be evaluated by physician regarding initiation of anti-diabetic medication and its complications.
- Diabetes must be managed closely throughout the treatment of drug-resistant TB. If the patient is on oral hypoglycaemic agents, it is recommended to switch to insulin for the duration of the MDR/RR-TB treatment.
- None of the anti-TB drugs are contraindicated. However, patients with diabetes and MDR/RR-TB may be at increased risk of adverse events since many of the anti-TB drugs have side effects that place diabetic patients at special risk.
- Patients with longstanding diabetes may have underlying renal impairment that can be worsened by the second-line injectable drugs.
- Neuropathy is a common complication of diabetes and can be worsened by several drugs used to treat MDR/RR-TB such as linezolid, fluoroquinolones, and cycloserine.
- Patients with diabetes may have decreased gastric motility (gastroparesis) and may be at increased risk of nausea and vomiting with medications like ethionamide or other MDR/RR-TB drugs.
- The concomitant use of metformin at high doses and linezolid may increase the risk of lactic acidosis.
- Baseline optic nerve or retinopathy or maculopathy may worsen after linezolid use; hence, eye evaluation is recommended before and during treatment.
- Regarding potential baseline renal damage, amikacin and streptomycin should be used with caution.

Below are the recommendations when treating patients who have MDR/RR-TB and diabetes (from DR-TB: A survival guide for clinicians, Curry, 2022 updates).

- Treat and monitor diabetes to achieve optimal glucose control.
- Follow renal function carefully and avoid injectables or use intermittent dosing if there is pre-existing or newly developing renal impairment.
- Treat symptoms of gastroparesis aggressively with gastric motility agents such as metoclopramide.

[1] Tegegne, B. S., Mengesha, M. M., Teferra, A. A., Awoke, M. A., & Habtewold, T. D. (2018). Association between diabetes mellitus and multi-drug-resistant tuberculosis: evidence from a systematic review and meta-analysis. Systematic reviews, 7, 1-13.

- If painful neuropathy develops, change the offending drug, if possible. If that cannot be done safely, consider use of agents such as tricyclic anti-depressants, gabapentin, and/or adding or increasing the dosage of Vitamin B-6.
- Consider therapeutic drug monitoring (particularly if extensive disease, uncontrolled diabetes, gastroparesis, or renal dysfunction) to be sure that adequate blood levels are being obtained, and adjust doses if levels are low. This also applies to RIF and/or other drugs used for INH mono-resistance.

TABLE 4.16: Common glucose-lowering drugs used for managing DM in TB patients

Characteristic	Metformin	Insulin	Sulphonylurea derivates
Drug of choice	First choice	Use if targets for HbA1c or FBG cannot be reached or if there is symptomatic hyperglycemia Preferred if HBA1C > 10%	Add-on Used in case there is a contraindication or intolerance to metformin Use sulphonyl urea only if insulin not available
Risk of hypoglycemia	No	Yes	Yes
Starting dose (od = once a day. bid = twice a day)	500 mg od or bid, titrated to a maximum dose of 2000 mg daily If low body weight (<18.5 kg/m2), poor appetite, GI intolerance: keep the dose below 1gm per day	Blood sugar >300 Give (human insulin 30/70) 12units pre-lunch and 6 units pre- dinner Increase AM dose if PP >200 Increase PM dose if FBS >120 If insulin glargine available and if sugar higher than 180 and below 250 can add 10 units basal insulin per day as the starting point, and adjust according to fasting and PP.	Gliclazide 40-80 mg OD Glibenclamide 2.5-5 mg OD Glimepiride 1-2 mg OD Glipizide 5 mg OD
Interaction with rifampicin	Not clinically relevant	None	Yes, 30-80% lower efficacy with rifampicin
Main side effects	Gastrointestinal Lactic acidosis	Hypoglycemia	Hypoglycemia
Use in reduced kidney function (GFR = glomerular filtration rate)	Dose adjustment if eGFR <45 ml/min Contraindication if eGFR <30 ml/min*	Can be safely used	Increased risk of hypoglycemia Preference gliclazide
Cardiovascular events	Recognized benefit	Neutral	Neutral

*eGFR = estimated glomerular filtration rate.
if measurement of eGFR cannot be done, metformin should not be given to patients with known chronic kidney disease without approval from their treating physician.

4.4.1.4 DR-TB and HIV Co-infection

The treatment of DR-TB in PLHIV is not different from the treatment in HIV-negative people. They can receive BPaLM/BPaL, OSSTR or a longer regimen, based on eligibility criteria.

- If the TB/HIV patient is already on ART, it is to be continued.
- If not yet on ART, it must be prescribed according to the recommendations of the National Center for AIDS and Sexually transmitted disease Control (NCASC) and started rapidly regardless of CD4 count, as soon as the patient is seen to tolerate the MDR/RR-TB treatment, possibly within 8 weeks.
- All TB/HIV patients must receive cotrimoxazole preventive therapy (CPT). All patients co-infected with HIV and MDR/RR-TB must be managed at the DR-TB Center.

The DR-TB treatment in PLHIV is complicated by:

- Cumulated drug toxicities
- Drug-drug interaction
- Other co-infections exacerbating drug toxicity
- Malabsorption of drugs leading to treatment failure
- Paradoxical worsening of TB symptoms when ART is started (Immune Reconstitution Inflammatory Syndrome or IRIS: see national HIV and AIDS Guidelines).

The risk of adverse drug reactions in PLHIV treated with second-line TB drugs increases with the degree of immunosuppression. ART and anti-TB drugs have potential overlapping or additive toxicities and the identification of the source of adverse effects is difficult. It is often impossible to link side effects to a single drug. Using agents with shared adverse effect profiles is not the preferred option but often, the benefit of the drugs outweighs the risk. Increased monitoring of adverse effects is recommended rather than disallowing a certain combination.

The main overlapping toxicities between the second-line drugs and the anti-retroviral drugs commonly used when treating TB/HIV co-infected patients (TDF, 3TC and EFV) are shown in Table 4.17.

TABLE 4.17: Potentially overlapping adverse effects between ART drugs and second-line drugs used to treat PLHIV with MDR/RR-TB

ART drug	Second-line drug	Adverse effect
EFV	Cs (Eto, FQ, H)	CNS toxicity Depression
EFV, AZT	Cs, Bdq	Headache
Many ART drugs	Z, H, Bdq (Eto, PAS, FQ)	Hepatotoxicity
AZT	Lzd (H)	Bone marrow suppression
AZT, 3TC	Ldz	Lactic acidosis
All ART drugs	Eto, PAS	Abdominal pain
Most ART drugs	Eto, PAS, Bdq, Dlm, H, E, Z	Nausea, vomiting
Most ART drugs	Most Second-line drugs	Skin rash
Most ART drugs	Bdq, Dlm, Mfx, Cfz	Prolongation of Q-T interval

Concomitant use of bedaquiline with efavirenz (EFV) is not recommended due to possible decrease of Bdq concentration. EFV should be replaced by Dorutegravir. Protease Inhibitors can be used with bedaquiline but should be administered with extreme caution and close clinical monitoring. Please see more information in below table.

TABLE 4.18: Possible drug-drug interactions between antiretrovirals and the new TB drugs

	Drugs	Instructions
ARVs to avoid with Bdq	Efavirenz (EFV) (Using EFV with Bdq) will result in low levels of Bdq	Substitute nevirapine (NVP) or integrase inhibitor instead of EFV. Allow a 5-day washout of EFV if possible (substitute NVP on day 1 and then start MDR/RR-TB regimen days later). If patient is critically ill with MDR/RR-TB, no washout period is necessary. ▪ When switching back to EFV after ending treatment with Bdq, this can be done immediately after Bdq is stopped
	Ritonavir containing protease inhibitors (PIs) (Using ritonavir with Bdq will result in high levels of Bdq)	If possible, use an ARV regimen with no PI. One possible solution is to substitute the PI with an integrase inhibitor (INSTIs), e.g., dolutegravir (DTG) or raltegravir (RAL). ▪ If a ritonavir-containing PI must be used, check ECG every two weeks.
ARVs to avoid with Dlm	None	Dlm has very little drug-drug interactions with ARVs, and no extra drug monitoring or regimen adjustment is needed.

Patients receiving ART and MDR/RR-TB treatment must be closely monitored. Daily DOT (Family/community DOT) is obligatory, because the large pill burden and the many side effects may compromise treatment adherence. Whenever adverse effects occur, they must be treated without delay. At the same time, it is important to be alert for signs and symptoms of mal absorption: diarrhoea, abnormal stools, poor nutritional status, evidence of vitamin deficiencies, weight loss, etc. Diarrhoea should be treated aggressively as it may lead to decreased drug absorption and impair correct treatment.

4.4.1.5 Patients with Extra pulmonary DR-TB

Patient with DR-TB with EP TB can be initiated in BPaLM /BPaL or OSSTR except those with severe form of EP TB (TB meningitis, Bone TB, Miliary TB, Disseminated TB, TB pericarditis).

4.4.1.5a DR-TB meningitis with brain tuberculomas

Patient with DR-TB meningitis should not be treated with the shorter regimen or with the standard MDR long-course regimen because several of the drugs in those regimens penetrate poorly into CSF and bone and soft tissues. Therefore, it is imperative to design appropriate regimen having sufficient drugs on board with appropriate penetration into soft tissues and bones and that cross the blood brain barrier.

Patients with TB in the CNS may present with reduced consciousness and may require hospitalization, nutritional support (e.g., nasogastric tube and use of dispersible or IV

medication) and, in advanced disease, intensive care. In all TB meningitis patients, the use of corticosteroids should be considered, to prevent disability and improve survival. Usually, when there is TB in the CNS, this is by hematogenous dissemination; therefore, it is important to search for the presence of TB in other organs such as lungs (e.g., bronchogenic or miliary TB), liver, spleen, and bone marrow. The following table should be followed while designing an effective regimen to treat DR-TB meningitis.

TABLE 4.19: Penetration of anti-TB drugs into the central nervous system (CNS)

Medication	CNS Penetration
Levofloxacin, moxifloxacin, linezolid, cycloserine, ethionamide, meropenem, pyrazinamide	Good penetration
Isoniazid in presence of isoniazid resistance, P-aminosalicylic acid, amikacin	Poor penetration, except in presence of meningeal inflammation
Ethambutol	Poor penetration
Bedaquiline, delamanid, clofazimine, Pretomanid	Limited data available

Source: WHO Operational Handbook on Tuberculosis, Module 5: Management of tuberculosis in children and adolescents

4.4.1.5 b Osteomyelitis and soft tissues EP MDR/RR-TB

- Bedaquiline and Delamanid: are with limited experience about penetration in soft tissues and bones
- Linezolid: Excellent bone and soft-tissue penetration; commonly used for osteomyelitis due to gram positive bacteria.
- Clofazimine: Cfz has been used extensively to treat leprosy lesions in soft tissue, though it is unclear if this means that bone and soft tissue penetration is adequate
- Imipenem/Meropenem: Both drugs have been used to treat osteomyelitis caused by other bacteria

Some forms of EP, when treated, may show a paradoxical worsening. This is quite common in patients co-infected with TB and HIV (Immune Reconstitution Inflammatory Syndrome or IRIS: see national HIV AND AIDS Guidelines). In certain types of EP, and if IRIS occurs, adjuvant steroid therapy may be helpful.

4.4.1.6 Patients with hepatitis

Many anti-TB medications have the potential to cause hepatotoxicity, and their use must be carefully contemplated in the setting of severe liver dysfunction. Possible anti-TB drug that causes hepatotoxicity; Z, H, Cfz, PAS, Eto/Pto, Bdq, FQ, Amx/Clv. Fortunately, the most important second-line anti-tuberculosis drugs used for treatment of drug-resistant disease do not affect the liver. Among the first-line drugs, Z is the most hepatotoxic, followed by H. Among the second- line drugs, Eto and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with fluoroquinolones. Lfx is less hepatotoxic than Mfx.

Hepatitis itself is not contraindication to start DR-TB treatment unless liver enzymes are raised to unacceptable level i.e., 5-fold increase in liver enzyme or active jaundice. Patients with history of liver disease can receive the usual anti-TB drug regimens provided there is no clinical evidence of severe chronic liver disease, hepatitis virus carriage, recent history

of acute hepatitis or excessive alcohol consumption. 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.All drugs to be discontinued temporarily if liver enzymes are >5 time of the upper limit.

Treatment of drug-resistant TB in the setting of liver failure is complicated and depends on the degree of liver damage. A long-course regimen with at least 4 non-hepatotoxic drugs is required. However, as per newly WHO recommended regimen, the drugs from group A and B are safer to use and only in severe hepatic and renal failure Bdq and Lzd may be avoided. If a patient with acute hepatitis requires MDR/RR-TB treatment, it may not be possible to defer the treatment until the acute episode has resolved. A similar treatment to the one outlined above may have to be given. Viral hepatitis should be treated if medically indicated and treatment can occur during drug-resistant TB treatment.

4.4.1.7 DR Patients with renal failure

In DR-TB patients with renal insufficiency, the dosing of the second-line drugs that are cleared by the kidneys will have to be adjusted if the creatinine clearance is <30ml/minute. To calculate the creatinine clearance, see Annex 4. The general strategy is to increase the interval between dosing rather than to decrease. Standard doses are given unless there is intolerance. There should be careful monitoring for evidence of nephrotoxicity.

TABLE 4.20: Dose Adjustment in Renal Impairment

Drug	Recommended dose and frequency for patients with creatinine clearance <30 ml/min or for patients receiving haemodialysis (unless otherwise indicated dose after dialysis)
Amikacin	12-15 mg/kg per dose two or three times per week (not daily)
Levofloxacin	750-1000 mg per dose three times per week (not daily)
Moxifloxacin	No adjustment necessary
Cycloserine	250 mg once daily, or 500 mg/dose three times per week
Terizidone	Recommendations not available
Prothionamide	No adjustment necessary
Ethionamide	No adjustment necessary
Para-aminosalicylic acid	4 g/dose, twice daily maximum dose
Bedaquiline	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution).
Linezolid	No adjustment necessary
Clofazimine	No adjustment necessary
Imipenem/cilastin	For creatinine clearance 20-40 ml/min dose 500 mg every 8 hours; for creatinine clearance <20 ml/min dose 500 mg every 12 hours
Meropenem	For creatinine clearance 20-40 ml/min dose 750 mg every 12 hours; for creatinine clearance <20 ml/min dose 500 mg every 12 hours
High dose isoniazid	Recommendations not available
Pyrazinamide	25 mg/kg/dose, thrice weekly
Ethambutol	15-25 mg/kg/dose, thrice weekly

4.5 ADJUVANT THERAPIES AND INTERVENTIONS

4.5.1 Pyridoxine

Several side effects related to the nervous system can be prevented by the daily administration of pyridoxine. Pyridoxine (vitamin B6) should be given to all TB patients who receivehigh dose of INH and cycloserine . The usual dosage is 50mg per day in children and 100mg per day in adults. If Cycloserine is part of the treatment regimen, the recommended dose is 50 mg for every 250 mg of Cs prescribed: see **Table 4.21**.

TABLE 4.21: Daily dosing of pyridoxine according to daily administration of cycloserine

Daily dose of cycloserine	Daily dose of pyridoxine
250mg	50mg
500mg	100mg
750mg	150mg
1000mg	200mg

4.5.2 Steroids

Steroids are useful in patients with TB meningitis and TB pericarditis, and for children with miliary TB or obstruction of the bronchi because of mediastinal TB adenitis. Their use may also be considered in patients with severe respiratory insufficiency. The usual dosage is prednisone 1mg/ kg/day, to be tapered off gradually to arrive at a maintenance dose of 5mg/day. Steroids will also be given if a severe paradoxical reaction (IRIS) occurs, especially in patients with TB/HIV co- infection.

Corticosteroids are immunosuppressive and therefore can weaken the body's response to fight TB; hence, they 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 patient's deterioration. Oral treatment can be given, but when a more immediate response is needed, injectable corticosteroids are often used initially.

4.6 SURGERY

Surgery is an adjunct to chemotherapy. If the lung lesions are not extensive, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR/RR-TB regimen. The role of pulmonary surgery is beneficial to reduce the amount of lung tissue with intractable pathology and to reduce bacterial load and thus improve prognosis.

- The surgery should be performed under infection control measures
- The benefit of the surgery is when patients have no other associated factors for poor prognosis
- It is considered an adjunct to chemotherapy and appears to be beneficial for improved outcome.
- It is not indicated in patients with extensive bilateral disease.

- Minimum two months of therapy should be given prior to resection surgery to decrease the bacterial infection in the surrounding lung tissue.
- Surgery should be performed by a trained thoracic surgeon in patients with localized disease and result may reduce morbidity and mortality. Prognosis could be better when partial lung resection is performed after culture conversion and full course of treatment is given with effective regimen.

CHAPTER 5

MANAGEMENT AND MONITORING ASPECTS OF DR

5.1 PREPARATION PRIOR TO STARTING SECOND-LINE TREATMENT

Before second-line treatment can be prescribed, the patient must be thoroughly evaluated clinically, radiologically, and biomedically, according to the list in TABLE 5.1. These examinations are performed at the DR-TB Center. The initial evaluation serves to establish a baseline (for comparison when investigations are done during treatment) and may identify patients who are at risk for adverse side effects or poor outcomes. Prior to initiating treatment, all patients must receive albendazole.

TABLE 5.1: Baseline clinical, instrumental and laboratory examination*

Medical history including mental illness, drug or alcohol dependence, seizures		
Clinical examination including body weight and height, blood pressure, temperature		
Chest X-ray		
ECG		Calculate the Q-T interval with Fridericia's correction (QTcF): see Annex 3
Sputum smear examination		needed as baseline for follow-up examinations during treatment
Laboratory examinations	Complete Blood Count	RBC count, haemoglobin, hematocrit, WBC count, WBC differential count, platelet count
	Liver function tests (LFT)	bilirubin, AST, ALT, albumin
	Thyroid function tests (TFT)**	TSH, T3, T4
	Hepatitis B and C	Determine viral load if positive for hepatitis B or C
	Uric acid	
	Renal function tests (RFT)	serum creatinine (calculate the estimated creatinine clearance based on the Cockcroft-Gault equation: see Annex 4), serum potassium (also magnesium and calcium if potassium is low) and sodium
	Serum glucose	If hyperglycemia: refer to table (TB-DM)
	HIV test	
Pregnancy test (for women of childbearing age)		
Visual acuity		
Peripheral neuropathy assessment		

*Diagnostic tests (Xpert MTB/RIF, culture and DST, LPA) are not included here.
** Usually not required except pt who will be on Eto (OSSTR) and Eto in LTR and any one with BL prolonged QTcF.

5.2 TREATMENT ADMINISTRATION

5.2.1 The need for strict adherence to treatment

Full adherence to DR-TB treatment is essential to prevent the amplification of resistance and increase the chances of cure. Adherence to DR-TB therapy is particularly difficult because of the lengthy treatment regimens, the high daily pill burden, the frequent and serious drug adverse reactions, and the indirect social and economic costs to patients associated with access to care. Inadequate second- line therapy would also have serious public health consequences. Therefore, all patients receiving DR-TB therapy should be on 100% DOT (Community, family, etc.), preferably during the whole course of treatment. Patient centric care including community DOTS where feasible will be prioritized, and service will be decentralized as program expands.

DOT, early and effective management of adverse effects of drugs and monitoring and follow-up of the non-adherent patients are very important to ensure maximum adherence to treatment. In addition, patient-centered care will further increase the chances of successful treatment outcome by providing:

- Counselling: health education and counselling must be provided to all patients and their family members at all levels of the health care system, from the peripheral health center to the district hospital to the DR-TB Center. It is started at the initial point of contact and must be continued at every visit by the patient to a health facility.
  The patients should receive counselling on
  - DR-TB, the duration of treatment
  - the organization of the treatment (hospital/ambulatory)
  - requirements for regular monitoring
  - infection control
  - the need for regular treatment (DOT) and
  - the consequences of irregular treatment or pre-mature cessation of treatment.

  It is advisable to involve close family members during the counselling since family support is an essential component in the management. Patients should be informed regarding the possible side effects of the drugs and advised to report if they experience any unusual problem. Female patients of childbearing age should receive special counselling on family planning because pregnancy should be avoided during second- line treatment.
- Psychosocial and emotional support to strengthen self-esteem through empathy, trust, encouragement, and care. Having DR-TB can result in severe emotional stress for patients and their families. The long duration of DR-TB therapy combined with the side-effects of the drugs may contribute to depression, anxiety and further difficulty with treatment adherence. A multidisciplinary approach by a support team (doctor, social worker, nurse and treatment supporter) is recommended.
- Socioeconomic and nutrition support can enable patients and their families to adhere to DR-TB treatment and reduce the impact that the disease and treatment have on their quality of life. Patients must have access to any socioeconomic services such as nutritional and transportation support and health insurance they may qualify for. Maximal support should be given to patients with the highest needs.

5.3 ORGANIZATION OF THE TREATMENT

5.3.1 Hospitalization

- Admission for treatment is not mandatory but it may be required based on the disease severity and assessment by treating physician.
- Admission of DR-TB patients requires appropriate structures where proper infection control measures can be observed to prevent transmission to staff and other patients **(see Chapter 7)**.
- Patients who are not seriously ill can be accommodated in hostel-like structures where they can get proper care and monitoring until they are ready for ambulatory care. Severely ill patients need to be hospitalized in a specialized DR-TB ward.
- The following group of patients may be considered for hospitalization
  - Respiratory insufficiency
  - Hemoglobin <8.0g/dl
  - Body Mass Index (BMI) <18kg/m^2
  - Central nervous system(CNS) MDR/RR-TB
  - Clinically unstable
  - Unstable social situations that require intensive multi-disciplinary management
  - Administration of intervenous therapy
  - Infection control challenges in the patients home environment
  - Recurrent treatment interruption where previous outpatient treatment has been unsuccessful
  - Patient preference for inpatient care.

5.3.2 Ambulatory treatment under strict DOT/ treatment support

Ambulatory care must be practice under strict DOT/treatment support. During the initial stage of treatment, while awaiting the results of the mWRDs, the patients must remain close to the DR-TB Center where they will have to present themselves every day to receive their drugs. Once the results have been received and the treatment regimen is finalized, treatment may be continued at the DR-TB Treatment Center or in a DR-TB Treatment Sub-Center. All structures providing treatment to DR-TB patients should observe proper infection control measures.

- If it is not possible for the patient to visit the treatment Center/sub-Center on a regular daily basis, community-based DOT (CBD)/Family based DOT may be an alternative option. Community based DOT/Family based DOT requires very close daily monitoring. The patient's family must be well informed and motivated to collaborate, a reliable DOT provider(Community volunteer or any one family member) must be appointed, and regular supervision by the TB focal person is essential. If the patient needs to receive injections, this must be arranged either at a nearby health facility.
- The DOT provider should be a person whom the patient is comfortable with. This may be a health worker /family members trained to deliver second-line anti-TB medicines. The DOT provider should have the appropriate training, skills require to provide proper DOT and support.

- Every month, patients treated in an ambulatory setting must go to the nearest DR-TB Center or Sub-Center where the monthly follow-up investigations can be performed. The DOT provider and the treatment supporter must make sure that the patient does not miss the monthly appointments.
- A DR-TB patient on ambulatory treatment may be contagious, particularly during the early weeks or months of treatment. It is therefore extremely important that proper infection control measures are observed, not only in the treatment Centers/sub-Centers but also at the patient's home and by the patients themselves. This will require a lot of discipline by the patients, but they need to understand their responsibility and social duty to protect the community from exposure to drug resistant germs.

5.4 DRUG ADMINISTRATION

Many of the second-line drugs cause gastro-intestinal upset, which is an important cause of non-adherence to treatment, many patients refuse to take certain medications or even the full treatment.

- To improve adherence, not all drugs have to be taken together, some may be administered in split doses, and some may be given together with food. The only drugs that should never be given with food are H and Cs, while other drugs (Cfz, Bdq and Dlm) must be taken with food to improve absorption.
- The other drugs can be taken with or without food, but some (Eto, PAS) are better given with food to reduce gastro-intestinal upset. TABLE 5.2 shows a summary of how the second-line drugs are preferentially ingested.
- If split doses are given, DOT is required for every intake.
  - The daily dose of Eto can be built up gradually: 250mg once daily on days 2 to 4; 2 x 250mg/day on days 5 to 7; 250mg in the morning, 500mg in the evening from day 8 onwards if patient >50kg.
- Amikacin is given by deep intramuscular injection. The injection site must be changed every day to avoid painful reactions in the injected area.
  - For every injection, a sterile syringe, a sterile needle for preparing and pulling up the solution and another sterile needle for the injection must be used. These can only be used once and must be disposed of in a safe way (contaminated waste).
- Imipenem and cilastatin injection comes as powder to be mixed with liquid to be injected intravenously. When it is injected intravenously, it is usually infused over a period of 20 minutes or 1hour every 6 or 8 hours. Imipenem may cause side effects some of which can be serious (severe diarrhoea, anaphylaxis, Steven Johnson's syndrome edifficulty breathing or swallowing, seizures).

TABLE 5.2: Mode of administration of the second-line drugs

With or without food	Drug	Number of daily doses
Never with food	H	1
	Cs	2 or 3
Can be with or without food	E	1
	Z	1
	Lzd	1
Possible with food but avoid drug intake within at least 2 hours of coffee, antacids (especially aluminum-containing), vitamin supplements or mineral supplements (such as iron, magnesium, calcium, or zinc) or medication containing divalent cations (such as didanosine or sucralfate)	Lfx	1 (children <5 years: 2/ day)
	Mfx	1
Best taken with food to reduce G.I. upset	Pa	1
	Eto	2 (highest dose in the evening: e.g., 250mg in the morning, 500mg in the evening)
	PAS	2-3 (children: 2-4)
To be taken with food to improve absorption	Cfz	1
	Bdq	1
	Dlm	2
	Amx-clv	2

5.5 FOLLOW-UP MONITORING INVESTIGATIONS DURING AND AFTER COMPLETION OF TREATMENT

5.5.1 Monitoring of DR-TB

Follow-up monitoring examinations are essential to monitor the response of the patient to the treatment and to detect side effects of the drugs early. The frequency of the examinations depends on the treatment regimen (BPaLM/BPaL, OSSTR or LR), the drugs that are administered and the treatment duration.

For patients treated in an ambulatory setting, the follow-up examinations can take place at the nearest DR-TB Center with the required laboratory facilities. If a specialized test (e.g., TFT) cannot be performed, a sample may be sent to the nearest laboratory that can do the test. When sending a sputum specimen to theTB Reference Lab for culture, the timing (within 72 hours) and the cold chain must be maintained.

5.5.2 Baseline and follow up monitoring of patients taking BPaLM/BPaL regimen for DR-TB

Response to treatment should be monitored based on Monthly sputum smear microscopy and culture (ideally at the same frequency). It is also important to follow up patients after the completion of treatment to ensure that there is no treatment relapse or unexpected adverse events.

Patients on BPaLM/BPaL regimen should be monitored for the following adverse events: hepatotoxicity, nephrotoxicity, cardiac toxicity, myelosuppression, neuropathy, optic neuritis, lactic acidosis, and acute pancreatitis.

The monitoring schedule should consider the following:

- laboratory and ECG monitoring should be continued at monthly intervals for the duration of treatment (i.e., 9 months in case of treatment prolongation);
- in the case of electrolyte disturbances, haematologic or ECG abnormalities, more frequent monitoring may be performed; and
- more frequent monitoring may be advisable in specific situations; for example, in older people, PLHIV, those affected by hepatitis (caused by hepatitis B virus [HBV] or hepatitis C virus [HCV]), those with diabetes mellitus, those with moderate to severe hepatic or renal impairment, or those with baseline anemia or visual disturbances (e.g., glaucoma, cataract or colour blindness).

Patient is considered failure and treatment regimen must be terminated or permanently changed to new treatment regimen due to any following:

- Adverse drug reactions
- Persistent positive sputum culture (no conversion or reversion) from months 4 to the end of the treatment.
- Acquired drug resistance to drugs in the regimen during the treatment (i-e baseline is susceptible and monitoring culture demonstrates resistance)

TABLE 5.3: Baseline, routine, and post-treatment monitoring examinations schedule for the BPaLM/BPaL regimen

Examination	Baseline	Two weeks	Monthly	End of treatment	Post treatment (After 6- and 12-months)
Clinical evaluation					
Clinical assessment [a]	✓	✓	✓	✓	✓
Psychosocial assessment [b]	✓	✓	✓	✓	✓
Weight/BMI	✓	✓	✓	✓	✓
Performance status	✓				
Peripheral neuropathy screening	✓	✓	✓	✓	
Visual acuity and colour discrimination screening	✓	✓	✓	✓	
Assessment and follow-up of adverse events	✓	✓	✓	✓	✓
Outcome consultation				✓	✓
Bacteriological evaluations					
Sputum smear	✓		✓	✓	✓
Sputum culture	✓		✓	✓	✓
Sputum DST [c]	✓		✓ If smear or culture positive		
Other samples (smear/ culture/DST)	✓		✓ If no documented response to treatment		
Radiology, ECG, and laboratory evaluations					
Chest X-ray	✓			✓	✓
ECG	✓	✓	✓	✓	
Full blood count	✓	✓	✓	✓	
Liver function tests (AST, ALT and bilirubin)	✓	✓	✓	✓	
Serum electrolytes	✓				
Urea, creatinine	✓				
Pregnancy test	✓				
HIV/HBV/HCV tests	✓				
RBS/HbA1c	✓				

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; RBS: Random blood sugar level; DST: drug susceptibility testing; ECG: electrocardiography; HbA1c: glycosylated haemoglobin; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; TB: tuberculosis; WHO: World Health Organization.

[a] Vital sign, TB symptom screen, pain, nausea, appetite and nutrition, diarrhoea and candidiasis. Clinical assessment should focus on monitoring the response to treatment and addressing common symptoms associated with TB treatment and long-term antibiotic use, with the goal of supporting adherence.

[b] Food security, housing, mental state and substance use. Psychosocial assessment should offer an opportunity to assess supportive factors for treatment adherence and should be directly linked to relevant interventions wherever possible, as per country-specific questionnaires.

[c] Ideally, the patient should at baseline have a WHO-recommended rapid molecular test (for rifampicin and fluoroquinolone resistance). Other investigations, if available, include culture-based second-line DST, next-generation sequencing, and DST for the BPaLM component drugs.

5.5.3 Follow up monitoring of patients taking nine month all oral shorter regimen (OSSTR)

Response to treatment is monitored by monthly sputum smear microscopy and culture. Older children who had microbiological confirmation of TB disease should also be encouraged to produce respiratory samples for monitoring whenever possible. Treatment response can also be monitored through regular clinical assessment of signs and symptoms of TB disease, and children should be monitored for changes in weight, height and BMI using age-appropriate growth charts. Repeat radiological assessment during treatment is not always necessary because some radiological abnormalities may persist throughout and beyond treatment completion but do not necessarily indicate poor response or failure of treatment.

TABLE 5.4: Example of a monitoring schedule for patients receiving OSSTR

Time on treatment	Baseline	Months 0-2	Month 3–6	Months 7–9 (or11)
Clinical history and examination [a]	✓	✓ (monthly)	✓ (monthly)	✓ (monthly)
Treatment literacy and adherence counselling	✓	✓ (At every HCW interaction)	As required throughout treatment	
Substance use and mental health screen (with appropriate intervention and support	✓	✓ (monthly)	✓ (monthly)	✓ (monthly)
Weight / height / BMI (and nutritional support)	✓	✓ (monthly)	✓ (monthly)	✓ (monthly)
Family planning, and pregnancy testing	✓	✓ (monthly)	✓ (monthly)	✓ (monthly)
Respiratory sample for smear microscopy and TB culture (DST if indicated)	✓	✓ (monthly)	✓ (monthly)	✓ (monthly)
Chest X-ray (or other radiological assessment)	✓		✓	
HIV testing	✓		✓ (if previously negative, repeat every 3 months in high prevalence settings, or indicated)	✓ (if previously negative, repeat every 3 months in high prevalence settings, or indicated)
Finger-prick blood glucose	✓	Check regularly if clinically indicated		
Full blood count and differential (if receiving Lzd)		✓ (at weeks 2, 4 and 8 if receiving Lzd)	Repeat if clinically indicated	

Time on treatment	Baseline	Months 0-2	Month 3–6	Months 7–9 (or11)
Liver function tests (at least ALT, AST and bilirubin)	✓	Repeat regularly if clinically indicated: vomiting, right upper quadrant pain, jaundice or if person is unwell or has any evidence of liver injury		
Creatinine	✓	Repeat regularly if clinically indicated (i.e., if person becomes unwell, or if baseline creatinine was abnormal or renal drug dosing required)		
Serum electrolytes	✓	Repeat regularly if clinically indicated (i.e., if person becomes unwell, is vomiting, has diarrhoea or has QTcF prolongation)		
TSH (if receiving Eto)	✓	Repeat at 3 months if on Eto, or when QTcF is prolonged		
ECG (calculate QTcF)	✓	✓ (monthly)	✓ (monthly)	✓ (monthly)
Peripheral neuropathy and visual acuity screen (if receiving Lzd)[b]	✓	✓ (monthly)	Repeat regularly if clinically indicated	

ALT: alanine transaminase; AST: aspartate aminotransferase; BMI: body mass index; DST: drug susceptibility testing; ECG: electrocardiography; Eto: ethionamide; HCW: health care worker; HIV: human immunodeficiency virus; Lzd: linezolid; MDR/RR-TB: multidrug- or rifampicin- resistant TB; QTcF: corrected QT interval by Fridericia; TB: tuberculosis; TSH: thyroid stimulating hormone.

[a] Clinical assessment of TB signs or symptoms and adverse events.

[b] It may be difficult to perform detailed assessments for peripheral neuropathy or visual acuity in young children, but the risk of these events appears to be lower in this group; therefore, this should not be a reason to withhold linezolid from young children who would otherwise benefit from this drug.

Source: *WHO Operational Handbook on Tuberculosis; Module 4: Treatment (Drug-resistant tuberculosis treatment), 2022 update*

5.5.3 Follow-up examination during the longer treatment regimens

Any patient eligible for a longer regimen should undergo a pretreatment assessment to optimize the drug selection, reduce the chances of adverse events and thus increase the probability of the favorable treatment outcomes. The pretreatment assessment includes:

1. A detailed clinical history (including all comorbidities, medications and known intolerances), a physical examination, a blood test, chest X-ray or other imaging and bacteriological tests and
2. A list of current effective TB medicines available based on a clinical history of drugs taken before this treatment episode and guided by the DST results or sequencing of the most recent sample from the patient (or the index patient).
3. In addition to the eligibility criteria and preclinical assessment, a clinician should also consider:
   - Development of a personalized treatment approach (patient-centered approach) and close follow-up, including food support if needed, to increase bioavailability of drugs, improve the nutritional status and facilitate adherence.
   - Provision of advice on contraception for women of childbearing age.
   - Availability of ancillary medications (e.g., corticosteroids in the case of disseminated TB or TB meningitis or pericarditis, pretreatment blood transfusion in the case of severe anemia and nutritional support) and other interventions (e.g., intravenous [IV] medication in the case of severe malnutrition and malabsorption, insertion of

peripherally inserted central catheter, or surgery in the case of restricted options and meeting criteria for intervention); and

- Provision of counselling, depending on the patients' comorbidities (e.g., HIV or diabetes) or pre-existing conditions needing to be treated to optimize TB treatment outcomes.

The performance of sputum culture in addition to sputum smear microscopy is recommended to monitor the treatment response. Concomitant use of sputum smear microscopy and culture test results helps to identify patients whose bacteriology remains positive or reverts to positive following the initial conversion to negative. This combined testing will help clinicians to identify the patients whose treatment is likely to fail and thus to plan for alternative options and institute infection control measures in a timely manner.

In children, smear and culture monitoring of the treatment response may be challenging, in such patients, resolution of clinical symptoms and weight gain can be used as indicators of improvement. Tests should be performed more frequently if clinically warranted.

TABLE 5.5: Frequency of follow-up examinations during longer regimen

Examinations	Baseline	Treatment duration/ Month													Remarks
		1	2	3	4	5	6	7	8	10	12	14	16	18	
Clinical history and examination	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Treatment literacy and adherence counselling	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Substance use and mental health screen	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Weight/BMI nutritional support	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Family planning and pregnancy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Respiratory sample for Sputum smear)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Sputum culture (DST if indicated	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Chest X-ray or other radiological assessment	✓						✓				✓			✓	
ECG (Calculate QTcF)[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Monthly or as required
Complete Blood Count[2]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	2 weeks initially, then monthly if Lzd. If no Lzd: as required
HIV testing	✓	if previously negative, repeat every 3 months in high HIV prevalence settings, or if indicated													

Examinations	Baseline	Treatment duration/ Month													Remarks
		1	2	3	4	5	6	7	8	10	12	14	16	18	
Liver function tests (LFT)[3]	✓	Repeat regularly if clinically indicated: vomiting, right upper quadrant pain, jaundice or if person is unwell or has any evidence of liver injury													
Thyroid function tests (TFT)	✓			✓			✓				✓			✓	TSH, T3, T4 Only if Eto, Pto, or PAS is used
Uric acid	✓		✓		✓		✓		✓						Only if Z is used
Renal function tests (RFT)[4]		✓	✓	✓	✓	✓	✓								Only if Am is used
Serum glucose	✓	Repeat regularly if clinically indicated													
Peripheral Neuropathy Assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	See Annex 5
Audiometry only if Am is used	✓	✓	✓	✓	✓	✓	✓								
Visual acuity (for optic neuritis); Monthly if LZD used or as required	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Xpert MTB/XDR/LPA and DST	✓	On any cultures that are positive four months or beyond after treatment initiation													

1Calculate the Q-T interval with Fridericia's correction (QTcF): see Annex 3
2 RBC count, haemoglobin, haematocrit, WBC count, WBC differential count, platelet count
3 Bilirubin, AST, ALT, albumin
4 Serum creatinine (calculate the estimated creatinine clearance based on the Cockcroft-Gault equation: see Annex 4), serum potassium (also magnesium and calcium if potassium is low)

Frequency of examinations may be increased as needed according to the clinical evolution of the patient and the decision of the clinicians.

5.5.4 Follow up after completion of the DR TB treatment

After completion of the DR TB treatment, it is required to follow up patients for next two years. Follow up examination should be done every 6 months which includes:

- A clinical assessment
- Sputum smear examination
- Any additional lab or instrumental analysis as requested by the clinicians

5.5.5 Follow up evaluation schedule of Hr-TB patients

TABLE 5.6: Follow up evaluation schedule of INH-Resistant -TB patients

Regimen class		Hr-TB regimen
Duration		6 or 9 months (no separate IP/CP)
Clinical + Wt.		Monthly till the end of treatment
Bacteriological monitoring (same schedule) as DS TB by	Smear microscopy	At the end of the months 2,5 and 6
	Culture	At the end of the months 2,5 and end of treatment (month 6 and/or 9 if applicable) If the culture results of month 2 is positive, collect one repeat specimen for culture to rapidly ascertain bacteriological conversion/ reversion. If the repeat specimen is culture negative, then ensure specimen collection at the end of treatment
DST		If Smear/culture reversion found

Note: CBC, Liver and kidney function and other blood tests, based on clinical manifestations and other medications in use

5.6 MONITORING OF TREATMENT PROGRESS

The symptoms should improve within the first few months of treatment. If this is not the case, look for other possible causes and be alert for treatment failure. Treatment progress of DR-TB is monitored through sputum smear examinations and culture. However, the clinicians may encounter several challenges during treatment and progress monitoring:

- In children, bacteriological follow-up of the treatment is not possible most of the time. Progress will have to be monitored clinically. The evolution of the weight of the child is of particular importance.
- Bacteriological follow-up of EP DR-TB is difficult. Even if a specimen was obtained for the initial Xpert MTB/XDR or LPA, culture, and DST, obtaining follow-up specimens will usually not be feasible. Progress of EP DR-TB needs to be monitored clinically.
- Laboratory investigations, while useful to monitor side effects, contribute little to monitor response to treatment.
- Chest X-rays are not a sensitive indicator to monitor progress. Often, the radiological image remains unchanged.
- Sputum may become negative well before culture. Negative sputa are a very encouraging sign, but it is the result of the monthly cultures that will decide whether treatment is progressing well.

Sometimes, the sputum examination remains positive while the culture becomes negative. This is caused by the presence of dead bacilli and does not indicate treatment failure. Missing or contaminated results would not be counted. Once patient is converted and if there is one positive culture followed by at least two consecutive negative cultures and patient is clinically doing well, stable and improving, this positive culture may be ignored. If there are two positive cultures after conversion, then it should be followed by at least 4 negative cultures.

5.7 PALLIATIVE CARE

If a patient presents a treatment failure and an alternative treatment regimen is not possible, treatment will have to be suspended. Suspension of therapy should be carefully planned. It 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.

Several 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. Supportive care for MDR/RR-TB treatment failure includes:

- *Pain control and symptom relief:* Codeine with paracetamol gives relief from moderate pain but also helps control cough. Other cough suppressants can be added. If possible, stronger analgesics, including morphine, should be used to keep the patient adequately comfortable.
- *Relief of respiratory insufficiency:* Oxygen can be used to alleviate shortness of breath. Morphine also provides significant relief from respiratory insufficiency and should be offered if available.
- *Nutritional support:* Small and frequent meals are often best for a person at the end of life.
- *Regular medical visits:* When therapy stops, regular visits by the treating physician and support team should not be discontinued.
- *Continuation of ancillary medicines*: All necessary ancillary medications should be continued as needed to treat symptoms such as nausea, vomiting, depression, anxiety.
- *Psychological support* to the patient and family caregivers to assist in the planning of decisions related with the end of life and provide emotional support.
- *Respect for patient's beliefs and values*: The patient and family caregivers may seek and find comfort in spiritual and religious practices. The health-care providers should respect this.
- *Inpatient-care or homecare:* Home-based care should be offered to patients and families who want to keep the patient at home, whenever appropriate infection control practices must be followed. Institutional based end-of-life care should be available to those for whom home care is not feasible or desirable.
- *Preventive measures:* Oral care, prevention of bedsores, bathing and prevention of muscle contractures are indicated in all patients. Regular scheduled movement of the bedridden patient is very important.
- *Infection control measures* should be continued as the patient often remains infectious for long period of time.

5.8 MANAGEMENT OF CONTACTS OF MDR/RR-TB PATIENTS

A close contact of an MDR/RR-TB patient is someone who has been exposed to infection with drug resistant M. tuberculosis by sharing air space with a patient who has confirmed MDR/RR-TB. Close contacts are defined as people living in the same household or spending multiple hours a day together with the patient in the same indoor living space. They can be family members, colleagues, friends, roommates, and neighbours.

All close contacts of MDR/RR-TB patients should be identified through contact tracing and those who are symptomatic Should be evaluated for active TB. Special attention needs to be paid to children. The TB screening will include a complete clinical examination, an Xpert MTB/RIF/Ultra test of a sputum sample or other relevant specimen and a chest X-ray. If the Xpert MTB/RIF/Ultra result is RR, the patient must be sent to the nearest DR TB treatment center for further management.

Screening of contacts of MDR/RR-TB patients should be an ongoing process. Asymptomatic contacts need to be screened at diagnosis, at the end of the intensive phase and at the end of treatment. Contacts should also receive appropriate health information and education regarding TB and MDR/RR-TB.

TB Preventive Therapy for contacts of MDR/RR-TB Patients

Preventing the progression of DR TB infection to TB disease is an important pillar of DR TB elimination strategy. High quality data on the management of TPT in the contacts of DR-TB patients are lacking. There are few ongoing RCTs, the results of which are awaited. WHO guidelines currently recommend consideration of TPT for selected household contact for MDR/RR-TB such as children and PLHIV. The suggested regimen is to use levofloxacin for six months with or without other anti-TB drugs such as ethambutol or ethionamide (if tolerated), confirming the source patient regarding her/his drug resistance pattern (i.e., MDR/RR-TB with confirmed FQ susceptibility). However, there are no approved recommendation for TPT for patients in contact with pre-XDR or XDR patients. For more details, please refer to the National TPT Guidelines.

CHAPTER 6

ACTIVE DRUG SAFETY MONITORING & MANAGEMENT

6.1 DEFINITIONS

Active TB drug-safety monitoring and management (aDSM): active and systematic clinical and laboratory assessment of patients on treatment with new anti-TB drugs, novel MDR/RR-TB regimens, or extensively drug-resistant TB (XDR-TB) regimens to detect, manage and report suspected or confirmed drug toxicities. Although all detected AEs need to be managed, the core package of aDSM requires the reporting of serious AEs (SAEs) only.

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

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

Serious adverse event (SAE): is one that leads to any of the below:

- Death,
- life-threatening experience,
- hospitalization or prolongation of hospitalization,
- persistent or significant disability,
- or a congenital anomaly.

The definition includes SAEs that do not immediately result in one of these outcomes but may require an intervention to prevent it from happening. SAEs may require a drastic intervention, such as termination of the drug suspected of having caused the event.

AE of special interest: AE documented to have occurred during clinical trials and for which the monitoring program is specifically sensitized to report regardless of its seriousness, severity, or causal relationship to the TB treatment

AE of clinical significance: AE that is either a) Serious (SAE), b) Of special interest, c) Leads to a discontinuation or change in the treatment, or d) Is judged as otherwise clinically significant by the clinician.

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

Causal relationship is a relationship between an exposure (A) and an event (B) in which A precedes and causes B. This may refer to the causal association between an exposure to a TB medicine and the occurrence of an adverse reaction.

Causality assessment is the evaluation of the likelihood that a TB medicine was the causative agent of an observed adverse reaction.

Drug-safety profile is a description of the benefits, risks and toxicity of a given TB drug or regimen, specifying any known or likely safety concerns, contraindications, cautions, preventive measures, and other features that the user should be aware of to protect the health of a TB patient.

Signal: Reported information on a possible causal relationship between an adverse event and a TB medicine, the relationship being unknown or incompletely documented previously or representing a new aspect of a known association. Signal detection may not be part of practice in Nepal so far but may be a good future practice.

6.2 ACTIVE TB DRUG-SAFETY MONITORING AND MANAGEMENT (aDSM)

6.2.1 Objectives of aDSM

The overall objectives of aDSM are to reduce risks from drug-related harms in patients on second- line treatment for DR-TB and to generate standardized aDSM data to inform future policy updates on the use of such medicines.
The WHO framework for aDSM needs to be applied to patients on any type of MDR/RR-TB regimen, to ensure appropriate action and an acceptable level of monitoring for adverse events and prompt response to such events – alongside monitoring for treatment outcomes. There are three recommended levels of monitoring in aDSM:

Core package: The overall objectives of aDSM are to reduce risks from drug-related harms in patients on second- line treatment for DR-TB and to generate standardized aDSM data to inform future policy updates on the use of such medicines.

1. Requiring monitoring for and reporting of all SAEs
2. Intermediate package: includes SAEs as well as AEs of special interest
3. Advanced package: includes all AEs of clinical significance

For Nepal, Core Package of aDSM is adopted- which means, only serious AEs/ADRs are reported and all DR-TB patients on treatment are monitored under aDSM mechanism. The mild and moderate AEs should be monitored and managed from the service delivery facilities When AEs and ADRs are identified, they should be graded for seriousness and severity and SAEs reported as per the aDSM reporting pathway (Figure 6.1). Severity is defined by the impact on the patient's ability to function. It is graded on a scale of 1 to 5, as shown below in Table 6.1.

FIGURE 6.1: Pathway for aDSM Reporting in Nepal:

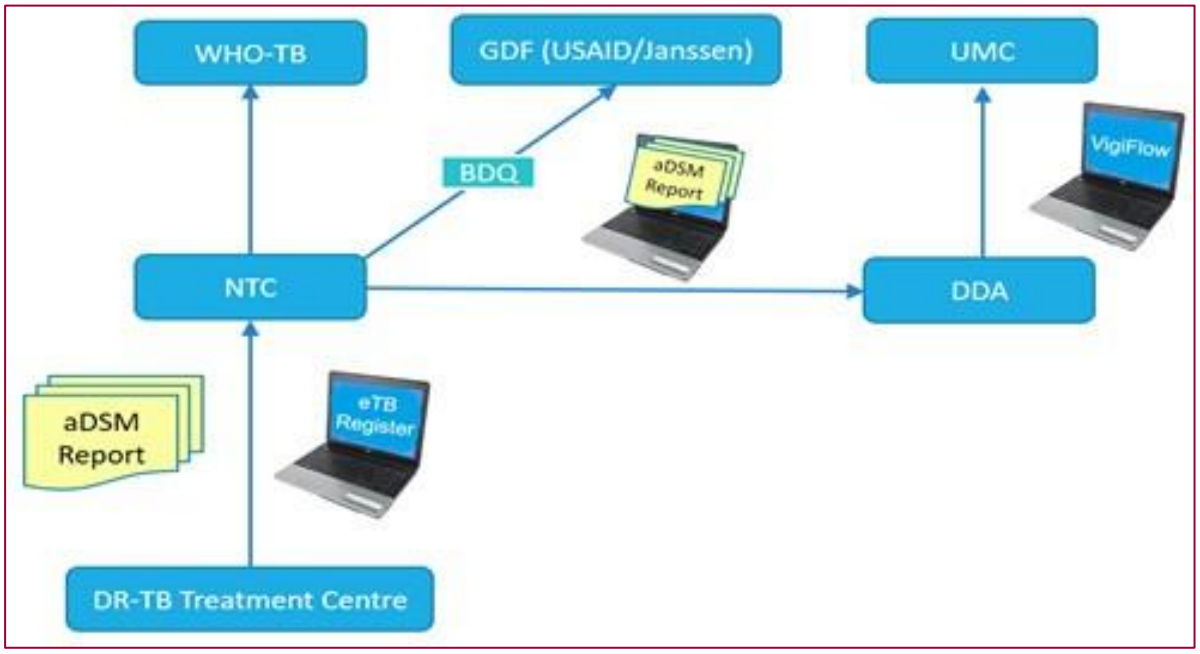


TABLE 6.1.: Grading of adverse events

Grade 1	Mild	Small or transient inconvenience that does not limit normal daily activity. No need for medical intervention or corrective treatment.
Grade 2	Moderate	Partial limitation of normal daily activity. In some, but not all patients, medical intervention or corrective treatment is necessary. No need to discontinue the treatment.
Grade 3	Severe	Limitation of normal daily activity. Medical intervention and corrective treatment, often requiring hospitalization, are necessary. The responsible drug may have to be stopped temporarily, until the symptoms have disappeared.
Grade 4	Life threatening	Very severe limitation of normal daily activity. Medical intervention and corrective treatment, requiring hospitalization, are necessary. The responsible drug may have to be stopped indefinitely.
Grade 5	Death	Death related to adverse event

Source: National DR-TB Guidelines 2019

6.2.2 Important elements of aDSM:

There are three essential activities of aDSM to achieve the objectives, namely:

1. Clinical and laboratory assessment
2. Clinical management, and
3. Recording and reporting

1. Clinical and Laboratory Assessment:

Active and systematic clinical and laboratory assessment should be done during treatment to detect drug toxicity and AEs.

- *Observe and listen to patients*: At every DOT encounter or other follow up visits, ask the patient and family members about clinical symptoms of common AEs, such as: nausea, vomiting, peripheral neuropathy, skin rash, psychiatric disturbance (headache, anxiety, depression, irritability, behavior change), jaundice, and symptoms of electrolyte wasting (muscle cramping, palpitations).
- *Perform routine clinical assessments at every visit*: This should include evaluation for treatment adherence and tolerance, psychosocial support, and if needed, consult with the psychiatrist, ophthalmologist, HIV specialist, etc. Clinical follow-up with the MDR/RR-TB physician for all patients is at a minimum as per set protocols.
- *Schedule regular laboratory screenings even without specific complaints*: Regular laboratory monitoring detects occult adverse effects. These tests should include creatinine (renal function), liver function tests, CBC, peripheral neuropathy assessment (PNA), TFT, ECG etc. Laboratory tests and procedures related to treatment should be available and accessible to patients, free of charge.

2. Management of AEs in a timely manner

Early detection of signs and symptoms is key to proper management of AEs that significantly impacts patient well-being, overall treatment acceptance, and adherence. Management includes measures taken to alleviate the signs and symptoms of adverse reactions with careful individual patient review, such as:

- Reassurance, if AE is minor
- Lowering the dose of the offending drug,
- Stopping the drug,
- Drug replacement.
- Providing ancillary medications and
- Other interventions (surgery, transfusion, psychological support, etc.). Ancillary medicines should be available and accessible to patients, free of charge.

3. Recording and reporting

All AEs must be recorded and reported using HMIS 6.10 form to NTCC either by email or through the online eTB Register (where functional). The reporting must be done in 24 to 48 hours of occurrence of any serious AEs/ADRs. Management of AEs/ ADRs are equally important as monitoring and reporting of the AEs/ADRs

For all SAEs, the first level Causality Assessment can be done at the DR-TB treatments centers by the treating doctor using the below Adverse Event Causality Assessment definitions and Flowchart.

6.3 MANAGEMENT OF AEs OR ADRS

Management of AEs and ADRs are equally crucial as monitoring and reporting. For several drugs, the toxicity is dose dependent. Reducing the dosage may be an effective method of managing these adverse effects. But attention! The reduced dose must still be effective! If the serum level of the drug is too low, it will compromise the treatment regimen. This is particularly the case for Eto and Cs. Lowering the dose by more than one weight class should be avoided. In some instances, very serious adverse events will be unavoidable to save a life.

Particular attention needs to be paid to the side effects of linezolid; a potent but toxic drug used as a part of standard regimen. Monitoring the adverse drug reactions of Lzd requires specific investigations.

TABLE 6.2: Severity grading scales and suggested action for common AEs

Severity grade	Grade 1 Mild	Grad 2 Moderate	Grade 3 Severe	Grade 4 Life- threatening	Grade 5 Death
1. Peripheral neuropathy Possible anti-TB drug: Lzd, Cs, H, S, Pa, H, FQ, Pto/Eto, E. Possible other causes: d4T, ddI					
Paresthesia (Burning, tingling, etc.)	Mild discomfort: No treatment required; and/ or BPNS (Brief Peripheral Neuropathy Screen) subjective sensory neuropathy score 1-3 on any side.	Moderate discomfort: Non-narcotic analgesia required; and/or BPNS subjective sensory neuropathy score 4-6 on any side.	Severe discomfort: Narcotic analgesia required with symptomatic improvement; and/ or BPNS subjective sensory neuropathy score 7-10 on any side.	Incapacitating; or not responsive to narcotic Analgesia	
Action	Stop Cs and Lzd. If symptoms improve, consider restarting these drugs. Consider restarting Lzd at a lower dose (300mg daily or 600 mg thrice weekly). If Cs is not essential to the regimen, consider suspending the drug.	Stop Cs and Lzd. Possible drug holiday for 1-2 wks, if symptoms improve, consider restarting these drugs by reducing the dose of Lzd to 300mg per day. Provide symptomatic relief	In most patients, permanent suspension of Lzd will be needed; in some patients, after 1-2 weeks drug holiday and reversion to Grade 2, consider restarting Lzd in reduced dose	Same as Grade 3.	
2. Myelosuppression (anemia, thrombocytopenia, or neutropenia) Possible anti-TB drug: Lzd,Pa, H. Possible other causes: AZT, cotrimoxazole					
Anemia	10.5 - 9.5 g/dL	9.4 - 8.0 g/dL	7.9 - 6.5 g/dL	< 6.5 g/dL	
Platelets decreased	75,000 - 99,999/mm^3	50,000 - 74,999 /mm^3	20,000 - 49,999/mm^3	< 20,000 /mm^3	
Absolute neutrophil count low	1500 - 1000/mm3	999 - 750/mm3	749 - 500/mm3	<500/mm3	
Action	Monitor carefully and consider reduction of dose of Lzd (300mg daily or 600	Monitor carefully and consider reduction of dose of Lzd (300mg daily	Stop Lzd immediately. In case of Grade 3 anemia, consider EPO. Restart	Stop Lzd immediately. Consider hemotransfusion or EPO. Restart at reduced dose	

Severity grade	Grade 1 Mild	Grad 2 Moderate	Grade 3 Severe	Grade 4 Life- threatening	Grade 5 Death
	mg thrice weekly).	or 600 mg thrice weekly); in case of Grade 2 neutropenia, stop Lzd immediately. In case of Grade 2 anemia, consider erythropoietin (EPO). Restart at reduced dose once toxicity has decreased to Grade 1.	at reduced dose once toxicity has decreased to Grade 1.	once toxicity has decreased to Grade 1.	
3. Prolonged QT interval Possible anti-TB drugs: Cfz, Bdq, Mfx, Dlm, Pa, and Lfx (a mild QT prolonging drug) Possible other causes: Other drugs, e.g., erythromycin, clarithromycin, quinidine, ketoconazole, fluconazole, antipsychotics (all have some risk, including haloperidol, chlorpromazine, and risperidone), many anti-nausea drugs (Ondansetron/Granisetron, Domperidone), methadone, and some anti-retroviral); genetic causes such as long QT syndrome; hypothyroidism					
Prolonged QTcF	QTcF 450 - 480 ms.	QTcF interval 481 - 500 ms.	QTcF>= 501 ms without signs/ symptoms of serious arrhythmia.	QTcF>= 501 or >60 ms change from baseline and one of the following: Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia.	
Action	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade1. Replete electrolytes as necessary.	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade 1. Replete electrolytes as necessary.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.	
4. Optic nerve disorder (optic neuritis) Possible anti-TB drug causes: Lzd, E, Eto/Pto, Cfz, rifabutin, H, S. Possible other causes: ddI					
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye (20/40[6/12] or better)	Limiting vision in the affected eye (worse than 20/40[6/12] but better	Blindness (20/200[6/60] or worse) in the affected eye	

Severity grade	Grade 1 Mild	Grad 2 Moderate	Grade 3 Severe	Grade 4 Life- threatening	Grade 5 Death
			than 20/200[6/60])		
Action	Stop lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	
5. Hepatitis Possible anti-TB drug causes: ZLzd, Cfz, Bdq. Possible other causes: unknown					
ALT (SGPT)	1.1 – 3.0 x upper limit of normal (ULN)	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	
AST (SGOT)	1.1 – 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	
Action	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Stop all drugs, including anti- TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.	Stop all drugs, including anti-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.	
6. Acute kidney injury Possible anti-TB drug causes: Am, Possible ART causes: Tenofovir (TDF)- rare					
Acute kidney Injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5-2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0mg/dL; hospitalization indicated	Life-threatening con-sequences; dialysis indicated	
Action	Consider stopping inject-able until creatinine has returned to baseline. Consider restarting the injectable at lower frequency (e.g., thrice weekly).	Stop injectable until creatinine has returned to baseline. Consider restarting the injectable at lower frequency (e.g., thrice weekly) or substitute with a non-	Stop injectable until creatinine has returned to baseline. Consider restarting the injectable at lower frequency (e.g.,thrice weekly) or substitute with a non-	Stop injectable until creatinine has returned to baseline. Consider restarting the injectable at lower frequency (e.g., thrice weekly) or substitute with a non- nephrotoxic drug.	

Severity grade	Grade 1 Mild	Grad 2 Moderate	Grade 3 Severe	Grade 4 Life- threatening	Grade 5 Death
		nephro-toxic drug.	nephrotoxic drug.		
7. Hypokalemia and hypomagnesemia Possible anti-TB drug causes: Am,S. Possible ART causes: TDF(rare)					
Hypokalemia	3.4 - 3.0 mEq/L	2.9 - 2.5 mEq/L	2.4 - 2.0 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnor- mal potassium with paresis, ileus or life- threatening arrhythmia	
Action	Continue injectable. Start oral potassium replacement therapy. Check serum magnesium and replace if necessary.	Continue injectable. Start aggressive oral potassium replacement therapy. Replace magnesium as necessary.	Continue injectable. Start IV potassium replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary.	Stop injectable temporarily. Start IV potassium replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary.	
Hypomagnesemia	0.60-0.70 mmol/L	0.45-0.59 mmol/L	0.30-0.44 mmol/L	<0.30 mmol/L	
8. Hypothyroidism Possible anti-TB drug causes: Eto/Pto, PAS. Possible ART causes: d4T					
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting iADL (instrumental activities of daily living)*	Severe symptoms: limiting self-care ADL*; hospitalization indicated	Life-threatening consequences: urgent intervention indicated	
Action	Continue anti-TB drugs.	Continue anti-TB drugs. Start thyroxine.	Continue anti-TB drugs. Start thyroxine.	Stop all anti-TB drugs. Start thyroxine.	
* https://www.payingforseniorcare.com/activities-of-daily-living#title2					
9. Hearing loss Possible anti-TB drug causes: S, Am. Possible other causes: none.					
Hearing loss**	Adults Enrolled on a Monitoring Program (ona1,2,4,3,6and8 kHz audiogram): threshold shift	Adult enrolled in monitoring program (ona1,2,3,4,6and8 kHz audiogram): threshold	Adult enrolled in monitoring program (on a 1, 2, 3, 4, 6 and8kHzaudio- gram):	Adults: profound bilateral hearing loss (Threshold> 80 dB HL at 2kHz and above); non-service able hearing Pediatric:	

Severity grade	Grade 1 Mild	Grad 2 Moderate	Grade 3 Severe	Grade 4 Life- threatening	Grade 5 Death
	of 15 - 25 dB aver- aged at 2 contiguous test frequencies in at least one ear or subjective change in the absence of a Grade 1 Threshold shift. Pediatric (on a 1, 2, 4,3, 6 and 8 kHz audiogram): threshold shift >20 dB at 8kHz in at least one ear.	shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear. Adult not enrolled in monitoring program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL. Pediatric (ona1,2,3,4,6and8 kHz audiogram): threshold shift>20 dB at 4 kHz and above in at least one ear.	threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated. Adult Not enrolled in monitoring program: hearing loss with hearing aid or intervention indicated; limiting self-care ADL. Pediatric (on a 1, 2, 3, 4, 6 and 8kHz audiogram): hearing loss sufficient to indicate therapeutic intervention, including hearing aids): Threshold shift >20dB at 3kHz and above in at least one ear; additional speech-language related services indicated.	audiologic indication for cochlear implant and additional speech-language related services indicated.	

TABLE 6.2a: WHO Classification grading scale for hearing loss

40dB Slight/Mild	41-60 dB Moderate	61-80 dB Severe	Over 81 dB Profound

Difficulty hearing and understanding soft speech, speech from a distance, or speech against a background of noise	Difficulty hearing regular speech, even at close distance.	May only hear very loud speech or loud sounds in the environment, such as a fire truck siren or a door slamming. Most conversation speech is not heard.	May perceive loud sounds as vibrations

TABLE 6.3: AEs, suspected agents, suggested management strategies

AE	Suspected agent	Suggested management strategies	Comments
Allergic reaction, anaphylaxis, and rashes	Any drug	1. For severe rashes (i.e., peeling skin, mucous membrane involvement and the patient being systemically unwell) and serious allergic reactions, stop all therapy pending resolution of reaction. Manage anaphylaxis as per standard emergency protocols. 2. Eliminate other potential causes of allergic skin reactions (e.g., scabies and other environmental agents). 3. For non-severe skin reactions, continue TB medications and manage symptoms with relevant ancillary agents: • antihistamines and calamine lotion. • hydrocortisone cream (localized rash). • oral prednisone (low dose, short course). • sunscreen (to prevent phototoxicity). • moisturizing lotion for dry skin (common with clofazimine, and in diabetic patients); and • topical benzoyl peroxide for acneiform rashes. 4. Following resolution of severe adverse cutaneous drug reactions, reintroduce drugs one at a time, with the drug most likely to cause the reaction being given 5. last; consider avoiding or substituting drugs that are highly likely to have caused	1. History of previous drug allergies should be carefully reviewed and noted on the treatment card. 2. A flushing reaction to Z is usually mild and resolves with time; it can be managed with antihistamines. 3. Hot flushes, itching and palpitations can be caused by isoniazid and tyramine-containing foods (e.g., cheese and red wine) - counsel the patient on avoidance of these foods. 4. Although rarely reported, patients (particularly adolescents) receiving MDR/RR-TB treatment regimens containing novel and repurposed agents sometimes experience a non-serious acneiform papular rash. Topical benzoyl peroxide may be helpful, but this rash eventually resolves without intervention. 5. Any drugs can cause urticaria (hives). Reintroduce each drug one at a time to identify the causative agent. Desensitization can be attempted if necessary. 6. Some antihistamines (e.g., diphenhydramine) are associated with QT prolongation; this risk must be

		a severe reaction, and do not reintroduce non-essential TB medications - this may necessitate a change in regimen if a standardized regimen has been used. 6. Permanently withdraw any drug confirmed to be the cause of a serious drug reaction, and counsel the patient on avoidance of the drug in future.	balanced with the benefits for the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility 7. of closer ECG monitoring, if required, in that setting. 8. Do not consider rechallenging any drugs that resulted in anaphylaxis or Stevens-Johnson syndrome.
Alopecia	H, Eto/Pto	1. Reassure the patient that hair loss related to TB medications usually resolves following completion of treatment. 2. It may be helpful to educate the patient on other causes of hair loss because these could also be investigated and addressed.	1. Alopecia occurs more commonly after prolonged exposure (>18 months) to TB medications. 2. Other possible causes of hair loss include childbirth, stressful life events, use of abrasive hair products, polycystic ovary syndrome, psoriasis, thyroid disease, mineral deficiencies, hereditary hair loss and ageing.
Arthritis and arthralgia	Z, Bdq, Lfx Mfx, H	1. Initiate therapy with NSAID (indomethacin or ibuprofen) for symptomatic relief. 2. Rule out other causes of arthralgia (e.g., trauma or injury). 3. If possible, decrease the dose of the suspected agent (probably Z) to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. 4. In severe patients with no improvement of symptoms, withdraw the suspected	1. Symptoms of drug-induced arthralgia often diminish over time, even without intervention. 2. If a joint is acutely swollen, red and warm, consider aspiration for diagnosis of gout, infection, autoimmune diseases and other causes. 3. Uric acid levels may be elevated in patients on Z. There is little evidence to support the addition of allopurinol, although it may be helpful if gout is

		agent or agents, and substitute with another effective drug if required – this may necessitate a change in regimen if a standardized regimen is used.	confirmed.
Candidiasis	Lfx, Mfx Mpm, Imp/cln, Lzd	1. Common types of yeast infection are usually easily treated with topical antifungal agents or a short course of oral systemic medications. 2. Presentation among immunosuppressed individuals can be severe and may require treatment with more potent agents. Patients presenting with severe symptoms should be retested for HIV.	1. The most common types of yeast infection associated with antibacterial treatment include vulvovaginal and penile candidiasis, oral thrush and cutaneous candidiasis. 2. Other common risk factors include pregnancy and uncontrolled diabetes.
CNS toxicity (dizziness, insomnia and headaches)	Lfx, Mfx, Dlm, Am, Trd/Cs, Mpm Bdq, Eto/ Pto, H, Pa	1. Consider other causes of CNS symptoms (e.g. arrhythmias, H-2 receptor antagonists, local anaesthetics, cancer, recreational substance use, stress, hyperventilation) and manage appropriately. 2. Rule out more serious causes of headaches, including raised intracranial pressure, pre-eclampsia, meningitis and other CNS infections – investigate thoroughly in patients coinfected with HIV. 3. Manage drug-related headaches with analgesic agents (ibuprofen, paracetamol) and encourage good hydration. Consider low-dose TCAs for refractory headaches.	1. Symptoms of QT prolongation can include dizziness and syncope; closer ECG monitoring may be indicated. 2. Drug-related headaches and dizziness are often self-limiting and ease over time. 3. Pyridoxine (vitamin B6) can help to prevent neurotoxicity during exposure to Trd/Cs and H. 4. High doses of TCAs are associated with QT prolongation; this risk must be balanced with the benefits for the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required, in that setting.

		4. Administer medications at a different time of day (e.g. before sleeping or early morning) to reduce the impact of specific CNS symptoms on daily activities. 5. For other CNS symptoms, consider decreasing the dose of the suspected agent to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. Also consider starting the drug at a low dose and gradually building up to the full dose over 2 weeks. 6. In severe cases with no improvement of symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required - this may necessitate a change in regimen if a standardized regimen is used.	5. Fullness in the ears and intermittent ringing are early symptoms of vestibular toxicity and symptoms generally do not improve on 6. withholding medications; in such cases, patients must be counselled to report these symptoms early and the injectable agent should be withdrawn. 7. Dlm has been associated with insomnia and sleep disturbance due to nightmares - this may become intolerable and require drug withdrawal, particularly in children.
Depression, suicidal ideation	Trd/Cs, Dlm Lfx, Mfx	1. Acknowledge and assess psychological and socioeconomic circumstances, emotional issues and level of control of other chronic conditions. Refer to available services for counselling and social support. 2. Screen for substance use and other mental illness using validated screening tools and refer to relevant services for intervention and support. 3. In patients where depressive symptoms are impacting adherence to treatment and other activities of daily living,	1. Although depressive symptoms may be expected upon diagnosis of MDR/RR-TB, and some TB medications may be associated with psychiatric AEs, do not underestimate the contribution of underlying psychological, emotional and socioeconomic conditions and chronic illness as contributing factors to 2. depression. Some patients may require medical intervention for depression even beyond completion

		antidepressant therapy may be indicated. SSRIs and TCAs may be considered but drug-drug interactions are common. 4. If possible, decrease the dose of the suspected agent (e.g. Cs) to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. 5. In severe s with no improvement of symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required - this may necessitate a change in regimen if a standardized regimen is used. 6. Always screen for symptoms and signs of suicidal ideation in patients with depressive symptoms - if indicated, withdraw all suspected agents and hospitalize the patient with 24-hour surveillance until stable.	of treatment for MDR/RR-TB 3. and they should be referred or followed up appropriately. 4. History of previous depressive illness is not a contraindication to the use of these agents listed but this might increase the likelihood of depression developing during MDR/RR-TB 5. treatment. If a patient has significant depressive symptoms at the start of treatment, avoid the use of Cs and Dlm, if possible. 6. SSRIs and TCAs are associated with QT prolongation; this risk must be balanced with the benefits for the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required, in that setting.
Diarrhoea and/or flatulence or bloating	PAS Eto/Pto, Mpm, Amx/ Clv, Lzd, Lfx, Mfx, Pa, S	1. Counsel patients that some degree of loose stools and flatulence is inevitable with these medications, but that these symptoms are likely to improve over time without having to withhold medication. 2. Encourage sufficient fluid intake. 3. Administer PAS only once daily if tolerated. 4. Treat persistent uncomplicated diarrhoea (no blood in stool and no fever) with loperamide.	1. Fever and diarrhoea or blood in stools suggest causes other than simple side-effects of TB medications: 2. Pseudomembranous colitis related to broad- spectrum antibiotics (including FQs) is serious and can be life threatening. Warning signs include fever, bloody diarrhoea, intense abdominal pain and increased white blood cells. 3. Parasites and common waterborne

		5. If diarrhoea is severe, check serum electrolytes and dehydration status and manage accordingly. In children with acute diarrhoea, supplement zinc (20 mg per 6. day) for 10-14 days to improve water and electrolyte absorption. 7. In severe cases with no improvement of symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required.	pathogens should be investigated and treated. 4. Consider lactose intolerance. 5. Loperamide must not be used in children aged below 2 years.
Electrolyte disturbances	Am S	1. Consider other causes of electrolyte imbalance (e.g. vomiting, diarrhoea, burns, diabetes and use of insulin, cardiac failure and use of diuretics) and manage accordingly. 2. Assess renal function and check other electrolytes (i.e. potassium, magnesium, calcium and phosphate) if possible. 3. Rehydrate and replace electrolytes as needed - if unable to check magnesium levels, consider magnesium supplementation in cases of refractory hypokalaemia. 4. Amiloride or spironolactone may help to reduce potassium and magnesium wasting. 5. Patients with severe hypokalaemia (<2.5 mmol/L) should be hospitalized for IV electrolyte replacement and cardiac monitoring.	1. Clinical symptoms (e.g. muscle weakness and cramps, dizziness, nausea and impaired concentration) may not be evident until the potassium level is <3 mmol/L. 2. Hypokalaemia, hypomagnesaemia and hypocalcaemia can prolong the QT interval; closer ECG monitoring is warranted until levels are corrected. 3. Oral potassium replacements may cause nausea and vomiting, and oral magnesium may cause diarrhoea.

Gastritis and abdominal pain	Eto/Pto, PAS, Cfz Lfx, Mfx, H, E, Z, Mpm, Dlm, Amx/clv	1. Abdominal pain may be associated with SAEs such as pancreatitis, lactic acidosis and hepatitis (see relevant sections). If these conditions are suspected, the most likely causative agent or agents should be withheld while awaiting further investigations and appropriate management. 2. If symptoms are consistent with gastritis (e.g. epigastric burning or discomfort, sour taste in mouth associated with reflux) initiate medical therapy with the use of H2 blockers (e.g. ranitidine) or proton-pump inhibitors (omeprazole). Avoid the use of antacids if possible because they reduce absorption of FQs, and to a lesser extent H and E. 3. If possible, decrease the dose of the suspected agent to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. 4. In severe cases with no improvement of symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required - this may necessitate a change in regimen if Cfz or an FQ is withdrawn.	5. Consider other causes of gastritis, such as NSAIDs or Helicobacter pylori infection, and manage accordingly. 6. Gastritis must be acknowledged and managed appropriately to provide relief to patients and facilitate adherence to TB treatment. 7. Proton-pump inhibitors can induce hypomagnesaemia and lead to QT prolongation; this risk must be balanced with the benefits for the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required, in that setting. 8. If antacids must be used, time their administration to avoid interference with TB medications (e.g. take antacid 2 hours before or 3 hours after TB medications). 9. Gastritis is common in pregnancy, but pregnant patients with persistent or severe abdominal pain must be investigated for other non-drug-related causes. 10. Severe abdominal distress has been reported with the use of Cfz and the drug should be withdrawn if it is considered to be the most likely cause.

Gynaecomastia	Eto/Pto, H	1. Consider other causes (e.g. obesity, older age, puberty in boys, recreational substances and other drugs) and educate the patient on possible causes. 2. Reassure the patient that changes in breast tissue that are related to TB medications are temporary and that the tissue will return to normal following completion of treatment.	1. Other drugs that can cause gynaecomastia include spironolactone, cimetidine, ketoconazole, risperidone, omeprazole and efavirenz.
Hepatitis	Z, H, Pa, Bdq Eto/Pto, Trd/Cs, PAS	1. Stop all drugs if liver enzymes are >5 times the upper limit of the normal range (regardless of symptoms), or if they are >3 times the upper limit along with symptoms and signs of drug-induced liver injury. Wait for liver enzymes to return to <3 times the upper limit of normal. 2. Investigate and treat other potential causes of hepatitis (e.g. viral hepatitis, alcohol induced hepatitis and other hepatotoxic drugs). 3. Reintroduce three of the least hepatotoxic TB drugs first: for example, Lzd, Dlm and an FQ. All three drugs can be started together to provide a backbone regimen. 4. Then introduce potentially hepatotoxic drugs one by one, every 5-7 days, while monitoring liver enzymes to identify the responsible drug. 5. If the most likely causative agent is not essential in the treatment regimen, do	1. Symptoms and signs of liver injury include nausea, vomiting, fatigue, malaise, pruritus, fever, right upper quadrant pain, tender liver and jaundice. 2. Hepatocellular drug-induced liver injury with jaundice (and raised total bilirubin levels) indicates a serious reaction (Hy's law) and presents a high risk for acute liver failure. 3. Viral serology should be carried out to investigate for hepatitis A, B and C. 4. History of previous drug-related hepatitis may suggest a likely causative agent or agents - counsel the patient and document in their file that these drugs must be avoided in future treatment. 5. Patients with alcohol or substance use problems may benefit from additional psychosocial intervention and adherence support.

		not reintroduce it. 6. Depending on the most likely causative agent, withdrawal of the drug may necessitate a change in treatment regimen.	6. Do not rechallenge with Z following a drug- induced liver injury.
Hypothyroidism	Eto/Pto, PAS	1. Exclude other causes (e.g. lithium, amiodarone, previous radioiodine therapy, pregnancy-associated thyroid dysfunction and Hashimoto's disease). 2. Consider thyroxine supplementation if TSH is raised 3. >5 IU/mL and free T4 is decreased, or the patient has symptoms of clinical hypothyroidism. 4. If TSH is >10 IU/mL, start levothyroxine at 50 mcg daily (start at a lower dose in older patients and those with significant cardiovascular disease). 5. Monitor TSH monthly and increase the dose by 12.5- 25 mcg until TSH normalizes. 6. Continue levothyroxine supplementation for the duration of exposure to the causative agent.	1. Symptoms of hypothyroidism include fatigue, drowsiness, cold intolerance, dry skin, coarse hair, constipation, depression and inability to concentrate. These can be difficult to distinguish from TB symptoms and drug side-effects; hence, routine TSH monitoring is recommended in patients receiving PAS or Eto/Pto. 2. Hypothyroidism can lead to QT interval prolongation; these patients may require closer ECG monitoring depending on their exposure to QT-prolonging drugs. 3. The combination of PAS and Eto/Pto increases the likelihood of hypothyroidism, but it is completely reversible upon discontinuation of these drugs.
Lactic acidosis	Lzd, H	1. Suspect lactic acidosis in patients presenting in shock or acutely ill while on treatment with Lzd or H. 2. Check electrolytes and measure serum lactate if the anion gap is >12 mmol/L or if there are other reasons to suspect	1. Clinical signs of lactic acidosis may include severe hypotension, altered mental state, tachypnoea and oliguria. 2. The calculated anion gap = sodium - (chloride + bicarbonate).

		lactic acidosis. 3. Withhold Lzd and H, and do not rechallenge if lactic acidosis occurs.	
Metallic taste	Eto/Pto H, Lfx, Mfx	1. Consider other causes (e.g. pregnancy, upper respiratory infections, underlying medical conditions and other drugs) and educate the patient on possible reasons for the change in their taste. 2. Sucking hard candy or chewing gum can be helpful. 3. Reassure the patient that changes in taste that are related to TB medications will return to normal following completion of treatment.	1. Other drugs leading to metallic taste include metformin, lithium and phenytoin. 2. Underlying conditions that can cause metallic taste include diabetes, zinc deficiency and Crohn's disease.
Myelosuppression	Lzd Mpm, H, Pa	1. Do not initiate or continue Lzd when serum haemoglobin <8 g/dL, neutrophils <0.75 x 10^9/L or platelets <50 x 10^9/L. Referral for hospitalization and blood transfusion may be required in these cases. 2. Investigate other causes of anaemia (e.g. TB and other chronic diseases, nutritional deficiencies, pregnancy and blood loss), neutropoenia (HIV and other viral infections, leukaemia and lymphoma) or thrombocytopenia (pregnancy, other drugs and autoimmune disorders), and manage appropriately. 3. Lzd may be introduced at the full dose if the haematological parameters improve	1. Lzd-induced myelosuppression usually affects red blood cells, but sometimes it affects only neutrophils or platelets in isolation. 2. In rare cases, Mpm and H can cause haemolytic anaemia. 3. Effective TB treatment, including with Lzd, usually leads to improvement of anaemia that is due to chronic disease; initial blood transfusion at the start of treatment may improve haematological parameters enough to allow Lzd to be initiated within an effective regimen. 4. Blood transfusions might also facilitate completion of the

		with blood transfusion at the start of treatment. 4. Lzd-induced myelosuppression tends to recur with ongoing exposure to Lzd following blood transfusion; Lzd should not be continued long term in these cases. 5. Do not drop the Lzd dose to subtherapeutic levels in response to this AE; rather, withdraw Lzd and substitute with another effective drug - this may necessitate a change in treatment regimen.	recommended duration of Lzd, to avoid substituting with other 5. medications or changing treatment regimens. 6. There have been some case studies reporting that pyridoxine (daily dose of 50 mg in adults) may protect against Lzd-induced anaemia, but the evidence is equivocal. 7. Iron supplements are unlikely to be useful in the acute management of Lzd-induced anaemia. 8. Unless indicated for severe confirmed iron deficiency anaemia, iron supplementation can be delayed until later in TB treatment, when the pill burden and side-effects of ferrous compounds can be better tolerated.
Nausea and vomiting	Eto/Pto, PAS, Amx/Clv, Bdq Lfx, Mfx, Mpm, H, E, Z, Cfz, Dlm, Ipm/cln, Pa, Lzd, S	1. Assess for danger signs (e.g. dehydration, electrolyte disturbances and hepatitis). Initiate rehydration therapy if indicated and correct electrolyte disturbances. Check haemoglobin and treat for bleeding ulcers in cases of haematemesis. 2. Exclude and manage other causes of new onset nausea and vomiting (e.g. hepatitis, pancreatitis, raised intracranial pressure, pregnancy or pre-eclampsia, and gastroenteritis). 3. Counsel the patient that these symptoms are common and usually worse at the start	1. Nausea is common in the early weeks of TB treatment; it usually abates with time, although some patients need adjunctive therapy. 2. Ongoing information, education and peer support may help patients to anticipate and cope with common symptoms. 3. Absorption of TB medications is often affected by the type and timing of food intake; however, the “ideal” administration of TB medications with or without food may have to be

		of treatment, and 4. that they often improve over time without having to withhold medication. 5. Encourage the patient to try different ways of taking their medication in relation to food and the timing of their usual daily activities: 6. Take Eto/Pto or PAS at a different time of day (e.g. just before going to sleep). 7. Eat a light snack before or after taking medication or try different foods. 8. Take Eto/Pto or PAS 2 hours after other TB medications. 9. Consider antiemetic(s) if nausea and vomiting persists: 10. Metoclopramide - administer 30 minutes before TB medications. 11. Ondansetron (or promethazine) - administer 12. 30 minutes before TB medications and again 8 hours later; can be used on its own or with metoclopramide. 13. If possible, decrease the dose of the suspected agent to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. 14. For non-remitting symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required - this may necessitate a change	altered if not tolerated by the patient. 4. Monitor renal function and replace electrolytes and fluids, as necessary, in cases of severe persistent vomiting. 5. Consider temporarily withholding the most likely causative agent and reintroduce it gradually by slowly increasing the dose over 2 weeks. 6. Ondansetron is a serotonin 5-HT3 receptor antagonist and has strong antiemetic properties. Different antiemetics, even from the same class, may be worth trying for some patients. 7. Ondansetron can prolong the QT interval; this risk must be balanced with the benefits for the patient, taking into account the patient's 8. exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required, in that setting. 9. Patients with "anticipatory nausea and vomiting" may benefit from a small dose of an anxiolytic (diazepam) 30 minutes before taking medications. 10. Antihistamines may be useful for nausea associated with CNS or vestibular toxicity.

		in regimen if a standardized regimen is used.	
Nephrotoxicity (renal toxicity)	Am	1. Investigate and manage other causes of renal toxicity (e.g. NSAIDs, diabetes, other medications, dehydration, congestive cardiac failure and urinary obstruction). 2. Discontinue the injectable agent and replace it with another effective TB medication if required. 3. Adjust doses of renally excreted TB medications according to creatinine clearance. 4. Monitor creatinine and electrolyte levels every 1-2 weeks until normal or stabilized.	1. A history of diabetes or renal disease is not a contraindication to using Am; however, patients with these comorbidities may be at increased risk of renal failure following exposure to this injectable agent; renal impairment may be permanent. 2. Renal dosing is recommended for selected TB medications in patients with creatinine clearance <30 mL/min.
Optic neuritis	Lzd, E	1. Withhold Lzd and E immediately in patients experiencing symptoms of optic neuritis. 2. Consider other causes of optic neuritis (e.g. autoimmune conditions, exposure to toxic substances such as methanol, and other bacterial or viral infections) and refer to an ophthalmologist. 3. Check blood sugar and diabetic control. 4. Do not reintroduce E. 5. Only consider reintroducing Lzd if other MDR/RR-TB treatment options are severely limited and optic neuritis has been definitively ruled out.	1. Symptoms of optic neuritis include ocular pain, loss of vision and flashing lights; symptoms are often unilateral. 2. All patients receiving Lzd and E must be counselled at the start of therapy to recognize the early symptoms of this potentially sight- threatening AE and seek medical assistance urgently. 3. Drug-induced optic neuritis is usually reversible with early cessation of the offending agent.

Ototoxicity (hearing loss, tinnitus and vertigo)	Am S	1. Withdraw the injectable agent if there is new or worsening tinnitus, dizziness, fullness in the ears or evidence of hearing loss; replace with another effective agent. 2. Check renal function because nephrotoxicity is also an AE associated with injectable agents, and a reduced creatinine clearance may lead to increased exposure to ototoxic medications, with exacerbation of symptoms. 3. Vestibular symptoms (e.g., dizziness and nausea) may improve with antihistamines such as meclizine or dimenhydrinate.	1. Audiology screening, to detect early changes and high-frequency hearing loss, is essential for patients requiring treatment with this injectable agent. 2. Aspirin and loop diuretics are also ototoxic and may exacerbate the effects of aminoglycosides.
Peripheral neuropathy	Lzd, H, Trd/ Cs Lfx, Mfx, Am	1. Manage baseline risk factors - correct and prevent vitamin or nutritional deficiencies, obtain better diabetic control, and educate the patient on possible causes of peripheral neuropathy. 2. Pyridoxine doses of 50 mg in adults (25 mg in children) should be administered for peripheral neuropathy prophylaxis; however, pyridoxine doses must not 3. be increased beyond 100 mg in adults because, paradoxically, this may contribute to worsening peripheral neuropathy symptoms. 4. Neuropathic pain relief may be achieved with NSAIDs or paracetamol (acetaminophen), TCAs, pregabalin,	1. Risk of peripheral neuropathy is increased in malnutrition, diabetes, heavy alcohol use, HIV, pregnancy, and co-administration of multiple suspected drugs; these conditions are not contraindications for the agents listed. 2. H inhibits the metabolic action of vitamin B6 and Trd/Cs increases its renal excretion; therefore, pyridoxine supplementation can protect against drug-induced vitamin B6 deficiency, which 3. leads to peripheral neuropathy; pyridoxine does not appear to protect against Lzd-induced peripheral

		gabapentin or carbamazepine. 5. Discontinue high-dose H if not considered essential in the regimen. 6. If possible, decrease the dose of the suspected agent (e.g. Trd/Cs) to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. 7. For worsening or non-remitting symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required - this may necessitate a change in regimen if a standardized regimen is used.	neuropathy. 4. Peripheral neuropathy can manifest in various ways and can be difficult to assess properly, especially in young children - ask about crying at night, pulling at feet, kicking off bed covers, weakness, clumsiness and changes in gait or balance. 5. Note that TCAs are associated with QT prolongation; this risk must be balanced with the benefits for the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required, in that setting. 6. Carbamazepine is a strong CYP3A4 inducer and should not be used with Bdq (the drug-drug interaction is likely to lead to subtherapeutic Bdq levels). 7. Many patients report improvement in symptoms when the offending agent is withheld; however, drug-induced peripheral neuropathy is common after prolonged drug exposure and may become irreversible (particularly with Lzd); good communication and joint decision-making with the patient is crucial when considering ongoing treatment with the

			suspected agent or agents.
Psychotic symptoms (hallucinations and delusions)	Dlm, Trd/ Cs, H, Lfx, Mfx	1. Consider other causes of psychotic symptoms (e.g. fever, CNS infections, head injury or trauma, emotional abuse, food or sleep deprivation, heavy metal poisoning, recreational substance use, and psychological and neurological conditions) and manage appropriately. 2. In severe cases - particularly if the patient is a potential risk to themselves or others - initiate antipsychotic therapy (e.g. haloperidol) and refer for hospitalization. 3. Check renal function because this may lead to reduced excretion and increased exposure to toxic drugs - amended dosing of TB medications may be required. 4. Increase pyridoxine to maximum daily dose (100 mg per day in adults) if Trd/Cs or H are used. 5. If possible, decrease the dose of the suspected agent (e.g. Trd/Cs or H) to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. 6. In severe cases with no improvement of symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required.	1. Prior history of psychotic symptoms or psychiatric disease is not a contraindication to the drugs listed but may increase the likelihood of psychotic symptoms developing during treatment with these drugs. 2. Drug-induced psychotic symptoms are generally reversible upon withdrawal of the offending agent. 3. Renal dosing is recommended for selected TB medications in patients with creatinine clearance 4. <30 mL/min. 5. Some patients who experience psychosis can tolerate these drugs along with an antipsychotic agent throughout MDR/RR-TB treatment, but this should only be considered if treatment options are limited and in consultation with a psychiatrist. 6. Haloperidol is known to prolong the QT interval; hence, closer ECG monitoring is recommended, particularly if the patient is receiving multiple other QT-prolonging TB medications.

QT prolongation	Cfz, Bdq, Mfx, Dlm, Pa, Lfx	1. Obtain a thorough drug history. 2. Ask about history of cardiac symptoms: chest pain, palpitations, dizziness or syncope. 3. Repeat the ECG when the patient is relaxed and at rest. 4. Manually calculate the QTcF interval by taking an average reading from multiple ECGs done at least 1 minute apart (if available). 5. Measure serum electrolytes (potassium, magnesium and calcium) and TSH, and correct if necessary. 6. In children under 20 kg, consider reducing the dose of Cfz. 7. For QTcF >460 ms, withhold non-essential 8. QT-prolonging concomitant medications (e.g. antihistamines) and use more frequent ECG monitoring. 9. For QTcF >480 ms, monitor ECGs more closely and withhold one or more QT-prolonging TB medications if the patient complains of cardiac symptoms. 10. For QTcF >500 ms, withhold all QT-prolonging medications and monitor ECG closely - refer for hospitalization if the patient has cardiac symptoms. 11. QT-prolonging drugs that are essential to the TB regimen may be rechallenged sequentially, with close ECG monitoring, once QTcF improves to <500 ms.	1. The QT interval is a physiological parameter that fluctuates throughout the day and is affected 2. by emotional state, hunger, anxiety, exercise, endocrine and metabolic disturbances, and exogenous substances. 3. A normal QT interval is usually considered as QTcF <450 ms but there is some borderline variation, which can also vary by gender; the corrected QT interval is considered prolonged if it is >450 ms in males and >470 ms in females. 4. Cfz exposure is relatively high in young children at recommended doses; reduction in dose 5. may reduce the risk of QT prolongation while maintaining drug efficacy in this population. 6. Many drugs have the potential to prolong the QT interval.[a] 7. Risk is increased with multiple QT-prolonging drugs and additional risk factors (electrolyte and thyroid disturbances). 8. Patients with prolonged QTc are at risk of developing cardiac arrhythmias such as TdP, which can lead to sudden death - this risk increases substantially with QTcF >500 ms.

		12. Withdraw the most likely QT-prolonging agent in cases of recurrent or persistent severe QT interval prolongation - this may necessitate a change in treatment regimen.	
Seizures	H, Trd/Cs, Mpm, Lfx, Mfx, Lzd, Ipm/cln	1. Consider other causes of seizures (e.g. fever, CNS infections, recreational drug use, hypo/hyperglycaemia, head injury and epilepsy) and manage appropriately. 2. Check blood sugar and serum electrolytes and correct as needed. 3. Check renal function because this may lead to reduced excretion and increased exposure to toxic drugs - amended drug dosing may be required. 4. Increase pyridoxine to maximum daily dose (100 mg per day in adults) if Trd/Cs or H are used. 5. Anti-convulsant therapy (e.g., sodium valproate) may be necessary to control seizures. 6. Withhold all suspected agents until seizures have stabilized and then reintroduce TB medications one at a time. Do not reintroduce H.	1. Seizures are a common complication of tuberculous meningitis. 2. Renal dosing is recommended for selected TB medications in patients with creatinine clearance 3. <30 mL/min. 4. Prior history of seizures is not a contraindication to the drugs listed, provided the patient's seizures are under control or the patient is receiving anti-convulsant therapy (or both); however, such patients may still be at increased risk of developing seizures during MDR/RR-TB treatment and these agents should only be used if therapeutic options are severely limited. 5. Phenytoin and carbamazepine are strong CYP3A4 inducers and should not be used with Bdq (the interaction is likely to lead to subtherapeutic drug levels).
Skin and sclerae hyperpigmentation	Cfz	1. Some degree of skin hyperpigmentation is inevitable with prolonged use of Cfz, and	1. This AE can be distressing and stigmatizing for some patients (particularly adolescents) and they

		patients should be informed of this at the start of treatment. 2. Occasionally, patients experience staining of the whites of their eyes; this may be mistaken for conjunctivitis. 3. Some patients may also complain of skin rashes and dry, itchy skin - this can be managed conservatively with moisturizing lotions and other topical agents. 4. Reassure the patient that drug-induced skin and sclerae changes will return to normal following completion of treatment.	may require extra psychological counselling and peer support. 2. This effect is likely to be exacerbated by prolonged sun exposure.
Tendonitis or tendon rupture	Lfx, Mfx	1. Mild to moderate tendonitis or partial tendon tears may be managed conservatively with rest, ice, compression, elevation, immobilization of the affected joint or tendon, and therapy with NSAIDs. 2. Patients with complete tendon rupture should be referred for surgical assessment and physiotherapy-led rehabilitation. 3. Unless MDR/RR-TB treatment options for the individual are severely limited, ongoing treatment with FQs should be avoided in patients with tendinopathy.	1. Prolonged exposure to FQ (beyond 1 week) increases the risk of tendonitis and tendon rupture. 2. Tendon rupture associated with FQ use is more common among diabetic patients and people aged over 30 years; men are at higher risk than women. 3. Patients who participate in sports that involve running, jumping or sudden movements should be counselled about the higher risk of tendon rupture while taking FQs. 4. Exposure to corticosteroids, both systemic and with local application, also contribute to tendon weakening

			and increase the risk of tendon rupture.

AE: adverse event; CNS: central nervous system; ECG: electrocardiogram; FQ: fluoroquinolone; HIV: human immunodeficiency virus; IU: international units; IV: intravenous; MDR/RR-TB: multidrug-resistant or rifampicin-resistant TB; NSAID: non-steroidal anti-inflammatory drug; QTcF: corrected QT interval per Fridericia's formula; SAE: serious adverse event; SSRI: selective serotonin reuptake inhibitor; TB: tuberculosis; TCA: tricyclic antidepressant; TdP: torsades de pointes; TSH: thyroid stimulating hormone.

Drugs: Am: amikacin; Amx: amoxicillin; Bdq: bedaquiline; Cfz: clofazimine; Clv: clavulanic acid; Cs: cycloserine; Dlm: delamanid; E: ethambutol; Eto: ethionamide; H: isoniazid; Lfx: levofloxacin; Lzd: linezolid; Mfx: moxifloxacin; Mpm: meropenem; Pa: pretomanid; PAS: p-aminosalicylic acid; Pto: prothionamide; Trd: terizidone; Z: pyrazinamide.

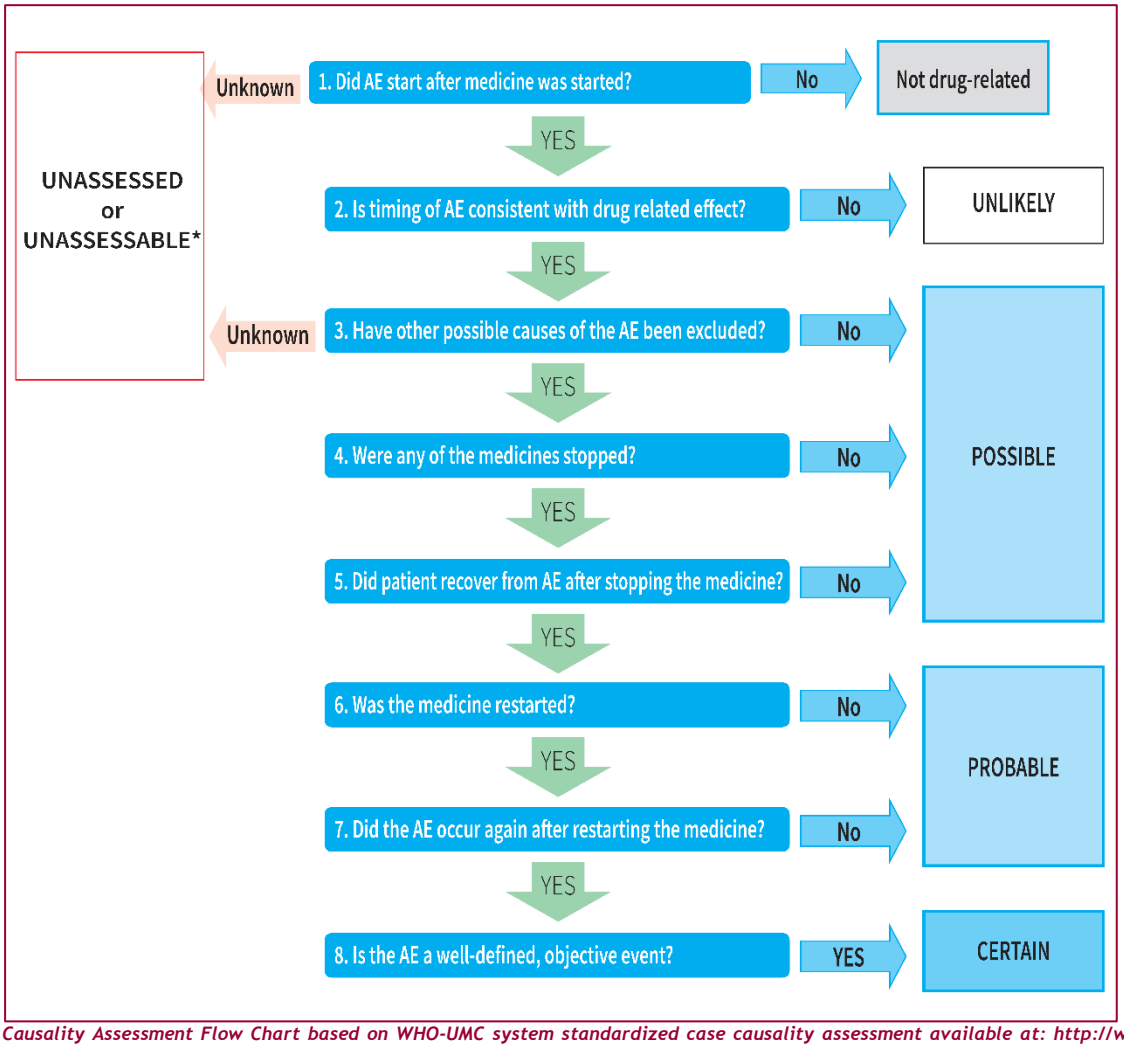
[a] For a list of drugs, see https://crediblemeds.org/.

Source: *WHO Operational Handbook on Tuberculosis, Module 4: Treatment (Drug-Resistant Tuberculosis Treatment), 2022 update, Web Annexes*

6.4 CAUSALITY ASSESSMENT OF THE SERIOUS ADVERSE EVENT (SAEs)

For all SAEs, the *first level Causality Assessment* can be done at the DR-TB treatment centers by the treating doctor using the below Adverse Event Causality Assessment definitions and Flowchart:

FIGURE 6.2: Causality assessment flowchart



Causality Assessment Flow Chart based on WHO-UMC system standardized case causality assessment available at: http://www.who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf

Notes:

1. Check the start date of each of the medicines and the onset date of the AE. If the AE started before the medicines was started, there is no causal relationship between the medicines and the AE. (Note: is a pre-existing condition got worse after starting medicine it may be a drug- related effect, in which case select 'yes' and go to step 2)

*Select UNASSESSED if unknown but awaiting further information. Select UNASSESSABLE if unknown and no further information can be obtained (eg, information not recorded at health facility)

2. **Is the time-to-onset of the adverse event consistent with a drug-related effect?** Consider known actions and pharmacokinetics (absorption, distribution, metabolism, and elimination) of the medicines and the pathology of the adverse event (how long would it take for condition to develop?)

3. **Are there other factors that could account for AE, such as:**
   - Condition for which medicines were prescribed?
   - Other illnesses?
   - Other medicines (including traditional/herbal medicines)?

   ** If other factors provide a more likely explanation for the AE, the casual association between the medicine and the AE is assesses as UNLIKELY

4. **DECHALLENGE**
   - Did the patient recover from the AE or show objective signs of improvement after the medicine was stopped? Is it biologically plausible that the response observed after stopping the medicine was due to the medicine being stopped?

5. **RECHALLENGE**
   - Was the re-challenge at the same dose or a lower dose? If the re-challenge was negative at a lower dose, consider whether the AE may have been a dose-related effect

The causal association can only be assessed as CERTAIN if the AE is a well-defined, objective event. (Vague, non-specific symptoms do not meet the criteria for CERTAIN)

When required, second level of Causality Assessment will be done by the national level by a Causality Assessment Team from the NTCC using the same Adverse Event Causality Assessment Flowchart. This will enable the findings from the first level causality assessment to be verified.

TABLE 6.4: The WHO-UMC Classification System for causality assessment

Causality term	Definition	Assessment criteria*
1. Certain	Clearly caused by the exposure There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Re-challenge satisfactory, if necessary
2. Probable/ Likely	Likely to be related to the exposure There is evidence to suggest a likely causal relationship and the influence of other factors is unlikely.	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Re-challenge not required
3. Possible	May be related to the exposure There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the patient's clinical condition, other concomitant treatments).	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
4. Unlikely	Doubtfully related to the exposure There is little evidence to suggest there is a causal relationship (e.g., the event did not occur within a reasonable time after administration of the study regimen). There is another reasonable explanation for the event (e.g., the patient's clinical condition, other concomitant treatment).	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations

5. Conditional or Unclassified	There is insufficient information about the ADRs to allow for an assessment of causality.	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
6. Unassessable or Unclassifiable	There is insufficient information about the ADRs to allow for an assessment of causality and NO MORE is expected.	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied for assessment

CHAPTER 7

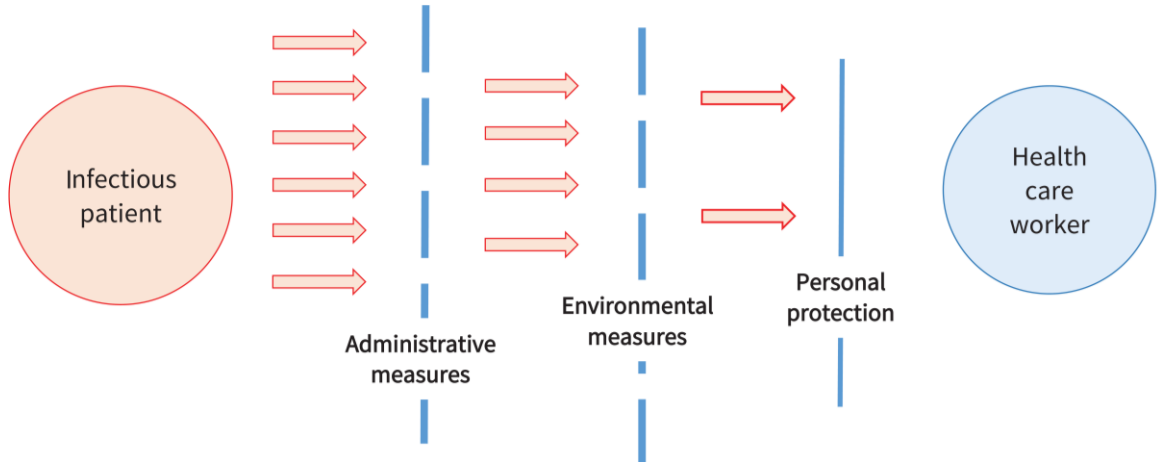
INFECTION CONTROL

TB infection control is a combination of measures aimed at minimizing the risk of TB transmission within populations. The foundation of infection control is early and rapid diagnosis, and proper treatment of TB patients.

7.1 GENERAL PRINCIPLES OF INFECTION CONTROL

There are three levels of infection control measures, operating at different points in the transmission process, and all are interdependent:

FIGURE 7.1 Three Layer of Infection Control



7.1.1 Administrative (managerial) controls

Administrative controls should be implemented as a priority because they have been shown to reduce transmission of TB in health-care facilities. Such controls are a vital part of sound infection control practices, which require people with TB symptoms to be promptly identified, separated, and treated. Administrative control includes:

- Develop and implement written policies and protocols to ensure:
  - Rapid identification of TB patients (e.g., improving the turn-around time for obtaining sputum results)
  - Isolation of patients with PTB
  - Rapid diagnostic evaluation
  - Rapid initiation treatment
  - Educate, train, and counsel HCWs about TB
- To the extent possible, avoid mixing TB patients and HIV patients in the hospital or clinic setting
- Find cases Actively, Separate temporarily and Treat effectively (FAST) is intensified, refocused administrative approach to TB transmission control in healthcare facilities.

- Active case finding with cough screening followed by rapid molecular diagnostics, which enables prompt treatment of unsuspected drug-sensitive and drug-resistant TB, thereby decreasing TB transmission. The basic principle for FAST are as follows:
  - TB is spread in institutions predominantly by coughing patients with unsuspected TB or unsuspected drug resistance
  - Most potentially infectious patients can be identified by cough surveillance
  - Coughing TB patients most likely to be infectious can be diagnosed using rapid molecular sputum tests
  - By dramatically reducing the duration of institutional exposure through effective treatment, transmission among patients and to health care workers will be reduced proportionately

    For detail, please refer to FAST Strategy

7.1.2 Environmental controls

- Environmental controls include methods to reduce the concentration of infectious respiratory aerosols (i.e., droplet nuclei) in the air, and methods to control the direction of infectious air.
- Such measures include:
  - Use of ventilation systems.
  - Use upper-room germicidal ultraviolet irradiation (GUV) fixtures, at least when adequate ventilation cannot be achieved

7.1.2.1 Use of ventilation systems

Adequate ventilation in health-care facilities is essential for preventing transmission of airborne infections and is strongly recommended for controlling spread of TB. The choice of ventilation system will be based on assessment of the facility and informed by local programmatic, climatic, and socioeconomic conditions. Any ventilation system must be monitored and maintained on a regular schedule.

Kind of ventilation systems:

Natural Ventilation

- Created using external airflows generated by natural forces such as: Wind, Differences in temperature
- Naturally ventilated rooms can achieve very high ventilation rates (ACH) under ideal conditions, but natural ventilation is unpredictable.

Maximize Natural Ventilation

- Openings on opposite walls (cross ventilation)
- Openings are unrestricted (stay open)
- 10% of floor space should be openable- window-area on each wall
- Upper levels of the building
- Building and openings are oriented to use the prevailing wind, without obstruction by other nearby buildings

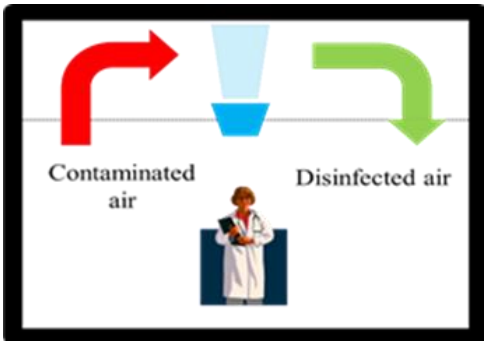
Mechanical ventilation

- Well-designed, maintained and operated fans (mixed-mode ventilation) can help to obtain adequate dilution when natural ventilation alone cannot provide sufficient ventilation rates.
- In some settings, mechanical ventilation (with or without climate control) will be needed.
- This may be the case, for example, where natural or mixed-mode ventilation systems cannot be implemented effectively, or where such systems are inadequate given local conditions (e.g., building structure, climate, regulations, culture, cost and outdoor air quality).

7.1.2.2 Use of upper room or shielded germicidal ultraviolet irradiation fixtures

Priority should be given to achieving adequate ACH using ventilation systems. However, in some settings it is not possible to achieve adequate ventilation; for example, because of climatic changes (e.g., in winter or during the night) or building structure, or because transmission of TB would pose a high risk of morbidity and mortality (e.g., in MDR/RR-TB wards). In such cases, a complementary option is to use upper room or shielded germicidal ultraviolet irradiation (GUV) devices. This environmental control does not provide fresh air or directional airflow.

FIGURE 7.2 UVGI



7.1.3 Personal respiratory protection

Personal respiratory protection aims to protect the health workers in areas where the concentration of droplet nuclei cannot be adequately reduced by administrative and environmental controls. Health workers should use high filtration masks (N95) or "respirators" to protect them against the inhalation of airborne infectious droplets. The patients should wear a surgical mask to reduce the spread of droplets.

7.1.3.1 Respirator Vs Surgical Mask

TABLE 7.1: Features of respirators and surgical masks

RESPIRATORS	SURGICAL MASKS
• Designed to filter out droplet nuclei from being inhaled by the health-care worker and other individuals. • Should properly fit different face sizes and features. • Should NOT be worn by the patient	• Designed to stop droplet nuclei from being spread (exhaled) by the patient. • Should NOT be worn by the healthcare worker

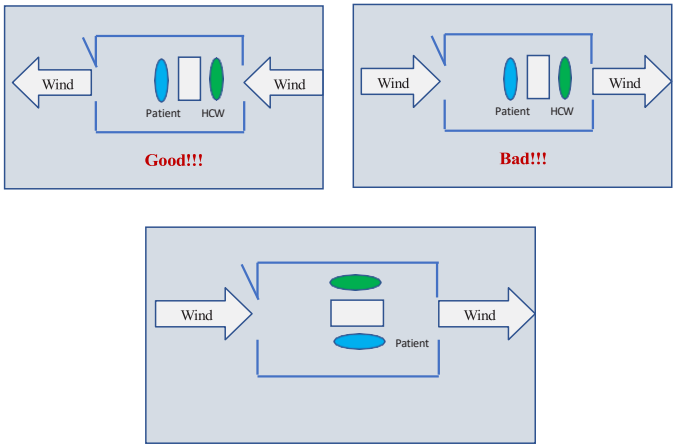
Personal respiratory protection by themselves is insufficient to prevent TB transmission. They will not be worn continuously and are likely not to be in use when unsuspected TB cases are encountered. Administrative and environmental controls are more important.

7.2 INFECTION CONTROL AT TB CONSULTATION ROOM

The rooms for TB consultation, counselling and health education should be arranged according to sound infection control principles:

- Both windows and door should be open all the time.
- Direct sunlight gets into the room easily
- A stand fan ensures an airflow direction toward the opened window
- Patient and health staff sit in front of each other across the airflow
- Exhaust fan to extract the air
- One patient at a time should be received in the room
- The patient should wear a surgical mask
- Staff and family should wear N95 mask
- Appropriate cough hygiene must be observed by the patient

FIGURE 7.3: Natural Ventilation



7.3 DR-TB PATIENT ISOLATION ROOM

The DR-TB isolation room should have large open windows allowing direct sunlight into the room, a closing door, a stand fan to establish an air flow direction toward the window, and preferably a UV light installation with a shield to protect the eyes from direct exposure to it. The UV light should be turned on for 15 to 20 minutes every 12 hours (in the morning and evening), preferably with the patients not being in the room. An exhaust fan may help to extract the air from the room. The DR-TB room should be isolated from the other departments, especially the out-patient clinic, the HIV ward, the pediatric ward and other high risk group departments.

DR-TB infectious patients in the isolation room must always wear a surgical mask. If no masks are available, the patients should use a handkerchief or a piece of cloth to cover their mouth when talking, coughing, sneezing, or speaking. The patients should refrain from spitting on the floor but should spit in a sputum cup that will be later burned.

Health workers must wear high filtration (N95) masks, fitted correctly, every time they meet DR- TB patients or enter the DR-TB ward.

Instructions on how to wear masks should be posted at all entries of the DR-TB area for staff, patients, and visitors. DR-TB patients should not receive many visitors and avoid contact with small children until sputum smear or culture conversion. Good infection control measures for visitors and small children include:

- Meeting in a room with good ventilation or outside
- Patient wearing surgical mask and visitor wearing high filtration (N95) mask
- Room disinfected by appropriate use of UV light

7.4 INFECTION CONTROL AT HOME

Contagious or potentially contagious patient may have to be isolated at home. The following infection control measures can be taken:

- If feasible, the patient should stay and sleep in a specific room separated from the other family members.
- If possible, the isolation room should have good ventilation with a large, opened window, direct exposure to sunlight, and preferably with good air flow direction (natural or with fan).
- Other people should not enter the room unless necessary. If they do so, patient must a surgical mask.
- At all stages the patient should be encouraged to stay outside.
- The patient should eat separately, outside or in the room.
- The patient should wear a surgical mask all the time when in contact with other people.
- Strict coughing hygiene must be observed by the patient, inside as well as outside the house.
- If other people come to see the patient, they should meet outside. They need to keep a safe distance and duration of contact should be kept as short as possible.
- The patient should avoid contact with children or other high-risk groups and restrict close contacts with other people during the contagious period.

Role of TB patient in infection control:

- Patient should maintain a well-balanced diet to keep the immune system strong
- Patient should TB patient to stop smoking and minimize intake of alcohol
- Patient should wear mask and hold a cloth or handkerchief over mouth when coughing
- Patient should not spit on the floor but in a container (preferably disposable) and dispose of properly

7.5 HEALTH WORKER AND INFECTION CONTROL

Always follow recommended infection control procedures in your work in the health facility. Be aware of possible signs and symptoms of TB in yourself. If one or more of these develop, report promptly for assessment and care. If you are diagnosed with TB, start treatment promptly and adhere to treatment until it is completed.

Health workers should decrease their risk factors for TB disease to the extent possible e.g., Living healthy live-styles, stress free, stop smoking, or following treatment for diabetes, knowing their HIV status or getting retested periodically etc. If a health worker is HIV-infected, he/she may decrease his/her risk of developing TB by taking CPT, ART and IPT as appropriate. Health workers who have positive HIV status should be given alternative of work area by the employers.

CHAPTER 8

MONITORING & EVALUATION FOR TB CONTROL PROGRAM

8.1 TB RECORDING AND REPORTING TOOLS

TABLE 8.1: HMIS Recording and Reporting Tools Used in National TB Program

SN	HMIS/TB Number	Tools
I	HMIS 1.4	TB Referral Slip
2	**HMIS 6.1**	**Presumptive TB register**
3	**HMIS 6.2**	**Laboratory Request Report Form**
4	**HMIS 6.3A**	**Laboratory Register (Microscopy)**
5	**HMIS 6.3B**	**Laboratory Register (GeneXpert)**
6	**HMIS 6.3C**	**Laboratory Register (Culture DST)**
7	**HMIS 6.3D**	**Laboratory Register (LPA)**
8	HMIS 6.4A	DSTB Treatment Management Card
9	HMIS 6.4B	DSTB Treatment Card- Patient
10	**HMIS 6.4C**	**DR-TB Treatment Management Card**
11	**HMIS 6.4D**	**DR-TB Treatment Card- Patient**
12	HMIS 6.5A	TB Treatment Master Register
13	**HMIS 6.5B**	**DR-TB Treatment Register**
14	**HMIS 6.6**	**Contact Screening and Contact Examination Form**
15	**HMIS 6.7**	**Contact Investigation TPT Register**
16	HMIS 6.8	TB Preventive Therapy Card
17	**HMIS 6.9**	**TB Referral form (Community, Private)**
18	**HMIS 6.10**	**aDSM Adverse Event Recording and Reporting Form**

**The bold letters represent forms/registers applicable for DR-TB*

HMIS 6.1 Presumptive TB register

Once a patient is suspected of having TB in the OPDs/Clinics, then they are registered in the Presumptive TB Register at the OPDs by the treating physicians/health care workers. Presumptive TB Register contains sociodemographic information of TB patients, history of TB, where the patient is referred to for diagnosis, diagnosis result details, TB management suggested and details where the patient is referred for management (DOT/ DR-TB centers). The new serial number will be assigned at the beginning of each month while using this register. The register is the same for both DS and DR-TB.

HMIS 6.2 Laboratory Request Form

These forms are filled by OPDs/clinics for diagnosis of DS/DR-TB and or from DR-TB Treatment Centers for follow up purpose. There is only one Laboratory Request Form that will be used for both DS and DR-TB diagnosis as well as follow up. Once the tests are done, the lab reports back the test results of Smear Microscopy and Xpert MTB/RIF or Xpert MTB/RIF-Ultra testing using the same form. Results of LPA and Culture DST are given in separate form using Laboratory Report Form (LPA and Culture DST).

The Form is divided broadly into 2 parts.

- **Part 1** is for Laboratory Test request, which has sub-sections for different requesting different types of tests
  A. Microscopy
  B. Xpert MTB/RIF or Xpert MTB/RIF-Ultra
  C. LPA
  D. Culture/DST
  E. DR/TB Baseline and follow-up patients
  F. HIV Test
- **Part 2** is for reporting the results of smear and Xpert MTB/RIF testing.

HMIS 6.3 Laboratory Registers

These registers are present in the Laboratories where the bacteriological test for TB are carried out. The registers are separate for different types for laboratory process even within the same Laboratory.

- HMIS 6.3A: Laboratory Register (Microscopy)
- HMIS 6.3B: Laboratory Register (Xpert)
- HMIS 6.3C: Laboratory Register (Culture DST)
- HMIS 6.3D: Laboratory Register (LPA)

HMIS 6.4C DR-TB Treatment Management Card

This card is used to record the patient personal history related to the disease, tests and results, daily DOT, treatment outcome etc. This card is kept in DR-TB center and/or sub center.

HMIS 6.4D DR-TB treatment Card-Patient

This card is kept by the patient, and it records the daily DOT, lab tests and results, treatment outcome, contact no. of DOT supervisor etc. The patient while visiting DR-TB center/sub center will take this card with him/her. After medication, the daily DOT is recorded in the card by the DOT supervisor and give it back to patient for his knowledge.

HMIS 6.5B DR Tuberculosis Treatment Register

This register is kept at the DR-TB treatment center. It records patient personal details, registration category, diagnosis and follow up monitoring results, HIV test results, Treatment outcome and others. This register should be used to report monthly in HMIS and to report in DHIS 2 tracker online system.

HMIS 6.6 Contact Screening and Contact Examination Form

Though the patient is registered in the DR-TB center, the DOT center which referred the patient to the DR-TB Treatment center is responsible for carrying out the contact investigation and inform the DR-TB treatment center of the finding. Volunteers are given out these Contact Investigation Forms with details of DR-TB index s, which they use while carrying out contact investigation in the community. If there are presumptive DR-TB among contacts identified during screening, a separate Referral Form (HMIS 6.9) is filled out and issued by the volunteers and referred for further diagnosis. All the information is then recorded for all contacts screened in this form and are submitted back to the DOT/ DR-TB centers. The same form will be used to access contacts of drug-sensitive and/or drug-resistant TB.

HMIS 6.7 Contact Investigation TPT Register

The detail of the contacts from the Contact Screening and Contact Examination Form (HMIS 6.6) are recorded in this form at the DOT/ DR-TB center.

HMIS 6.9 TB Referral Form (Community, Private Sector)

These forms are present in the treatment centers and are provided to the community health volunteers (esp. FCHVs). These are used while referring presumptive TB patients from the community (during contact tracing) to the health facilities for further diagnosis or can also be used for referring a TB patient if they have side effects or requiring other tests and follow up, which they identify in the community.

HMIS 6.10 aDSM Adverse Event Recording/Reporting Form

This form is used to record any adverse events experienced by the patient during the treatment. It includes the description of the adverse events, laboratory assessment done, medicines, DR-TB regimen, concomitant medicines, vaccine, traditional herbal medicines, action taken in responses to AE, Responses to the action taken, re-challenge information, casualty assessment at the treatment center and other relevant information. A final AE/SAE summary is also recorded in this form. This form should be submitted by each DR-TB treatment center to NTCC.

HMIS 9.3/9.4/9.5 Report (DR-TB)

This report should be submitted monthly through integrated health management information system. Health facility based upon HMIS 6.5B records will prepare the report on the monthly basis. It includes the type of DR-TB, Age/Sex of the registered patients, HIV status, contact investigation, treatment outcome and other relevant information. The case wise details is reported in the DHIS 2 online tracker system.

For more details, please refer to HMIS Recording & Reporting Guidelines, 2078 B.S.

8.2 MONITORING OF DR-TB CASE DETECTION AND TREATMENT ACTIVITIES

Monitoring DR-TB control activities are important to assess progress and identify areas that need improvement.

Monitoring at central level (NTCC)

- The proportion of DR-TB patients detected (all forms) among presumptive TB patients at different levels (national, provincial, and local level). The monitoring is done for all forms of TB.
- The proportion of detected DR-TB patients enrolled under treatment.
- Treatment outcomes of DR-TB patients enrolled under treatment.

Monitoring at the DR-TB treatment center

- Daily treatment adherence of DR -TB patients registered in their center.
- Carrying out regular follow up activities of each DR-TB patients.
- The proportion of adverse events of DR-TB patients and management of adverse events.
- Regular (monthly) follow up of DR-TB patients (for daily adherence and follow up tests) managed by Treatment Sub-centers.
- Regular (monthly) follow up of DR-TB patients (for daily adherence and follow up tests) managed under CBDOT/Family based DOT program.
- Treatment outcome of each registered DR- TB patient.
- Contact investigation of index DR-TB patients and the proportion of presumptive contacts diagnosed and managed with TB.
- Proportion of registered DR-TB patients enrolled in National Health Insurance Program.
- Proportion of registered DR-TB patients who received nutritional and transportation support.

Monitoring at the DR-TB treatment sub-center

- Daily treatment adherence of DR-TB patients managed from their center.
- Assurance of follow up test done by the registered DR-TB patients.
- Supervision of DR-TB patients being managed under CB-DOT/Family based DOT assigned under their center.

TB Treatment Outcome indicators

TABLE 8.2: Treatment outcome category of DR-TB patients – Longer Regimen

Category	Definition
Cured*	Treatment completed as recommended by the national policy (minimum 18 months with 16 months past culture conversion) without evidence of failure AND 3 (three) or more consecutive cultures taken at least 30 days apart are negative 1.1 To declare cure, the patient should have 3 (three) consecutive negative cultures reported by the end of treatment, ensuring that cultures are done as per national policy 1.2 If there is 1 (one) positive culture by the end of treatment, this positive culture should be followed by 3 (three) negative cultures
Treatment completed	Treatment completed as recommended by the national policy (minimum 18 months) without evidence of failure BUT no record that 3 (three) consecutive cultures taken at least 30 days apart are negative.
Treatment failed	Treatment terminated or need for permanent regimen change of at least 2 (two) anti-TB drugs because of: 1.1 Lack of conversion by the end of 6 months of treatment or in case of injectable by the end of intensive phase, OR 1.2 Bacteriological reversion in the continuation phase after conversion to negative, OR 1.3 Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, OR 1.4 Adverse drug reactions (ADRs), leading to permanent treatment termination *Note:* • *If an MDR TB patient has 4 (four) positive cultures and is on month 6 (six) of treatment, it is suggested to repeat DST to SLDs and act accordingly as per the result. Please note that there may be a delayed response to treatment in XDR TB patients.* • *In case of reversion after 6 (six) months of treatment; repeat LPA/DST to SLDs, continue with treatment and decide as per the result of LPA/DST.*
Died	A patient who dies for any reason during treatment
Lost to follow-up	A patient whose treatment was interrupted for 2 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. The sum of Cured and Treatment completed is commonly used as an indicator of favorable outcome, or Treatment success.

** The outcome Cured is restricted to pulmonary bacteriologically confirmed TB cases only.*

TABLE 8.3: Treatment outcome category of DR-TB patients – OSSTR

Category	Definition
Cured*	Treatment completed without evidence of failure AND 3 (three) or more consecutive cultures taken at least 30 days apart are negative after the initial phase.
Treatment completed	Treatment completed without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the initial phase.
Treatment failed	The patient will be declared failure if meets one of the following criteria: • Acquired resistance to FQ • Sputum smear positive at month 6 (six) along with poor clinical and radiological response or worsening by the end of initial phase • There are 2 (two) positive cultures taken at least 30 days apart in continuation phase of treatment OR • One culture positive in the last 3 (three) months of treatment and recent follow up months smears are also positive Clinical decision in consultation with TWG has been made to permanently terminate treatment early because of poor clinical or radiological response or adverse events. *Note: Changing or switching treatment to longer regimen due to SAEs is not failure*
Died	A patient who dies for any reason during treatment
Lost to follow-up	A patient whose treatment was interrupted for 2 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. The sum of Cured and Treatment completed is commonly used as an indicator of favorable outcome, or Treatment success.

** The outcome Cured is restricted to pulmonary bacteriologically confirmed TB cases only.*

TABLE 8.4: Treatment outcome category of DR-TB patients – BPaLM/BPaL

Category	Definition
Cured*	Treatment completed as of the standard treatment duration of 6 (six) months (if extended, 9 month for BPaL) without evidence of failure and 3 consecutive cultures following 4 month culture is negative.
Treatment completed	Treatment completed as of the standard treatment duration of 6 (six) months (If extended, 9 month for BPaL) without evidence of failure but no record of 3 consecutive cultures are negative
Treatment failed	The patient is considered failure if: • Adverse drug reactions • Persistent positive sputum culture (no conversion or reversion) from months 4 to the end of the treatment • Acquired drug resistance to drugs in the regimen during the treatment (i-e baseline is susceptible and monitoring culture demonstrates resistance) • No clinical response
Died	A patient who dies for any reason during treatment
Lost to follow-up	A patient whose treatment was interrupted for 2 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. The sum of Cured and Treatment completed is commonly used as an indicator of favorable outcome, or Treatment success.

** The outcome Cured is restricted to pulmonary bacteriologically confirmed TB cases only.*

ANNEXURES

1. DRUG INFORMATION SHEETS
2. GRADING OF THE SEVERITY OF ADVERSE DRUG EVENTS
3. CALCULATING THE QT INTERVAL
4. CALCULATING THE CREATININE CLEARANCE
5. PERIPHERAL NEUROPATHY DIAGNOSTICS
6. GASTRIC ASPIRATE JOB AID
7. DR-TB RECORDING AND REPORTING FORMS

ANNEX 1 DRUG INFORMATION SHEET

The drug information described below is adopted from the WHO Operational Handbook on Tuberculosis, Module 4: Treatment (Drug-Resistant Tuberculosis Treatment), 2022 update, Web Annexes

The drugs are described in the alphabetical order as follows:

1. **Amikacin (Am)**
2. **Bedaquiline (B or Bdq)**
3. **Clofazimine (C or Cfz)**
4. **Cycloserine (Cs) or terizidone (Trd)**
5. **Delamanid (Dlm)**
6. **Ethambutol (E)**
7. **Ethionamide (Eto) or prothionamide (Pto)**
8. **Imipenem-cilastatin (Imp-Cln)**
9. **Isoniazid high dose (Hh)**
10. **Levofloxacin (Lfx)**
11. **Linezolid (L or Lzd)**
12. **Meropenem (Mpm)**
13. **Moxifloxacin (M or Mfx)**
14. **Para-aminosalicylic acid (PAS)**
15. **Pretomanid (Pa)**
16. **Pyrazinamide (Z)**
17. **Streptomycin (Sm)**

Amikacin (Am) **Drug class: aminoglycosides**	
Activity against M. tuberculosis, mechanism of action and metabolism	Target: M. tuberculosis inner metabolism. Inhibits protein synthesis. Irreversibly binds to bacterial 30S ribosomal subunits. Leads to misreading of t-RNA (meaning that bacteria are unable to synthesize proteins) and hence interferes with bacterial growth. Activity: Mainly bactericidal, high early bactericidal activity. Half-life and excretion: Half-life is usually 2–3 hours. Primarily excreted unchanged through the kidney by glomerular filtration.
Cross-resistance	Cross-resistance with capreomycin and kanamycin has been reported.
Dose[a]	Amikacin is recommended by WHO only in adults aged >18 years. • Adults: 15–20 mg/kg/day in a single daily dose, 6–7 days per week (upper daily dose is 1 g). • Adults > 60 years old: Lowering of amikacin dosage is advised. A lower starting dose of 10 mg/kg/day (max 750 mg) 5–7 times a week may be used. Alternatively, a 15 mg/kg/dose may be administered thrice weekly. • Renal failure or dialysis: Consider replacing amikacin with another agent. Otherwise, a 12–15 mg/kg/dose after dialysis, twice or thrice weekly (not daily) may be considered. Amikacin should be used with caution.
Administration	IV or IM. Intraperitoneal and intrathecal administrations have been reported; however, intrathecal administration is not advised provided there are oral TB medications with high CSFpenetration.
Formulation and Preparation	Available as 500 mg/2 mL solution for injection, ampoules and vials. For IV solution, mix with 100 mL or 200 mL of sterile diluent (e.g. D5W) or any other compatible solution. In paediatric patients, the volume of diluent used will depend on the amount of amikacin tolerated by the patient. The solution should be infused over 30–60 minutes for adults. It should not be mixed with any other parenteral medicine administered concurrently. IM absorption is complete within 4 hours and peak concentrations are achieved in 1–2 hours; however, absorption can be delayed if the same site is used repeatedly.
Storage	The solution in the original vial is stable at room temperature (15–25 °C). Reconstituted solutions can be stored at 2–8 °C for not more than 12 hours. Once at room temperature, it should be used within 24 hours.
Oral absorption	There is no significant oral absorption.
CSF penetration	Penetration is more effective in inflamed meninges.
Special circumstances	Use during pregnancy or breastfeeding: Should be avoided during pregnancy because of documented cases of congenital deafness. It is excreted into human milk; it is considered compatible with breastfeeding but should be used with caution (i.e. monitor for infant thrush and diarrhoea). Use in renal disease: Should be used with extreme caution; where possible, concentrations should be monitored in patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis (see under Dose section, above). 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 patients with ascites due to cirrhosis). It is presumed to be safe in severe liver disease; however, it should be used with caution because patients with severe liver disease may progress rapidly to hepato-renal syndrome.

	Diuretic use: Co-administration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity. Older people: There is increased risk of ototoxicity and nephrotoxicity owing to potential baseline damage in both organs.
Adverse reactions	Overall tolerance: It is badly tolerated, giving local pain with IM injections or lengthy infusions. Toxicity is associated with prolonged use and dose accumulation. Common: Proteinuria. Occasional: Nephrotoxicity (9% for general population, may be lower with thrice weekly administration), ototoxicity (hearing loss, increased risk with advanced age and prolonged use) and vestibular toxicity (vertigo, ataxia and dizziness); and electrolyte abnormalities, including hypokalaemia (which may prolong the QTc interval), hypocalcaemia and hypomagnesaemia. Uncommon: Neuropathy and rash.
Contraindications	Hypersensitivity to aminoglycosides. Renal, hepatic, vestibular or auditory impairment: In such cases, it should be used only with extreme caution.
Drug interactions	Loop diuretics: Co-administration of furosemide and aminoglycoside antibiotics carries an increased risk of ototoxicity and hypokalaemia.
Food interactions	None.
Monitoring	Monitoring of renal function should include: • creatinine at least monthly (more frequently if there is renal or hepatic impairment); • creatinine clearance if there is baseline renal impairment or any concerns; and • electrolytes: baseline follow-up with monthly minimum potassium, magnesium and calcium if possible. Audiology examination: document baseline and monthly results. Vestibular examinations: question patient regularly about vestibular symptoms and perform serial vestibular exams. If possible, in patients aged over 60 years or with altered renal function, peak serum concentrations should be monitored.
Patient instructions and alerting symptoms	Patients should be instructed to inform their health care provider immediately if any of the following occur: • problems with hearing, dizziness or vertigo; • rash or swelling of the face; • trouble breathing; • swelling, pain or redness at the IV site; or • muscle twitching or weakness.

Bedaquiline (B or Bdq) Drug class: diarylquinoline	
Activity against M. tuberculosis, mechanism of action and metabolism	Target: M. tuberculosis inner metabolism. Inhibits ATP synthesis, leaving the bacteria without sources of energy that are needed for replication and also for latency. Activity: High bactericidal activity, but it may take 7–14 days to manifest a bactericidal effect. Sterilizing activity: Significant; able to support reduction in duration of treatment. Half-life and excretion: has a 5.5-month half-life, with slow release of bedaquiline from peripheral tissues, which may have implications in toxicity and in cases of loss to follow-up (sustained monotherapy). Is hepatically metabolized by CYP3A4 (cytochrome p450) leading to the formation of its main metabolite M2, which does not contribute significantly to antimycobacterial activity compared with the parent compound. Bedaquiline is mainly eliminated in faeces. The renal clearance of the unchanged drug is insignificant.
Cross-resistance	Cross-resistance has been reported between bedaquiline and clofazimine, through efflux pump-mediated resistance and other mechanisms.
Dose[a]	• Adults: 400 mg once daily for 2 weeks, followed by 200 mg once daily, thrice weekly for 22 weeks. The maximum daily dose is 400 mg. For patients treated with the BPaLM/BPaL regimen (>14 years), bedaquiline can also be administered 200 mg once daily for 8 weeks, followed by 100 mg once daily until the end of treatment. • Children: There is no age restriction (See Table 4.8 for weight-based dosing in adults and children). • Renal failure or dialysis: No dose adjustment is needed for mild-to- moderate renal insufficiency. It should be used with caution in patients requiring renal dialysis (See Table 4.8 for weight-based dosing in adults and children).
Administration	Oral. In children, 100 mg tablets can be administered whole, or crushed and suspended in water without affecting bioavailability. Vigorous stirring or shaking is needed before administration. The 20 mg tablets can be administered whole or crushed and dispersed in <1–3 mL of water per tablet (maximum of 5 tablets in 5 mL of water), or crushed and mixed with food.
Formulation and preparation	20 mg scored, dispersible tablet. 100 mg uncoated tablets.
Storage	Tablets can be stored at room temperature (15–30 °C). Tablets removed from the original packaging should be stored in a tight, light-resistant container and labelled with an expiration date that should not exceed 3 months.
Oral absorption	Administration with food (ideally high-fat meals) leads to a twofold increase in bioavailability.
CSF penetration	Studies involving a small number of participants indicate that bedaquiline and M2 (main metabolite) penetrate well into the CSF of patients with pulmonary TB with a presumably intact blood-brain barrier.

Special circumstances	Use in pregnancy or breastfeeding: No fetal harm was found in animal studies. The drug accumulates significantly in breast milk, and breastfed infants receive doses of bedaquiline equivalent to maternal doses Use in renal disease: No dosage adjustment is required in patients with mild-to-moderate renal impairment. It should be used with caution in patients requiring peritoneal dialysis or haemodialysis. Therapeutic drug monitoring may be useful, if available. Use in hepatic disease: Bedaquiline should be used with caution because it is metabolized in the liver. No dosage adjustment is required in patients with mild-to-moderate hepatic impairment. It has not been studied in patients with severe hepatic impairment and should be used with extreme caution in such patients, and only when benefits outweigh risks. Clinical monitoring for bedaquiline-related adverse reactions is recommended.
Adverse reactions	Overall tolerance: Well tolerated. Occasional: Nausea, arthralgia (joint pain) and headache (~10%). QTc prolongation (estimated QTc increased by 10–15 msec, maximal at week 15). Overall QTc prolongation in cohorts using bedaquiline and other QTc-prolonging drugs was 2.7%, with median appearance at 2.5 months. Uncommon: Hyperuricaemia, phospholipidosis (accumulation of phospholipids in the body tissues) and elevated transaminase are an early signal for increased risk of pancreatitis.
Contraindications	Hypersensitivity to bedaquiline. Taking other medications that are strong inducers of CYP3A (e.g. rifamycins and carbamazepine). Use with caution in potential situations that may increase QT interval: Such situations are patients aged >60 years, heart failure, long QT syndrome, history of TdP, hypokalaemia, untreated hypothyroidism, low BMI, HIV infection, concomitant use of other QT-prolonging drugs. Any syncopal event (such as fainting) or palpitations should prompt an immediate medical evaluation and ECG. In several retrospective cohort studies on the incidence of QTc prolongation and cardiac events, the increase was modest, and no arrhythmias or related deaths were reported even when bedaquiline and delamanid were co-administered. Discontinue or do not use in the presence of: • clinically significant ventricular arrhythmia; • a QTcF interval of >500 msec (confirmed by repeat ECG); • severe liver disease; or abnormal electrolytes.
Drug interaction	Metabolized by CYP3A4 (cytochrome p450). • Co-administration with rifamycins (e.g. rifampicin, rifapentine and rifabutin) significantly reduces concentrations of bedaquiline (<50%). Other strong CYP3A4 inducers (e.g. efavirenz, phenytoin and glucocorticoids) may also require caution and dose adjustment • CYP3A4 inhibitors (e.g. azole antifungal drugs, some macrolides and PIs) can increase the level of bedaquiline. Substitution of the PI with an integrase inhibitor (e.g. dolutegravir or raltegravir) is suggested. If a ritonavir-boosted PI must be used, an ECG should be performed every 2 weeks for the first 8 weeks. Use with other medicines that direct or indirectly prolong the QT interval may cause additive prolongation that requires caution and monitoring. Such medicines include TB drugs (fluoroquinolones, clofazimine and delamanid) and ancillary and common drugs (azoles, macrolides, metoclopramide, efavirenz, furosemide, hydrochlorothiazide, citalopram, escitalopram, methadone, antiarrhythmics and others).

Food interactions	Administered with food; ideally, with high-fat meals (which increases the oral bioavailability).
Monitoring	Ideally, an ECG should be obtained before initiation of treatment, and at least 2, 12 and 24 weeks after starting treatment. Bedaquiline should be stopped if the QTc >500 msec, and ECGs and potassium levels should be monitored regularly until the QTc returns to normal. More frequent monitoring is recommended if cardiac conditions, hypothyroidism or electrolyte disturbances are present. Liver function tests should be done at baseline, then monthly.
Patient instructions and alerting symptoms	Medication is to be taken with food. Alcohol should be avoided. Patients should be instructed to inform their health care provider immediately if any of the following occur: • baseline heart problems, fast or irregular heartbeat, or if the patient faints; or • liver problems (hepatotoxicity): severe nausea or vomiting, stomach pain, jaundice, fever, weakness, itching, unusual tiredness, loss of appetite, light-coloured stool, dark-coloured urine, and yellowing of the skin or the whites of the eyes.

Clofazimine (C or Cfz) **Drug class: iminophenazine**	
Activity against M. tuberculosis, mechanism of action and metabolism	Target: M. tuberculosis cell wall; clofazimine is highly lipophilic and it interferes with the proton-motive force, leading to membrane- destabilizing effects and, ultimately, ATP production. Activity: Studies suggest bactericidal and sterilizing effect. Half-life and excretion: Tissue half-life is estimated to be around 25–70 days. Metabolized by the liver and very slowly eliminated, mainly by bile in the faeces.
Cross-resistance	Cross-resistance has been reported between bedaquiline and clofazimine through efflux pump-mediated resistance and others.
Dose	• Adults: 100 mg daily (upper daily dose is 100 mg). • Children: See Table 4.8 for weight-based dosing in adults and children. • Renal failure or dialysis: No adjustment required. See Table 4.8 for weight-based dosing in adults and children.
Administration	Oral. Capsules should be taken whole. Tablets can be taken whole or dispersed. Clofazimine tablets dissolve slowly (~5 minutes) in water (5 mL and 10 mL for the 50 mg and 100 mg tablets, respectively). The suspension should be stirred before administration.
Formulation and preparation	50 mg tablets or capsules. 100 mg tablets or capsules.
Storage	Should be stored below 30 °C. Capsules should be protected from moisture.
Oral absorption	70% absorption after an oral dose.
CSF penetration	There are limited data available regarding CNS penetration.

Special circumstances	Use during pregnancy or breastfeeding: There are limited data; recommended during pregnancy when benefits outweigh risk. The drug passes into human breast milk. Infants exposed to it in utero or during breastfeeding may appear more deeply pigmented. Use in renal disease: No dosage adjustment required. Use in hepatic disease: Partially metabolized by the liver; use caution or adjust the dose for severe hepatic impairment.
Adverse reactions	Overall tolerance: Well tolerated. Common: In 75–100% of patients receiving clofazimine there will be an orange, pink or brownish-black discolouration of the skin, conjunctivae and bodily fluids (owing to deposits, primarily in fatty tissues). The drug is often rejected by adolescents or in societies where body image is highly important. Also causes dry skin (ichthyosis and xerosis) and itching. Frequent: QT prolongation (10–20 msec). Uncommon: Photosensitivity, abdominal pain and obstruction or bleeding, due to the deposition of drug and formation of crystals in the intestinal mucosa.
Contraindications	Allergy to clofazimine.
Drug interactions	Use with other medicines that direct or indirectly prolong the QT interval may cause additive prolongation that requires caution and monitoring: • anti-TB drugs: fluoroquinolones, bedaquiline and delamanid; and • ancillary and common drugs: azoles, macrolides, metoclopramide, efavirenz, furosemide, hydrochlorothiazide, citalopram, escitalopram, methadone, antiarrhythmics and others.
Food interactions	To be administered with a meal, to avoid stomach upset and improve absorption.
Monitoring	Monitor clinical signs and symptoms. Perform ECG if other QT interval-prolonging agents are given concomitantly.
Patient instructions and alerting symptoms	To be taken with food to avoid stomach upset and improve absorption. May discolour skin and body secretions to orange, pink or brownish- black. This effect goes away after stopping the medicine but may take a long time to do so (months to years). Patients should avoid the sun and use strong sunscreens. Patients should be instructed to inform their health care provider immediately if any of the following occur: • abdominal pain, severe nausea, vomiting, black stools or diarrhoea.

Cycloserine (Cs) or terizidone (Trd) **Drug class: analogue of D-alanine**	
Activity against M. tuberculosis, mechanism of action and metabolism	Cycloserine (Cs) or terizidone (Trz) are considered equivalent drugs and are commonly used interchangeably. Terizidone is formed by two molecules of cycloserine combined. There is no significant safety difference between the two drugs. Target: M. tuberculosis cell wall. These drugs block the formation of the peptidoglycan layer (which has a structural role, especially in the Gram-positive cell wall). Activity: Bactericidal or bacteriostatic (low bactericidal activity), depending on concentration. Half-life and excretion: Has a half-life of 10 hours. Renally excreted.
Cross-resistance	There is no cross-resistance with other drugs.

Dose[a]	• Adults: 10–15 mg/kg/day (upper daily dose is 1 g). • Children: See handbook Annex for weight bands. • Renal failure or dialysis: 250 mg once daily or 500 mg, thrice weekly; monitor drug concentrations, if possible, to keep peak concentrations <35 mcg/mL. Pyridoxine (vitamin B6): commonly used to limit cycloserine toxicity but there are insufficient data to support systematic administration of vitamin B6 to adults or children on these drugs. See Table 4.8 for weight-based dosing in adults and children.
Administration	Oral. Capsules should be taken whole. However, dissolving the content of the capsules in 10 mL of water and administering the volume corresponding to the correct milligram dose may facilitate administration in younger children, although bioavailability is uncertain.
Preparation	125 mg mini capsule (only available for cycloserine). 250 mg capsule.
Storage	Should be stored at room temperature (15–25 °C) in an airtight container. Protect from moisture.
Oral absorption	Modestly decreased by food (best to take on an empty stomach); not significantly affected by antacids or orange juice.
CSF penetration	Concentrations in CSF approach those in serum.
Special circumstances	Use during pregnancy or breastfeeding: Not well studied; there is exposition in utero and these drugs are present in milk but no teratogenicity has been documented. Use in renal disease: Cycloserine is cleared by the kidney and requires dose adjustment for renal failure (see under Dose section, above). Use with caution. Use in hepatic disease: These drugs are liver friendly, but hepatotoxicity and jaundice have been reported.
Adverse reactions	Overall tolerance: Variable; poorly tolerated by many patients due to common neuropsychiatric toxicity. Common: Inability to concentrate, lethargy, neuropathy (30%) and depression (10%). Frequent: Psychosis (7.6%). Occasional: Seizures (3%), jaundice, suicidal ideation and skin problems. Severe CNS side-effects can be associated with peak concentrations >35 mcg/mL but may also be seen in the normal therapeutic range, especially in patients with pre-existing mental health conditions.
Contraindications	Pre-existing significant neurological or mental health conditions including seizure disorders, depression, anxiety, psychotic disease, personality disorder or alcohol and other substance abuse.
Drug interactions	Increased risk of CNS toxicity when given with isoniazid. Co-administration with delamanid may increase the risk of neuropsychiatric adverse events, especially in children.
Food interactions	Best taken on an empty stomach, with juice or antacids. If food is taken, large high-fat meals should be avoided, as should alcohol, which increases the risk of convulsions.

Monitoring	Baseline and monthly monitoring for depression should be done using a tool (e.g. the Beck Depression Index). If therapeutic drug monitoring is possible, peak concentrations should be obtained within the first 1–2 weeks of therapy and monitored serially during therapy. The peak concentration should be kept at <35 mcg/mL. When administering delamanid and cycloserine concurrently, monitoring for neuropsychiatric side-effects is important. These events should be reported through the national pharmacovigilance system.
Patient instructions and alerting symptoms	Patients should be instructed to inform their health care provider immediately if any of the following occur: • seizures; • shakiness, trouble talking or thinking or loss of memory; • depression or thoughts of hurting themselves or others; and • anxiety, confusion or personality changes (e.g. aggressive behaviour).

Delamanid (Dlm) **Drug class: nitro-dihydro-imidazooxazole (nitroimidazole)**	
Activity against M. tuberculosis, mechanism of action and metabolism	Target: M. tuberculosis cell wall. Inhibits the synthesis of methoxy- mycolic and keto-mycolic acid, which are mycobacterial cell wall components. Activity: Bactericidal, potent in vitro activity. Potential sterilizing activity as nitroimidazooxazole derivatives are thought to generate reactive nitrogen species, including nitrous oxide, which causes cell poisoning. Half-life and excretion: The prodrug is activated by mycobacterial nitroreductase and binds tightly to plasma proteins. It is metabolized mainly by albumin and to a lesser extent by the CYP3A4 isoenzyme in the liver (cytochrome P450). The half-life is 30–38 hours. It is excreted primarily in the faeces, with less than 5% excretion in the urine.
Cross-resistance	There is limited published information about resistant mutations, frequencies and their correlation with clinical relevance.
Dose[a]	• Adults: 200 mg daily (upper daily dose is 200 mg). • Children: No age restriction. Dispersible tablets are the preferred option. See Table 4.8 for weight-based dosing in adults and children. • Renal failure or dialysis: No dose adjustment needed for mild- to-moderate renal insufficiency; there are no data regarding use in patients with severe renal impairment. Initially, delamanid is not recommended for patients with severe renal impairment.
Administration	Oral. The use of the 25 mg dispersible tablet formulation is preferred in children. Delamanid adult tablets (50 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole, and they can be used in young children or people who cannot swallow tablets whole if the dispersible tablet formulation is not available.
Formulation and preparation	25 mg dispersible tablet. 50 mg film-coated tablets.
Storage	Should be stored at room temperature (15–25 °C) and in the original package, to protect from moisture.
Oral absorption	Absorption is increased with a standard meal (about 2.7-fold compared with fasting); 25–47% of the delamanid dose is absorbed following oral administration with food.

CSF penetration	One study suggests that, despite relatively low total CSF drug levels, delamanid achieves adequate concentrations in brain tissue and the oral formulation may be sufficient to have a role in treating TB meningitis.
Special circumstances	Use during pregnancy or breastfeeding: Data on the use of delamanid in pregnancy are limited. Animal data show no evidence of teratogenicity. The manufacturer allows its use in pregnant women in their compassionate-use protocol. Although the case series of pregnant women on delamanid is small, all neonates had excellent birth outcomes, suggesting that pregnant women in need should not be denied access. In animals, delamanid and its metabolites appeared in breast milk. There is no information from studies in humans, but it is usually not recommended during breastfeeding. Use in renal disease: No dosage adjustment is required in patients with mild-to-moderate renal impairment, but delamanid is not recommended for patients with severe renal impairment. Use in hepatic disease: No dosage adjustment is required in patients with mild hepatic impairment, but delamanid is not recommended in patients with moderate-to-severe hepatic impairment. Use in cardiac disease: Patients with various cardiac risk factors, including QTc interval prolongation, should not receive delamanid unless the potential benefits of treatment are expected to outweigh the possible risks. For all patients, an ECG is recommended before starting treatment, and then monthly throughout treatment. Patients with serum albumin levels <3.4 g/mL (but at least 2.8 g/mL) or with cardiac risk factors should receive more frequent ECG monitoring. Serum electrolytes should be checked and corrected as needed. Use in malnourished patients: Delamanid is contraindicated in patients with serum albumin levels <2.8 g/mL. However, recent PD and PK studies suggest no alterations linked to albumin levels. Use beyond 6 months and in combination with bedaquiline is considered safe.
Adverse reactions	Overall tolerance: Well tolerated, low toxicity profile. Occasional: QTc prolongation (5–15 msec average, peak at 8 week). Overall QTc prolongation in cohorts using delamanid, bedaquiline and other QTc-prolonging drugs was 2.7%, with median appearance at 2.5 months, with no cardiac deaths reported. Other effects are nausea, vomiting, dizziness, insomnia, anxiety, hallucinations, night terrors and upper abdominal pain.
Contraindications	Hypersensitivity to delamanid. Serum albumin levels <2.8 g/mL. Use with caution in patients sensitive to lactose. Discontinue or do not use in the presence of: • clinically significant ventricular arrhythmia; • QTcF interval of >500 msec (confirmed by repeat ECG); • severe liver disease; or • abnormal electrolytes. Use with caution in situations that may increase QT interval: In patients aged >60 years, heart failure, long QT syndrome, history of TdP, hypokalaemia, untreated hypothyroidism, low BMI, HIV infection and concomitant use of other QT-prolonging drugs. Any syncopal event (e.g. fainting) or palpitations should prompt an immediate medical evaluation and ECG. In several retrospective cohort studies on the incidence of QTc prolongation and cardiac events, the increase is modest and no arrhythmias or related deaths were reported, even with bedaquiline and delamanid co-administration.
Drug interactions	Low potential for drug–drug interactions. Concomitant administration of strong CYP3A inducers (e.g. rifampicin and

	carbamazepine) should be avoided. Co-administration with strong CYP3A inhibitors (e.g. ritonavir and ketoconazole): frequent monitoring of ECG should be considered. No interactions have been found between delamanid, dolutegravir and the main antiretroviral drugs. Delamanid may attenuate vitamin K-dependent blood clotting, and increase prothrombin time and activated partial thromboplastin time. Use with other medicines that directly or indirectly prolong the QT interval may cause additive prolongation, which requires caution and monitoring: • anti-TB drugs: fluoroquinolones, clofazimine and bedaquiline; and • ancillary and common drugs: azoles, macrolides, metoclopramide, efavirenz, furosemide, hydrochlorothiazide, citalopram, escitalopram, methadone, antiarrhythmics and others. Co-administration with cycloserine may increase the risk of neuropsychiatric adverse events, especially in children.
Food interaction	Delamanid should be taken with food, and alcohol should be avoided.
Monitoring	Before initiating delamanid, it is important to ensure that the albumin level is 2.8 g/dL or higher. ECG and baseline electrolytes should be obtained whenever possible before the initiation of treatment, and repeated if necessary (e.g. documented QTc prolongation or multiple QTc-prolonging risk factors). When administering delamanid and cycloserine concurrently, monitoring for neuropsychiatric side-effects is important. These events should be reported through the national pharmacovigilance system.
Patient instructions and alerting symptoms	Patients should be instructed to inform their health care provider immediately if any of the following occur: • history of heart problems, heart attack, congenital long QT syndrome or problems with heart rhythm; • liver or kidney disease; • HIV; or • pregnancy or planning to get pregnant.

Ethambutol (E) **Drug class: unspecified**	
Activity against M. tuberculosis, mechanism of action and metabolism	Target: M. tuberculosis cell wall. It inhibits the synthesis of arabinogalactan and lipoarabinomannan (special cell wall layer typically from Mycobacterium species), preventing division. Activity: Low bactericidal activity (bacteriostatic; 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 to other drugs. Half-life and excretion: has a half-life of 3.3 hours; mainly renal excretion (20–22% of a dose is eliminated unchanged in the faeces).
Cross-resistance	Not reported.
Dose[a]	• Adults: 15–25 mg/kg/day. Upper daily dose 1200 mg. • Children: See Table 4.8 for weight-based dosing in adults and children. • Renal failure or dialysis: 15–25 mg/kg/dose, thrice weekly (not daily). See Table 4.8 for weight-based dosing in adults and children.
Administration	Oral.
Formulation and preparation	100 mg dispersible tablets. 400 mg film-coated tablets. Crushing and dissolving 400 mg tablets in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole, and avoids fractioning solid formulations, although the bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	Should be stored below 30 °C.
Oral absorption	Has 80% bioavailability, independent of food intake.
CSF penetration	Penetrates meninges poorly.
Special circumstances	Use during pregnancy or breastfeeding: Ethambutol is considered safe in pregnancy; it can be used while breastfeeding but may appear in breast milk. Use in renal disease: Should be used with caution; ethambutol is cleared by the kidneys. Dose adjustment is required (see under Dose section, above) because there is an increased risk of toxicity. Use in obesity: Risk of chronic overdose; dose adjustment is required (see under Dose section, above). Use in hepatic disease: Considered safe.
Adverse reactions	Overall tolerance: Well tolerated; side-effects are commonly related to chronic overdose (e.g. wrong prescription, renal failure or overdose in obesity). Occasional: Decrease in visual acuity and colour vision (retrobulbar neuritis). The effect may be related to dose and duration of treatment; ethambutol should be stopped in cases of optic neuritis because irreversible blindness has been reported. Uncommon: Liver toxicities.
Contraindications	Pre-existing optic neuritis or severe visual problems; visual changes after ethambutol use.
Drug interactions	Low potential for drug–drug interactions. No major interactions with CYP450. Concomitant use with aluminium hydroxide-containing antacid should be avoided for at least 4 hours after ethambutol administration.
Food interactions	No interaction; food may reduce gastrointestinal irritation.

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. Each eye must be tested separately and both eyes tested together.
Patient instructions and alerting symptoms	Can be taken with food or on an empty stomach. Patients should be instructed to inform their health care provider immediately if any of the following occur: Any problems with vision changes, blurring, colour blindness, trouble seeing or eye pain.

Ethionamide (Eto) or prothionamide (Pto) **Drug class: carbothionamides group, derivatives of isonicotinic acid**	
Activity against M. tuberculosis, mechanism of action and metabolism	Ethionamide and prothionamide (a propyl-analogue of ethionamide) are both thioamides; they have similar efficacy and are considered interchangeable; however, ethionamide is more widely available. As with pyrazinamide, they are nicotinic acid derivatives related to isoniazid. Target: M. tuberculosis cell wall. Ethionamide and prothionamide are pro-drugs. Following enzymatic activation by mycobacterial EthA, the active metabolite inhibits the inhA enzyme, which is responsible for mycolic acid synthesis (mycolic acid is an essential part of mycobacterium cell wall), with a similar mechanism to isoniazid. Activity: Weak bactericidal (depending on the concentration of the drug attained in tissues, mostly bacteriostatic). Half-life and excretion: Has a half-life of 2–3 hours. Excreted via hepatic metabolism.
Cross-resistance	There is complete cross-resistance between ethionamide and prothionamide. In the case of mutation in the inhA gene, there is cross-resistance with isoniazid (high-level ethionamide and prothionamide resistance, but low-level resistance to isoniazid).
Dose[a]	• Adults: 15–20 mg/kg/day; upper daily dose is 1 g. Once-daily dosing is advised but clinicians can use 2 divided doses if tolerance is a problem, or until tolerance improves. Many individuals require gradual ramping up of the dose and treatment due to gastrointestinal upset. • Children: See Table 4.8 for weight-based dosing in adults and children. • Renal failure or dialysis: No change. • Pyridoxine (vitamin B6): There are insufficient data to support the systematic administration of vitamin B6 to adults or children receiving ethionamide and prothionamide. See Table 4.8 for weight-based dosing in adults and children.
Administration	Oral. • Crushing and dissolving 250 mg tablets in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; this avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Formulation and preparation	125 mg dispersible tablet (only ethionamide). 250 mg film-coated tablets (ethionamide and prothionamide).
Storage	Should be stored below 30 °C in a dry place.

Oral absorption	Has almost full oral bioavailability but there is potential for erratic absorption, possibly owing to associated gastrointestinal disturbances.
CSF penetration	Concentrations approach those in the serum; one paediatric study evaluating drug concentrations in the CSF suggested that ethionamide should be dosed at the higher end of the dose range for patients with meningitis.
Special circumstances	Use during in pregnancy or breastfeeding: These drugs are generally avoided during pregnancy owing to increased nausea and vomiting, risk of decreased TSH (fundamental for pregnant woman and the fetus) and limited reports of teratogenicity. TSH levels should be monitored and supplemented if necessary to prevent congenital hypothyroidism. There are few data about the use of these drugs during breastfeeding: it is estimated that 20% of the infant therapeutic dose will be passed on to the baby in breast milk (the infant should be supplemented with vitamin B6 if breastfed). Children: TSH levels should be monitored, and supplemented if necessary to avoid growth failure and permanent intellectual disability. Use in renal disease: No precautions are required for renal impairment. Use in hepatic disease: These drugs can cause hepatotoxicity similar to that seen with isoniazid; they should be used with caution in liver disease.
Adverse reactions	Overall tolerance: Poorly tolerated. Common: Most patients (adults and children) will experience dose-related gastrointestinal intolerance with ethionamide and prothionamide, resulting in nausea, vomiting, metallic taste, anorexia, abdominal discomfort, diarrhoea and weight loss. Symptoms are moderated by food or by taking the drugs at bedtime. Many individuals require gradual ramping up of the dose and treatment due to gastrointestinal upset. Premedication with an antiemetic is often helpful. Gastrointestinal upset may increase with concomitant use of para- aminosalicylic acid. Occasional: Hypothyroidism in adults is usually subclinical and reversible but has potential important consequences in pregnant woman and children, requiring monitoring of TSH and supplementation with levothyroxine. The risk of hypothyroidism increases when the drugs are used with para-aminosalicylic acid. Hepatotoxicity may occur, and the risk is increased by the concomitant use of rifampicin. Neurological side-effects (e.g. convulsions) may be exaggerated in patients also taking cycloserine. Uncommon: Gynaecomastia, hair loss, acne, impotence and menstrual irregularity.
Contraindications	Sensitivity to ethionamide and prothionamide or isoniazid.
Drug interactions	Temporarily raises serum concentrations of isoniazid. No major drug- drug interactions have been found but there is the potential for increased side-effects in the presence of other anti-TB medication (para-aminosalicylic acid, cycloserine, isoniazid and rifampicin).
Food interactions	Can be taken with or without food. Taking ethionamide and prothionamide with food may reduce gastrointestinal upset. Alcohol ingestion should be avoided because it may increase the risk of psychotic reactions.
Monitoring	TSH should be monitored for evidence of hypothyroidism requiring replacement therapy; therapeutic drug monitoring is required if malabsorption is suspected. Liver function tests should be monitored.

Patient instructions and alerting symptoms	Should be taken with food. Patients should be instructed to inform their health care provider immediately if any of the following occur: • convulsions, personality changes such as depression, confusion or aggression; • severe nausea and vomiting or dehydration; • yellowing of skin or eyes or dark-coloured urine; or • swollen breasts.

Imipenem-cilastatin (Ipm-Cln) **Drug class: beta-lactam - carbapenem**	
Activity against M. tuberculosis, mechanism of action and metabolism	Target: M. tuberculosis cell wall. Imipenem is a beta-lactam antibiotic belonging to the subgroup of carbapenems. It needs to be used in combination with clavulanic acid to block the ß-lactamase secretion present in bacteria such as M. tuberculosis, which otherwise inactivates most penicillins. Carbapenems have several mechanisms of action, including inactivating the penicillin-binding proteins and transpeptidases, inhibiting the biosynthesis of the peptidoglycan layer of the bacterial cell wall (creating lysis) or interfering with cell wall formation. Activity: Bactericidal and probably sterilizing activity. Half-life and excretion: Imipenem is rapidly degraded by renal proximal tubule dipeptidases; therefore, it is used in combination with the dipeptidase inhibitor cilastatin. Following IV injection, imipenem hasa half-life of 1 hour; following IM injection, it has a half-life of 1.3–5.1 hours. Cilastatin is partially metabolized renally. Imipenem is mainly excreted in the urine (70%).
Cross-resistance	Imipenem and meropenem may have cross-resistance, but evidence about M. tuberculosis is limited.
Dose[a]	These drugs should not be used in children aged <15 years. • Adults: 1000 mg twice daily. Upper daily dose 2000 mg. • Renal failure or dialysis: Adjustment in dose based on severity of renal failure; for example, 750 mg every 12 hours for creatinine clearance of 20–40 mL/min or 500 mg every 12 hours for creatinine clearance <20 mL/min. See the handbook Annex for weight-based dosing in adults.
Administration	No oral absorption. It can be administered IV or IM. Every dose is to be preceded by 30–60 minutes of administration of clavulanate (see amoxicillin–clavulanic acid medicine information sheet for dosing). IV: The infusion must be given slowly and can take 20–60 minutes to complete (or even longer in case of nausea). For long-term use as part of TB treatment, consider insertion of a peripherally inserted central catheter line.
Formulation and preparation	Powder for injection, 500 mg/500 mg in 10 mL vial.
Storage	The powder should be kept at room temperature (15–25 °C); the reconstituted product should be used within 2 hours and not frozen. Any unused product or waste material should be disposed of in accordance with local requirements.
Oral absorption	-
CSF penetration	Good CSF penetration. Meropenem is usually preferred for TB meningitis and for children because of the increased risk of seizures associated with use of imipenem.

Special circumstances	Use during pregnancy or breastfeeding: There is limited information regarding the use of this medicine in pregnancy; safety during breastfeeding is unknown. Use in renal disease: Dose adjustment is required (see under Dose section above); dose after dialysis. Use in hepatic disease: Elevated liver function test levels have been noted in up to 6% of patients, but no definite liver damage has been documented.
Adverse reactions	Overall tolerance: Poorly tolerated, owing to the disruption of daily life from lengthy infusions and the care of a peripherally inserted central catheter line, which may be needed for many months. Frequently: Diarrhoea, nausea or vomiting; yeast infection (thrush). Occasional: Pseudomembranous colitis (overgrowth of Clostridioides difficile). Uncommon: Seizures (noted with CNS infection), palpitations.
Contraindications	Carbapenem intolerance. Meningitis (use meropenem rather than imipenem-cilastatin).
Drug interactions	Low potential for drug-drug interactions. Ganciclovir: Increased risk of convulsions. Valproate: Imipenem reduces serum concentrations of valproate. Avoid concomitant use.
Food interactions	None.
Monitoring	Monitor clinical signs and symptoms.
Patient instructions and alerting symptoms	Ask patient about concomitant medication with ganciclovir or history of allergy to penicillins or cephalosporins. Patients should be instructed to inform their health care provider immediately if any of the following occur: • severe diarrhoea (watery or bloody); • seizures or epilepsy; or • fast or irregular heartbeat.

Isoniazid high dose (Hh) **Drug class: isonicotinic acid hydrazide**	
Activity against M. tuberculosis, mechanism of action and metabolism	Target: The M. tuberculosis cell wall. Isoniazid is a prodrug that after activation by the enzyme katG (bacterial catalase), blocks the action of the inhA enzyme that is responsible for the biosynthesis of mycolic acids, a major component of mycobacterial cell walls. Isoniazid is a first-line TB medicine that may be an effective as a second-line agent if used at high doses in the absence of high-level resistance. Activity: Strongly bactericidal against actively growing intracellular and extracellular M. tuberculosis. To date, isoniazid is considered the most bactericidal of the first-line and second-line drugs. Half-life and excretion: Primarily hepatic metabolism (N-acetyl transferase). The half-life is 0.5–1.6 hours in fast acetylators and 2–5 hours in slow acetylators (the acetylation rate in humans is genetically determined). Isoniazid is 50–70% excreted in the urine.
Cross-resistance	Mutations in the inhA promoter region may cause low-level resistance to isoniazid and resistance to thionamides.

Dose[a]	In DR-TB, a higher dose of isoniazid may be used as part of a shorter 9-month regimen. • Adults: 10–15 mg/kg/day. Standard daily dose is 300 mg/kg; high dose is 600 mg. • Children: See Table 4.8 for weight-based dosing in adults and children. • Renal failure or dialysis: 300 mg once daily. • Pyridoxine (vitamin B6): Should be used when high-dose isoniazid is administered. Pregnant and postpartum women and exclusively breastfed infants should always receive vitamin B6 while taking isoniazid. See the handbook Annex for weight-based dosing in children.
Administration	Oral.
Formulation and preparation	50 mg/5 mL oral solution. 100 mg dispersible tablets. 100 mg scored and unscored tablets. 300 mg scored and unscored tablets. Crushing and dissolving uncoated tablets (100 mg and 300 mg) in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; it also avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	The oral solution should be stored below 25–30 °C. Tablets should be stored below 30 °C and protected from light. The dispersible tablets should be protected from moisture.
Oral absorption	Well absorbed orally or intramuscularly. Best absorbed on an empty stomach (there is a >50% reduction in peak concentration if taken with a high-fat meal).
CSF penetration	Being a moderately lipophilic small molecule, the concentration in CSF is equivalent to that in plasma in inflamed meninges, but to only 20% of plasma concentrations in noninflamed meninges.
Special circumstances	Use during pregnancy or breastfeeding: Such use is not contraindicated. When breastfeeding, both infant and mother should receive pyridoxine supplementation. Use in renal disease: No dose adjustment is necessary in cases of renal failure, but pyridoxine supplementation should be used. Use in hepatic disease: It may exacerbate liver failure and should be used with caution.
Adverse reactions	Overall tolerance: Well tolerated. Frequently: Peripheral neuropathy: numbness, weakness, tingling, or burning pain in the hands or feet; nausea, vomiting and upset stomach; and abnormal liver function test results (transaminitis). Occasional: Hepatitis (higher risk in older age, alcohol misuse, pregnancy, viral hepatitis, fatty liver disease or nonalcoholic steatohepatitis and liver TB); and fever, chills, joint pain (arthralgia) and mild CNS effects (enhanced by concomitant use of cycloserine). Uncommon: Severe hypersensitivity (allergic) reaction; serious and sometimes fatal liver problems (more frequent in isoniazid monotherapy, less in rifampicin–isoniazid concomitant use); and drug-induced lupus.
Contraindications	Patients with high-level isoniazid resistance for whom an isoniazid- containing regimen has failed. History of allergic reaction to isoniazid or ethionamide or prothionamide.
Food interactions	Should be taken on an empty stomach (1 hour before or 2 hours after meals); absorption and bioavailability are reduced when administered with food. In case of stomach upset, isoniazid can be taken with a snack. Should be taken separately from antacids (which reduce absorption). Alcohol should be avoided because it may increase the risk of induced hepatitis and

	neuropathy. Caffeine and chocolate intake should be avoided, as should foods and supplements containing histamine and tyramine.
Drug interactions	Low potential for drug-drug interactions. Isoniazid is a weak CYP3A4 inhibitor and may increase the concentration of certain cytochrome P450 enzyme substrates such as phenytoin (increase concentration) and carbamazepine (risk of hepatotoxicity). Alcohol can lead to an increased risk of convulsions. There is an increased risk of CNS toxicity when isoniazid is given concomitantly with cycloserine.
Monitoring	Clinical monitoring and liver function testing should be undertaken, ideally monthly. 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.
Patient instructions and alerting symptoms	The medication should be taken on an empty stomach for better absorption. It should not be taken with a large fatty meal. In the case of stomach upset, isoniazid can be taken with a snack. The liquid suspension should not be refrigerated. Patients should avoid alcohol, antacids, chocolate, caffeine, and foods and supplements containing histamine and tyramine while taking this medicine. Patients should be instructed to inform their health care provider immediately if any of the following occur: • convulsions (seizures) or behavioural change; • flushing, sweating or headaches; • numbness, pain or tingling or burning of fingers or toes; • blurred vision or eye pain; • loss of appetite, tiredness, weakness, yellow skin or eyes or dark- coloured urine; or fever and skin rash that spreads and causes blistering and peeling.

Levofloxacin (Lfx) **Drug class: fluoroquinolone**	
Activity against M. tuberculosis, mechanism of action and metabolism	Target: Inner M. tuberculosis cell metabolism. A third-generation fluoroquinolone (along with moxifloxacin), it inhibits enzymes that are crucial for bacterial DNA replication. In M. tuberculosis it appears that DNA gyrase is the sole topoisomerase targeted. DNA gyrase is a tetrameric A_2B_2 protein (two A subunits and two B subunits). Inhibiting DNA gyrase (in any subunit) results in a blockade of DNA replication, inhibiting cell division and resulting in cell death of replicative and nonreplicative M. tuberculosis. The antimycobacterial activity of this fluoroquinolone depends on the molecule's affinity to target enzyme and efflux pumps, and the naturally low permeability of the M. tuberculosis cell wall. Activity: Levofloxacin is considered both highly bactericidal (excellent early bactericidal activity) and highly sterilizing. Half-life and excretion: The half-life of levofloxacin is 6–8 hours. It is mainly excreted unchanged in the urine.

Cross-resistance	In general, there is a class effect of cross-resistance among fluoroquinolones in vitro. Data suggest that levofloxacin and moxifloxacin may continue to demonstrate some activity, even against strains that have in vitro resistance to second-generation fluoroquinolones, such as ofloxacin. The pattern of resistance or susceptibility to the different fluoroquinolones depends on specific point mutation and is the subject of ongoing research.
Dose[a]	• Adults: 750–1125 mg/day (oral or IV); usually at least 750 mg/day, and the standard upper daily dose is 1.5 g. • Children: See Table 4.8 for weight-based dosing in adults and children. • Renal failure or dialysis: 750–1000 mg/dose, thrice weekly for creatinine clearance <30 mL/min. See Table 4.8 for weight-based dosing in adults and children.
Administration	Oral.
Formulation and preparation	100 mg dispersible tablet. 250 mg, 500 mg, 750 mg tablets film coated (may be scored in some markets). Crushing and dissolving film-coated tablets (100 mg and 300 mg) in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; it also avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	Should be stored below 30 °C, in a dry place, protected from light.
Oral absorption	Excellent oral absorption. Absorption can be reduced by ingestion of aluminium or magnesium antacids, sucralfate, metal cations (e.g. iron and multivitamin preparations with zinc). When use of these products is necessary, they should be administered at least 2 hours before or 2 hours after the fluoroquinolone.
CSF penetration	In general, fluoroquinolones achieve an effective concentration in the brain and meninges. Levofloxacin concentrations are at least 65% of the concentration in serum. Levofloxacin is also widely bioavailable in other organs and body fluids. It has been successfully used in the treatment of TB meningitis.
Special circumstances	Use during pregnancy or breastfeeding: It has been associated with arthropathy in canine models. There have been multiple case reports of fluoroquinolones being used safely in humans during pregnancy and breastfeeding. 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. It is presumed to be safe in severe liver disease. Marfan syndrome, Ehlers–Danlos syndrome or steroid use: Increased risk of tendon or aorta lesions • Diabetes: Increased risk of hypoglycaemia. • Long QT syndrome (patient or family member), hypokalaemia, malnutrition, hypothyroidism in those aged >60 years, multiple QT-prolonging drugs: Increased risk of QTc prolongation.
Adverse reactions	Overall tolerance: Generally well tolerated, with low potential for acute toxicity. Common: Diarrhoea, nausea and bloating, and arthralgia. Occasional: QTc interval prolongation (levofloxacin is considered safer than moxifloxacin); may decrease or alter glycaemia (this is true of all third-generation fluoroquinolones); and tendon rupture, especially Achilles tendon.

	Uncommon: Peripheral neuropathy, mood or behaviour changes, insomnia and aortic dissection.
Contraindications	Fluoroquinolone intolerance. It should be used with caution in situations that may increase the QT interval: patients aged >60 years, heart failure, long QT syndrome, history of TdP, hypokalaemia, untreated hypothyroidism, low BMI, HIV infection and concomitant use of other QT-prolonging drugs. Any syncopal event (e.g. fainting) or palpitations should prompt an immediate medical evaluation and ECG. In several retrospective cohort studies on the incidence of QTc prolongation and cardiac events, the increase was modest, and no arrhythmias or related deaths were reported even with co-administration of bedaquiline and delamanid. Discontinue or do not use in the presence of: • clinically significant ventricular arrhythmia; • a QTcF interval of >500 msec (confirmed by repeat ECG); or abnormal electrolyte levels.
Drug interactions	Low potential for drug–drug interactions. Concomitant steroid use may increase risk of tendon rupture. Multivalent cation-containing products including antacids and metal cations may decrease absorption. The intravenous formulation should not be co-administered through the same IV line as a multivalent cation, such as magnesium. Warfarin: The effect of this drug may be enhanced. Prothrombin time and INR should be monitored, and the patient should be monitored for bleeding. Antidiabetic agents: Carefully monitor blood glucose.
Food interactions	Can be taken with or without food, without a clinically significant impact on absorption or bioavailability. There are no major interactions between milk or dairy products and third-generation fluoroquinolones. Antacids (especially those containing aluminum), mineral supplements (e.g., iron or magnesium) or multivitamins should be taken more than 2 hours before or after this medication.
Monitoring	No specific laboratory monitoring is required. Ideally, an ECG should be obtained before initiation of treatment, and at least 2, 12 and 24 weeks after starting treatment. Levofloxacin should be stopped if the QTc >500 msec, and ECGs and potassium should be monitored frequently until the QTc returns to normal. More frequent monitoring is recommended if cardiac conditions, hypothyroidism or electrolyte disturbances are present.
Patient instructions and alerting symptoms	This medication should be taken with or without food. Antacids (especially aluminum-containing ones), mineral supplements (e.g., iron or magnesium), or multivitamins should be taken more than 2 hours before or after of this medication. This medicine may cause sun sensitivity; sunscreens should be used. Patients should be instructed to inform their health care provider immediately if any of the following occur: • pain, swelling or tearing of a tendon (such as the back of your ankle, elbow), or muscle or joint pain; • severe diarrhea (watery or bloody); • seizures, epilepsy, change in mood or behavior; or low blood sugar symptom (i.e., headache, hunger, sweating, irritability, dizziness, nausea, fast heart rate, or feeling anxious or shaky).

Linezolid (L or Lzd) **Drug class: oxazolidinones**	
Activity against M. tuberculosis, mechanism of action and metabolism	Target: Bacterial ribosome. Linezolid blocks protein synthesis at the bacterial ribosome. It interferes with translation of the bacterial mRNA into proteins by binding to the 23S ribosomal RNA component (part of the large ribosome subunit). Without the capacity to synthesize proteins, bacterial reproduction and subsistence is not possible. Activity: Has modest early bactericidal activity in vitro, and probable sterilizing and excellent bioavailability in tissues. Half-life and excretion: Maximum plasma concentrations are reached in about 1–2 hours after dosing. The half-life is estimated as 5–7 hours. About 31% binds to plasma proteins (mainly albumin). It is primarily metabolized by the liver (biotransformation routes are unclear) and subsequently eliminated by the kidneys, with minor faecal elimination.
Cross-resistance	Cross-resistance between linezolid and other oxazolidinones in M. tuberculosis is not fully documented.
Dose[a]	• Adults: 600 mg, once daily, upper daily dose is 1.2 g. • Children: See Table 4.8 for weight-based dosing in adults and children. • Renal failure or dialysis: No dose adjustment is required. However, accumulation of the two primary metabolites may occur; hence, it should be used with caution. • Pyridoxine (vitamin B6): There are insufficient data to support the systemic administration of vitamin B6 to adults or children on linezolid. However, some studies suggest an effect on myelotoxicity prevention and thrombocytopenia improvement. See Table 4.8 for weight-based dosing in adults and children
Administration	Oral.
Formulation and preparation	100 mg/5 mL powder for oral liquid. Following reconstitution, the solution should be mixed gently before administration; it should not be shaken. 150 mg dispersible tablet. 600 mg coated tablet. Crushing and dissolving film-coated tablets (600 mg) in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; also, it avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	The powder for the oral liquid should be stored below 25 °C, protected from light and moisture. The reconstituted suspension may be stored at room temperature for 21 days. Tablets should be stored below 25 °C, protected from light and moisture.
Oral absorption	It is extensively absorbed following oral administration and has an absolute bioavailability of about 100%.
CSF penetration	It has excellent CSF and brain penetration.
Special circumstances	In patients with pre-existing haematological conditions, it should be used with extreme caution. Use during pregnancy or breastfeeding: Studies in animals have shown evidence of an increased occurrence of fetal damage. There are limited data in humans but no reports of increased malformation or other direct or indirect harmful effects on the human fetus. Drug levels appear in breast milk at lower than the usual infant dose. Use in renal disease: No dose adjustment is recommended, but metabolites may accumulate. Use in hepatic disease: Despite hepatic metabolism, it is rarely associated with increased transaminases.

Linezolid (L or Lzd) **Drug class: oxazolidinones**	
	Use in diabetes mellitus: There is increased risk of lactic acidosis in patients being treated with metformin. Hypoglycaemia has been reported in patients receiving insulin or oral hypoglycaemic agents and linezolid. Use in patients with cerebrovascular or cardiovascular disease, pheochromocytoma, carcinoid syndrome or untreated hyperthyroidism: Linezolid may exacerbate symptoms of those conditions. Use in patient with depression: Administration of linezolid concurrently with even common SSRIs can lead to serious reactions such as serotonin syndrome or neuroleptic malignant syndrome- like reactions. See the sections on Adverse reactions and Drug interactions.
Adverse reactions	Overall tolerance: Poorly tolerated. Frequently/common: • Nausea, vomiting and diarrhoea. • Myelosuppression, which may manifest within the first 2 months of treatment with decreased platelet or white blood cell counts and anaemia. • Optic nerve toxicity and peripheral neuropathy tend to develop after several weeks of treatment and may lead to irreversible blindness or disabling permanent neuropathy. Nerve toxicity is usually a reason to stop linezolid. Occasional: Pseudomembranous colitis, vaginal candidiasis, hypoglycaemia, serotonin syndrome and lactic acidosis; and arrhythmia (tachycardia), transient ischaemic attacks, pancreatitis, seizures. Uncommon: Stevens–Johnson syndrome, angioedema and alopecia.
Contraindications	• Hypersensitivity to oxazolidinones. • If patient is taking another MAO inhibitor medication or has used one in the past 14 days, linezolid should not be taken. • Should be used with extreme caution with antidepressants, antimigraine and other medications (see section on Drug interactions, and balance risk of serotonin syndrome versus benefit). • Should not be used concomitantly with stavudine or didanosine. • Should be used with extreme caution with lamivudine, zidovudine and abacavir. • Should be used with extreme caution if metformin is used at a high dose; in such cases, it is best to consider a change to other oral antidiabetic medication or insulin to limit the risk of lactic acidosis. • Should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis or carcinoid syndrome.

Linezolid (L or Lzd) **Drug class: oxazolidinones**	
Drug interactions	There is a high potential for drug-drug interactions. There are no CYP450 enzyme system interactions but linezolid is an MAO inhibitor, and combination with other drugs may increase the risk of severe clinical conditions and linezolid-induced toxicities. Increased risk of pancytopenia: Zidovudine and co-trimoxazole. Increased risk of lactic acidosis: Metformin, stavudine, didanosine, lamivudine, zidovudine and abacavir. Increased risk of serotonin syndrome: Because linezolid is an MAO inhibitor, there is increased risk with SSRIs, SNRIs, TCAs, serotonin 5-HT1 receptor agonists, bupropion, anti-seizure medication, opioid analgesics, buspirone, antiemetics, anti-Parkinson's medication, sympathomimetic agents, vasopressive agents, dopaminergic agents and common medications used for influenza or congestion and bought over the counter such as dextromethorphan, pseudoephedrine , diphenhydramine or guaifenesin .
Food interactions	Oral absorption is not significantly affected by co-administration with food; thus, it may be taken with or without food, but taking with food may alleviate stomach irritation. Increased risk of tyramine toxicity: Patients should avoid tyramine-containing foods and supplements such as aged cheese, fava beans, cured foods, dried meats, pickled foods, sauerkraut, kimchi, soy sauce, teriyaki sauce, fish sauce and red wine, tap beers and liquors.
Monitoring	Patients should be monitored for: • peripheral neuropathy and optic neuritis, through visual eye acuity (both eyes) and Ishihara tests every 2 months or, if symptoms develop, clinical examination for peripheral neuropathy monthly; • complete blood count weekly during the initial period, then monthly, and thereafter as needed based on symptoms; and • pH, anion gap and lactate levels in case of suspected lactic acidosis (hyperlactatemia, if lactate >2.0 mmol/L and confirmed lactic acidosis at >4.0 mmol/L), hypotension, lethargy or clinicalworsening without a clear explanation.
Patient instructions and alerting symptoms	The medication can be taken with or without food but patients should avoid tyramine-containing foods (see list in Food interactions section, above). Patients should be asked about any medicines or supplements taken, especially metformin, antidepressants and common cold medications (see Drug interactions section above). Patients should be instructed to inform their health care provider immediately if any of the following occur: • pain, numbness, tingling or weakness in the extremities; • unusual tiredness, weakness, hypotension; • black, tarry stools or severe diarrhoea; • unusual bleeding or bruising; • changes in vision; or • headache, nausea or vomiting, sweating, rigidity, tremor, or change in mood, behaviour or consciousness.

Meropenem (Mpm) Drug class: beta-lactam – carbapenem	
Activity against M. tuberculosis, mechanism of action and metabolism	Target: M. tuberculosis cell wall. Meropenem is a beta-lactam antibiotic belonging to the subgroup of carbapenems. It must be used in combination with clavulanic acid to block the ß-lactamase secretion present in bacteria such as M. tuberculosis, which otherwise inactivates most penicillins. Carbapenems, through several mechanisms (e.g. inactivation of the penicillin-binding proteins and transpeptidases), inhibit the biosynthesis of the peptidoglycan layer of the bacterial cell wall, causing lysis or interfering with cell wall formation. Activity: Has bactericidal and probably sterilizing capacity. One study found a better efficacy profile with meropenem than with imipenem. Half-life and excretion: Meropenem is stable to renal dipeptidases and does not require cilastatin. It is mainly excreted in the urine (70%) and has a half-life of about 1–1.5 hours in adults and children.
Cross-resistance	Imipenem and Meropenem may have cross-resistance, but evidence with M. tuberculosis is very limited.
Dose[a]	• Adults: 1 g (20 mL) IV thrice daily or 2 g twice daily. Each dose is preceded by 125 mg clavulanate (administer clavulanic acid 60 minutes before each dose of meropenem). Upper daily dose is 6000 mg. • Children: See Table 4.8 for weight-based dosing in adults and children. • Renal failure or dialysis: The adjustment to the dose is based on the severity of renal failure; for example, 750 mg every 12 hours for creatinine clearance of 20–40 mL/min or 500 mg every 12 hours for creatinine clearance <20 mL/min.
Administration	IV only (no IM recommended); there is no oral absorption. Clavulanate should be given orally 30–60 minutes before an IV dose of meropenem (every 8 hours) For long-term use in TB, insertion of a peripherally inserted central catheter line should be considered.
Formulation and preparation	Powder for injection or infusion (1 g) is to be reconstituted (1 g in 20 mL) with water for injection or 0.9% sodium chloride or 5% glucose solution for infusion before administration.
Storage	Powder should be stored below 25–30 °C. Reconstituted solution storage conditions vary; hence, the specific product label should be checked.
Oral absorption	Not applicable
CSF penetration	Has adequate CSF penetration and is recommended in case of TB meningitis (where meropenem is preferred over imipenem).
Special circumstances	Use during pregnancy or breastfeeding: It is considered safe but there is little information regarding lengthy use in TB use during pregnancy. Meropenem is excreted into human milk, and its safety during breastfeeding is unknown. Use in renal disease: Dose adjustment is required in renal disease (see under Dose section, above); dose after dialysis. Use in hepatic disease: Liver disease does not alter the pharmacodynamics of meropenem.
Adverse reactions	Overall tolerance: It is poorly tolerated because of important disruption to daily life owing to IV administration and the need to care for a peripherally inserted central catheter line, sometimes for many months. Frequently: Headache, diarrhoea, nausea or vomiting, and yeast infection (thrush). Occasional: Anaemia and pseudomembranous colitis (overgrowth of Clostridioides difficile). Uncommon: Seizures (noted with CNS infection), but rare compared with imipenem; and elevated liver enzymes, haematologic toxicity and hypersensitivity.

Contraindications	Carbapenem intolerance.
Drug interactions	Low potential for drug–drug interactions. Co-administration of probenecid inhibits renal excretion of meropenem. Co-administration of valproic acid or divalproex sodium reduces the serum concentration of valproic acid, potentially increasing the risk of seizures.
Food interactions	None.
Monitoring	Monitoring of clinical signs and symptoms.
Patient instructions and alerting symptoms	The patient should be asked about concomitant medication with valproic acid and whether they are allergic to penicillins or cephalosporins. Patients should be instructed to inform their health care provider immediately if any of the following occur: • severe diarrhoea (watery or bloody); • skin rash, hives or itching; • pale skin, unusual tiredness; or swelling in the face, throat or lips, wheezing or trouble breathing.

Moxifloxacin (M or Mfx) **Drug class: fluoroquinolone**	
Activity against M. tuberculosis, mechanism of action and metabolism	Target: Inner M. tuberculosis metabolism. A third-generation fluoroquinolone (the other is levofloxacin), which inhibits enzymes that are crucial for bacterial DNA replication. In M. tuberculosis it appears that DNA gyrase is the sole topoisomerase targeted. DNA gyrase is a tetrameric A_2B_2 protein (two A subunits and two B subunits). Inhibiting DNA gyrase (in any subunit) results in blockade of DNA replication, inhibiting cell division and resulting in cell death of replicative and nonreplicative M. tuberculosis. The particular antimycobacterial activity of the third-generation fluoroquinolones depends on their molecule affinity to target enzymes and efflux pumps, and the naturally low permeability of the M. tuberculosis cell wall. Activity: Moxifloxacin is considered both highly bactericidal (it has excellent early bactericidal activity) and highly sterilizing. Based on in vitro data, moxifloxacin anti-TB activity is higher than the other current fluoroquinolones. Half-life and excretion: The half-life of moxifloxacin is 11.5– 15.3 hours. It is mainly metabolized via glucuronide and sulfate conjugation, and 45% is excreted as the unchanged drug in urine and faeces.
Cross-resistance	In general, there is a class effect of cross-resistance among fluoroquinolones in vitro. Data suggest that levofloxacin and moxifloxacin may continue to demonstrate some activity, even against strains that have in vitro resistance to second-generation fluoroquinolones such as ofloxacin. The pattern of resistance or susceptibility to particular fluoroquinolones depends on specific point mutations, which is the subject of ongoing research.
Dose[a]	• Adults: 400 mg daily (oral or IV). High dose is 600–800 mg daily, depending on weight band. • Children: See Table 4.8 for weight-based dosing in adults and children. • Renal failure or dialysis: No dose adjustment is required. See the handbook Annex for weight-based dosing in children and adults.
Administration	Oral.

Formulation and preparation	100 mg dispersible tablet (poor palatability; taste-masking studies are ongoing). 400 mg film-coated tablet. Crushing and dissolving film-coated tablets (400 mg) in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; also, it avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	Should be stored below 30 °C, protected from light. Dispersible tablets should be stored in a dry place.
Oral absorption	Has good oral absorption (90% bioavailable). It should be administered at least 4 hours before or 8 hours after antacids or other medications (e.g. iron, magnesium, calcium, zinc, vitamins and sucralfate), because they may interfere with absorption.
CSF penetration	In general, fluoroquinolones achieve an effective concentration in the brain and meninges. Moxifloxacin has good penetration in animal model studies and humans with TB meningitis, reaching high concentrations in the CSF in the presence and absence of meningeal inflammation. It has been used successfully in TB meningitis.
Special circumstances	Use during pregnancy or breastfeeding: Associated with arthropathy in canine models. there are multiple case reports of fluoroquinolones being used in humans safely during pregnancy and breastfeeding. Use in renal disease: Excretion is unchanged during renal failure; there are no data on the effect of dialysis. Use in hepatic disease: Moxifloxacin is rarely associated with hepatotoxicity, but should be used with caution. No dose adjustment is required for mild-to-moderate liver disease. Marfan syndrome, Ehlers–Danlos syndrome or steroids use: In these situations, there is increased risk of tendon or aorta lesions Diabetes: Increased risk of hypoglycaemia. Long QT syndrome (in the patient or a family member), hypokalaemia, malnutrition, hypothyroidism in patients aged >60 years or taking multiple QT prolonging drugs: Increased risk of QTc prolongation.
Adverse reactions	Overall tolerance: Generally well tolerated, with a low potential for acute toxicity Common: Diarrhoea, nausea and bloating, and arthralgia. Occasional: QTc interval prolongation (it is considered the most QTc-prolonging of the fluoroquinolones, causing an estimated QTc increase of 10–20 msec). Headache and dizziness. All third- generation fluoroquinolones may cause dysglycaemia. Tendon rupture, especially Achilles tendon. Uncommon: Peripheral neuropathy; mood or behaviour changes; insomnia; disturbances in mental abilities; aortic aneurysm rupture and aortic dissection.
Contraindications	Fluoroquinolone intolerance. Use with caution in situations that may increase QT interval: Patients aged >60 years, heart failure, long QT syndrome, history of TdP, hypokalaemia, untreated hypothyroidism, low BMI, HIV infection, concomitant use of other QT prolonging drugs. Any syncopal event (e.g. fainting) or palpitations should prompt an immediate medical evaluation and ECG. In several retrospective cohort studies on the incidence of QTc prolongation and cardiac events, the increase was modest and no arrhythmias or related deaths were reported, even with co-administration of bedaquiline and delamanid. Discontinue or do not use in the presence of: • clinically significant ventricular arrhythmia; • a QTcF interval of >500 msec (confirmed by repeat ECG); or • abnormal electrolyte levels.

Drug interactions	Low potential for drug–drug interactions (the cytochrome P450 system is not involved in metabolism). Concomitant steroid use may increase the risk of tendon rupture. Multivalent cation-containing products (including antacids and metal cations) may decrease absorption. Warfarin: The effect of moxifloxacin may be enhanced. Prothrombin time and INR should be monitored, as should bleeding. Antidiabetic agents: Blood glucose should be carefully monitored. Concomitant use with antiarrhythmics Class IA (e.g., quinidine, ajmaline and disopyramide) and Class III (e.g. amiodarone, dronedarone and sotalol) should be avoided because the proarrhythmic effect may be enhanced.
Food interactions	Can be taken with or without food; food has little effect on absorption. There are no major interactions with milk or dairy products in third-generation fluoroquinolones. Antacids (especially those containing aluminium), mineral supplements (e.g. iron or magnesium) or multivitamins should be taken more than 2 hours before or after of this medication.
Monitoring	Symptomatic monitoring. Ideally, an ECG should be obtained before initiation of treatment, and at least 2, 12 and 24 weeks after starting treatment. Moxifloxacin should be stopped if QTc >500 msec, and ECGs and potassium should be monitored frequently until the QTc returns to normal. More frequent monitoring is recommended if cardiac conditions, hypothyroidism or electrolyte disturbances are present.
Patient instructions and alerting symptoms	Can be taken with or without food. Antacids (especially those containing aluminium), mineral supplements (e.g., iron or magnesium) or multivitamins should be taken within 2 hours of this medication. Patients should be instructed to inform their health care provider Immediately if any of the following occur: • pain, swelling or tearing of a tendon (such as the back of your ankle, elbow), or muscle or joint pain. • severe diarrhoea (watery or bloody). • seizures, epilepsy, change in mood or behaviour; or • low blood sugar symptom (e.g. headache, hunger, sweating, irritability, dizziness, nausea, fast heart rate, or feeling anxious or shaky).

Para-aminosalicylic acid (PAS) **Drug class: salicylic acid – anti-folate**	
Activity against M. tuberculosis, mechanism of action and metabolism	Target: M. tuberculosis cell wall and inner metabolism. Probably inhibits folic acid synthesis and thus slows cell growth and multiplication. Para-aminosalicylic acid may inhibit the synthesis of mycobactin (a cell wall component) leading to a reduction of iron uptake by M. tuberculosis and inhibiting cell wall synthesis. Activity: Very low bactericidal (bacteriostatic) activity. It is used as a companion drug to prevent resistance to other medicines. Half-life and excretion: the half-life of PAS is 1.5 to 2 hours, within 24 hours, more than 80% is excreted in the urine. More than 50% of the excreted PAS is acetylated.
Cross-resistance	No data available.
Dose[a]	• Adults: 8–12 g/day in 2–3 divided doses; upper daily dose is 12 g. Doses are given twice daily; however, if tolerated, the same dose can also be administered at one time. • Children: See Table 4.8 for weight-based dosing in adults and children. • Renal failure or dialysis: No dose modifications. See the handbook Annex for weight-based dosing in children and adults.
Administration	Oral. The powder should be reconstituted in water (100 mL) before administration.

	It should be taken with food to limit gastrointestinal disturbances.
Formulation and preparation	Sodium powder is used for the oral solution: 5.52 g sachet (equivalent to 4 g para-aminosalicylic acid).
Storage	Para-aminosalicylic acid sodium salt may be stored at room temperature.
Oral absorption	Absorption is incomplete, and sometimes requires increased doses to achieve therapeutic concentrations. Absorption is unaffected by food.
CSF penetration	Para-aminosalicylic acid poorly penetrates the meninges but penetrates better when the meninges are inflamed.
Special circumstances	Use during pregnancy or breastfeeding: The safety profile is unknown; however, it is used during pregnancy. There is limited information on its use while breastfeeding (a proportion goes into human milk). Use in renal disease: The inactive metabolite is cleared by the kidneys. It should be avoided in severe renal failure. Use in hepatic disease: It should be used with caution.
Adverse reactions	Overall tolerance: It is poorly tolerated. Common: Most patients experience gastrointestinal upset (although this is less with the Paser® formulation than with older preparations); nausea, vomiting, diarrhoea and abdominal pain. Frequently: Hypothyroidism in adults is usually subclinical and reversible but the consequences may be important in pregnant woman and children, necessitating TSH monitoring and levothyroxine supplementation. The risk of hypothyroidism increases when it is used with ethionamide and prothionamide. It reduces the absorption of vitamin B12; if significant erythrocyte abnormalities develop, vitamin B12 supplements should be considered. Uncommon: Hepatotoxicity and coagulopathy.
Contraindications	Allergy to aminosalicylic acid.
Drug interactions	There is a low potential for drug-drug interactions. Antacids cause fast dissolution of the acid-resistant coating, resulting in early release of para-aminosalicylic acid into the stomach. Ethionamide and prothionamide: If these are co-administered with para-aminosalicylic acid, it may intensify hypothyroidism and gastrointestinal effects (e.g., jaundice, hepatitis or hepatotoxicity, nausea, vomiting, diarrhoea, abdominal pain or anorexia). Rifamycins: Para-aminosalicylic acid reduces the absorption of rifamycins, and these drugs should be given 8–12 hours apart. Diphenylhydramine decreases the gastrointestinal absorption of para- aminosalicylic acid and should not be administered concomitantly.
Food interactions	The absorption is unaffected by food. Taking para-aminosalicylic acid with food may reduce gastrointestinal upset. To improve tolerance, it should be given sprinkled onto or stirred into yogurt or similar food.
Monitoring	Should monitor TSH, electrolytes, blood counts and liver function tests.
Patient instructions and alerting symptoms	It is better tolerated when taken with food. Gastrointestinal discomfort and diarrhoea usually improve over time. Patients should be instructed to inform their health care provider immediately if any of the following occur: • skin rash, severe itching or hives. • severe abdominal pain, nausea or vomiting. • unusual tiredness or loss of appetite; or black stools or bleeding.

Pretomanid (Pa) **Drug class: nitro-dihydro-imidazooxazole**	
Activity against M. tuberculosis, mechanism of action and metabolism	Target: M. tuberculosis cell wall and inner cell metabolism. Pretomanid is a prodrug that is metabolically activated by the Ddn enzyme or F420 co-enzyme, producing various active metabolites responsible for its anti-TB effects: • A des-nitro derivative is responsible for the induction of nitricoxide, leading to cell poisoning even in anaerobic conditions, and thus killing active and also dormant or latent bacteria. • Other metabolites inhibit mycolic acid biosynthesis, resulting in the inhibition of the bacterial cell wall biosynthesis. This mechanism is not yet fully understood, but data suggest that it involves the fasI and fasII, efpA and iniBAC cyd genes. Activity: It is bactericidal and has potent in vitro activity to kill actively replicating bacteria. It has excellent sterilizing capacity, as demonstrated in trials studying BPaL/BPaLM regimens. Half-life and excretion: It is a prodrug that requires bioactivation. It binds tightly to plasma proteins (86.4%). It has a half-life of 18 hours. Hepatic metabolism is by different routes, and no single major metabolic pathway has been identified. CYP3A4 (cytochrome P450) is responsible for 20% of its metabolism. About 53% is excreted in urine and 38% in faeces.
Cross-resistance	To date, there is limited published information about mutations that may lead to cross-resistance, their frequency, distribution and correlation with clinical relevance.
Dose[a]	• Adults: 200 mg once daily with food (upper daily dose is 200 mg). See the handbook Annex for weight-based dosing in the BPaLM/BPaL regimens. Pretomanid is not recommended by WHO for use in those aged <14 years.
Administration	Oral (it is better absorbed with food). Tablets should be taken whole; they should not be broken, crushed or chewed.
Formulation and preparation	200 mg tablet.
Storage	Should be stored below 30 °C and in the original package.
Oral absorption	Absorption is increased when it is taken with high-calorie and high- fat food.
CSF penetration	No data.
Special circumstances	Use during pregnancy or breastfeeding: There are no studies available on pretomanid use in pregnant women, and no pregnancy category has been assigned. Animal studies (of prenatal and postnatal development) showed changes in the fetus at toxic doses but not at equivalent doses used in humans. Pretomanid passes into breast milk. It is currently not recommended during pregnancy or breastfeeding. Use in renal disease: Safety, effectiveness and pharmacokinetics are unknown. Use in hepatic disease: Safety, effectiveness and pharmacokinetics are unknown. Use in cardiac disease: It is a QTc prolonging drug; hence, it should be used with caution in patients with predisposing factors for QTc interval prolongation. Use in malnourished patients: Unknown. Use beyond 6 months: Unknown. Use with caution in case of confirmed or suspected resistance to delamanid (potential cross-resistance).
Adverse reactions	Overall tolerance: Well tolerated. The most common toxicities reported related to pretomanid were headache (32%), nausea (12%), contact dermatitis (11%), decreased haemoglobin level (11%), diarrhoea (9%) and dizziness (8%). Adverse events of special interest: In animal studies, toxic effects attributable to

	pretomanid were ocular disorders and male reproductive toxicity; however, a recent review of available evidence reported no changes in male hormones in four clinical trials, suggesting no association between pretomanid-containing treatment and testicular toxicity. Current evidence is considered sufficient to address the relative safety of pretomanid (although it is thought unlikely to affect male fertility). Other adverse events include: • convulsions; • ECG QT prolongation: 5 msec average, without significant clinical consequences; • hepatotoxicity (increase in GGT); and • myelosuppression (anaemia). There are several studies ongoing to further evaluate the efficacy and safety of pretomanid alone or in combination with other medicines.
Contraindications	It is currently contraindicated in patients for whom bedaquiline or linezolid is contraindicated.
Drug interactions	There is low potential for drug–drug interactions. No major interactions had been reported but data are limited. If possible, concomitant administration of strong CYP3A inducers should be avoided. In studies, rifampicin decreases the pretomanid AUC by 66%, and nevirapine decreases the pretomanid AUC by 35%. It should be used with caution with other QTc-prolonging medicines.
Food interaction	It should be taken with food; alcohol should be avoided owing to increased risk of hepatotoxicity.
Monitoring	Signs and symptoms of hepatotoxicity should be monitored, and liver function tests monitored at baseline, at 2 weeks and then monthly as needed. The BPaL regimen has been associated with hepatic adverse reactions. ECG and baseline electrolytes should be obtained whenever possible before the initiation of treatment and repeated if needed (e.g. documented QTc prolongation or multiple QTc-prolonging risk factors).
Patient instructions and alerting symptoms	It should be taken with food. The tablet should be swallowed whole and should not be crushed, chewed or broken. Alcohol should be avoided. Patients should be instructed to inform their health care provider immediately if any of the following occur: • history of heart problems, heart attack, congenital long QT syndrome or problems with heart rhythm; • liver or kidney disease; • HIV; or • pregnancy or planning to get pregnant.

Pyrazinamide (Z) **Drug class: synthetic derivative of nicotinamide**	
Activity against M. tuberculosis, mechanism of action and metabolism	Target: Inner M. tuberculosis metabolism with potential multiple mechanisms. Pyrazinamide is a prodrug that, via the pyrazinamidase enzyme, is activated into pyrazinoic acid (active form); it is highly active in acidic conditions in which most drugs become inactive and bacilli enter into nonreplicating, or latent or dormant forms. Pyrazinamide is the prototype for drugs that specifically targets dormant or latent M. tuberculosis forms. Under acidic conditions (found inside macrophages and in inflammation and caseum), pyrazinoic acid enters the cell wall and may destroy M. tuberculosis by:

Pyrazinamide (Z) Drug class: synthetic derivative of nicotinamide	
	• accumulating intracellularly, leading to acid bacterial cytoplasm; • accelerating energy consumption: bacilli efflux pumps on the cell wall are constantly pumping pyrazinoic acid out of the cell; • disrupting membrane potential and interfering with energy production of bacilli in acid medium; • potentially inhibiting fatty acid synthesis; and • binding to the ribosomal protein S1 (RpsA) and inhibiting trans-translation. Activity: Pyrazinamide has potent sterilizing capacity; it is able to kill dormant or latent bacilli; however, it has weak or no bactericidal activity, because the drug is only active against bacilli in acid media. Half-life and excretion: Peak plasma concentrations are attained within 2 hours, and the half-life is 9–10 hours (under normal conditions). About 10% binds to plasma proteins. It undergoes hepatic metabolism and 70% is excreted in the urine (mainly by glomerular filtration within 24 hours).
Cross-resistance	None reported.
Dose[a]	• Adults: 20–30 mg/kg/day. Upper daily dose 2000 mg. • Children: See Table 4.8 for weight-based dosing in adults and children. • Renal failure or dialysis: 25 mg/kg/dose, thrice weekly (not daily). See Table 4.8 for weight-based dosing in adults and children
Administration	Oral.
Formulation and preparation	150 mg dispersible tablet. 400 mg tablet. 500 mg tablet. Crushing and dissolving uncoated tablets (400 mg and 500 mg) in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; also, it avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	Should not be stored above 25–30 °C. Dispersible tablets should be protected from moisture.
Oral absorption	Well absorbed from the gastrointestinal tract.
CSF penetration	Being a moderately lipophilic small molecule, concentrations in the CSF are equivalent to those in serum in patients with inflamed meninges.
Special circumstances	Use during pregnancy or breastfeeding: Has no known teratogenicity. It is distributed into breast milk but is commonly used while breastfeeding. Use in renal disease: It is cleared by the kidneys; dosage adjustment may be needed; for example, when changing to thrice weekly dosage and after dialysis. Use in hepatic disease: It should be used with caution. Patients with pre-existing liver disease (alcohol abuse, nonalcoholic steatohepatitis, chronic viral hepatitis or TB hepatitis) should be carefully monitored. It is associated with hepatotoxicity in about 1% of patients. Hepatotoxicity can be severe and can worsen treatment outcomes. Use in patients with gout: The drug to be avoided if the patient has frequent or ongoing gout. Use in diabetes mellitus: It should be used with caution.

Pyrazinamide (Z) **Drug class: synthetic derivative of nicotinamide**	
Adverse reactions	Overall tolerance: Variable. Common (>10%): Asymptomatic hyperuricemia is an expected effect and should not be treated or considered pathologic. The drug should be discontinued only if hyperuricemia is accompanied by an acute gout-associated arthritis. Arthralgia (pain in large and small joints) and gastrointestinal effects (nausea, vomiting and anorexia). Frequently (5-10%): Arthralgia (pain in large and small joints that are not inflamed) and gastrointestinal effects (nausea, vomiting and anorexia). Occasional (>1%): Hepatotoxicity can occur at any time and appears to be dose related. Transient increase in ALT/AST (<4 times the ULN) is the most frequent presentation. However, severe liver injuries, including some fatalities, have been reported. The drug should be discontinued in symptomatic or asymptomatic patients with an ALT concentration >4-5 times the ULN, and in patients who have serum bilirubin concentrations above the ULN. Gout is described as sudden, severe attacks of pain, swelling, redness and tenderness in one or more joints, most often in the big toe, with or without hyperuricaemia. It may cause photosensitivity and dermatitis. Rare (<1%): Sideroblastic anaemia, hypersensitivity reactions and effects on blood clotting.
Contraindications	Hypersensitivity to pyrazinamide. Severe hepatic damage. Acute gout or frequent flares.
Drug interactions	There is low potential for drug-drug interactions. If used with other hepatotoxic drugs, the effects can accumulate.
Food interactions	The absorption is unaffected by food.
Monitoring	Liver function (AST, ALT, and bilirubin) should be monitored at baseline and monthly if possible. Patients should be closely monitored if they are at risk for drug-related hepatitis (e.g. alcohol abuse, nonalcoholic steatohepatitis or chronic viral hepatitis) and if signs or symptoms of hepatotoxicity occur.
Patient instructions and alerting symptoms	May be taken with or without food. Pyrazinamide may cause a rash after sun exposure (so sun exposure should be limited). It should not be used if there is active gout with frequent flares or if the patient presents with severe liver disease (e.g. alcohol abuse, nonalcoholic steatohepatitis or chronic viral liver infections). Patients should be instructed to inform their health care provider immediately if any of the following occur: • skin rash, severe itching or hives; • pain or swelling in the joints; • yellowing of the skin or eyes or dark urine; or • unusual tiredness or loss of appetite.

Streptomycin (Sm) **Drug class: aminoglycosides**	
Activity against M. tuberculosis, mechanism of action and metabolism	Target: M. tuberculosis inner metabolism. Streptomycin binds to the bacterial ribosome small subunit (30 S or 16 S rRNA), leading to mistranslation of proteins and also disruption of the cytoplasmic membrane. Activity: It has important bactericidal activity (medium-high early bactericidal activity) and the potential for sterilizing activity. Excretion and half-life: Reaches peak serum concentration within 1 hour after IM administration, and 50% is eliminated in the urine within 24 hours after IV or IM administration.
Cross-resistance	Mutations at the eis gene may confer resistance to amikacin but not to streptomycin.
Dose[a]	Streptomycin is recommended by WHO only in adults aged >18 years. • Adults: 12–18 mg/kg/day in a single daily dose, upper daily dose is 1 g. • Renal failure or dialysis: 12–15 mg/kg/dose, twice or thrice weekly (not daily). It should be used with caution. • See the handbook Annex for weight-based dosing. • Markedly obese individuals (e.g. BMI >35): The dose should be adjusted because of decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations. For dosing in obese adults who conform to weight bands corresponding to the following adjusted weights: - ideal body weight (men): 50 kg plus 0.9 kg/cm >1.52 m; and ideal body weight (women): 45 kg plus 0.9 kg/cm >1.52 m. Serum concentrations should be monitored closely, if possible.
Administration	It is not absorbed orally. Aminoglycosides (amkacin and streptomycin) are administered parenterally as an IM injection, and in some cases may be administered IV. IM absorption may be delayed if the same site is used consistently. Intrathecal and intraperitoneal administration have been tried in the past.
Formulation and preparation	The powder for injection (1 g, vial) requires reconstitution with water for injection (at 200 mg/mL, 250 mg/mL or 400 mg/mL) before administration. For IV use, the concentration may be decreased.
Storage	The powder for injection should be stored below 30 °C. The reconstituted solution may be stored at room temperature for 1 week, protected from light.
Oral absorption	There is no significant oral absorption.
CSF penetration	Penetration is better in inflamed meninges.
Special circumstances	Use during pregnancy or breastfeeding: The drug should be avoided during pregnancy owing to documented cases of congenital deafness. It is excreted into human milk, and is considered compatible with breastfeeding but should be used with caution (the infant should be monitored for thrush and diarrhoea). Use in renal disease: It should be used with extreme caution. Concentrations should be monitored in patients with impaired renal function, if possible. Interval adjustment is recommended for renal impairment or dialysis (see under Dose section above for dosage under renal disease or dialysis). Clearance by haemodialysis is variable. Use in hepatic disease: Drug concentrations are not affected by hepatic disease (except for a larger volume of distribution for patients with ascites due to cirrhosis). It is presumed to be safe in liver disease; however, it should be used with caution because patients with severe liver disease may progress rapidly to hepato-renal syndrome. Diuretic use: Co-administration of loop diuretics and aminoglycoside antibiotics increases the risk of ototoxicity.

Streptomycin (Sm) Drug class: aminoglycosides	
	Older people: There is increased risk of ototoxicity and nephrotoxicity due to potential baseline damage in both organs. Children: It should be used with extreme caution. There is a risk of ototoxicity with important consequences (e.g. effects on verbal communication, cognitive and emotional development linked to school performance and future disability).
Adverse reactions	Overall tolerance: Generally, it is poorly tolerated, due to local pain from IM injections or lengthy infusions. Common: IM injection pain, permanent hearing loss (10–12%) and vestibular toxicity including nausea, vomiting and vertigo. Frequently: Electrolyte abnormalities, including hypokalaemia, hypocalcaemia and hypomagnesaemia. Watery or bloody diarrhoea may occur months after the last dose; vaginal itching or discharge; and eosinophilia. Occasional: Nephrotoxicity (typically transient), paraesthesia of face and neuropathy, weakness and neuromuscular blockage.
Contraindications	Hypersensitivity to aminoglycosides. Pregnancy: Congenital deafness can occur with streptomycin and kanamycin use during pregnancy. Children: Owing to the important consequences of ototoxicity. Older people or adults with renal, vestibular or auditory impairment.
Drug interactions	There is low potential for drug–drug interactions. It should be used with caution with other drugs that might be nephrotoxic or may change the electrolyte balance (e.g. loop diuretics) or in clinical conditions such as dehydration. The ototoxic effects of aminoglycosides, including streptomycin, are potentiated by the co-administration of ethacrynic acid, furosemide, mannitol and other diuretics.
Food interactions	No alcohol or food interactions.
Monitoring	Patients should be carefully monitored for early signs of hearing loss and vestibular dysfunction, to prevent permanent damage to sensorineural cells. Baseline and monthly audiology exams should be documented. Renal function should be monitored by documenting creatinine at least monthly (and more frequently if there is renal or hepatic impairment). Serum concentrations should be monitored serially for patients with impaired renal function, if possible.
Patient instructions and alerting symptoms	The patient should be informed of the potential harm to the fetus, so should be advised on contraception methods and a pregnancy test should be administered before drug initiation. Patients should be instructed to inform their health care provider immediately if any of the following occur: • problems with hearing, dizziness or balance; • decreased urination; • watery or bloody diarrhoea; • swelling, pain or redness at IV site; or • muscle twitching or weakness.

[a] See Table 4.8 for weight-based dosing in adults and children

ANNEX 2 GRADING OF THE SEVERITY OF ADVERSE DRUG EVENTS

Parameters	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life threatening
Hemoglobin (g/dl)	8,0 - 9,40	7,0 - 7,99	6,5 - 6,99	< 6,50
Leucocytes (/mm3)	3 000 - 3 900	2 000 - 2 999	1 000 - 1 999	< 1 000
Neutrophiles (/mm)	1 000 - 1 500	750 - 999	500 - 749	< 500
Platelets (/mm3)	75 000 - 99 000	50 000 - 74 999	20 000 - 49 999	< 20 000 or diffuse petechiae
Serum bilirubin (µmol/l)	1,25 - 2,50 x N	> 2,50 - 5,00 x N	> 5,00 - 10,00 x N	> 10,00 x N
SGOT (IU/l)	1,25 - 2,50 x N	> 2,50 - 5,00 x N	> 5,00 - 10,00 x N	> 10,00 x N
SGPT (IU/l)	1,25 - 2,50 x N	> 2,50 - 5,00 x N	> 5,00 - 10,00 x N	> 10,00 x N
Alkaline phosphatase (IU/l)	1,25 - 2,50 x N	> 2,50 - 5,00 x N	> 5,00 - 10,00 x N	> 10,00 x N
Gamma GT (IU/l)	1,25 - 2,50 x N	> 2,50 - 5,00 x N	> 5,00 - 10,00 x N	> 10,00 x N
Serum creatinine (µmol/l)	1,00 - 1,50 x N	> 1,50 - 3,00 x N	> 3,00 - 6,00 x N	> 6,00 x N or dialysis required
glycemia, fasting (mmol/l)	6,1 - 7,0	> 7,0 - 16,5	> 16,5 without ketosis	Ketoacidosis or hyperosmolarity (>27,8 mmol/l without acidosis)
Serum potassium (mEq/l)	3,2 - 3,4	2,8 - 3,1	2,5 - 2,7	< 2,5
Serum calcium (mmol/l)	1,95 - 2,10	1,75 - 1,94	1,50 - 1,74	< 1,50
Uric acid (TU/l)	1,25 - 2,5 x N	2,6 - 5,0 x N	5,1 - 10 x N	> 10 x N
Nausea	Transient; normal food intake	Food intake compromised for less than 3 days	Food intake compromised for more than 3 days	Food intake limited to liquids; hospitalisation required
Vomiting	Transient; 2 - 3 episodes/ day or duration ≤ 1 week	Repeated; 4 - 5 episodes/day or duration > 1 week	Solid/liquid vomiting for 24 hours; orthostatic hypotension; perfusion required	Hospitalisation for hypovolemic shock

Parameters	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life threatening
Hearing problems	Mild hearing deficiency: 20 to 40 dB of hearing loss; difficulty to hear sounds of weak intensity, complex noises and low or distant voices	Moderate hearing deficiency: 40 to 70 dB of hearing loss; speech is heard but poorly understood or only under-stood through lip reading	Severe hearing deficiency: 70 to 90 dB of hearing loss; speech is heard only if spoken loudly close to the ear	Extreme hearing deficiency: > 90 dB of hearing loss; speech cannot be heard at all
Lengthening of the QT interval	N.A.	Male: 450< <500 ms Female: 470< <500 ms	> 500ms	> 500ms with clinical signs (ventricular arrythmia, syncope, torsade de pointe)
Hypothyroidism	Sub clinical	Manifest hypothyroidism without complications; treatment required	Severe hypothyroidism with multiple clinical signs; to be treated urgently; hospitalization may be required	Myxoedematous coma
Cutaneous and/or mucous eruptions	Moderate erythema and itching	Extended maculopapular eruptions with or without itching	Extended papular-vesicular or oozing eruptions; palpable purpura	Any bullous condition of skin or mucosa (type Lyell or Stevens Johnson); diffuse erythema with fever, with or without other hypersensitivity signs; necrosis of the skin, requiring surgical excision
Acute hypersensitivity, with or without dermatological signs	N.A.	Acute localized urticaria	Giant urticaria; Quincke's oedema	Anaphylactic shock
Psychosis	Minor anxiety	Anxiety requiring treatment or moderate depression	Major anxiety or manifest depression requiring treatment	Acute psychosis with suicidal tendencies, manic state and hallucinatory delirium;

Parameters	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life threatening
				hospitalization required
Arthritis	Joint pain	Joint pain with or without joint effusion or presenting moderate functional loss	Manifest arthritis with or without joint effusion or presenting important functional loss	N.A.
Loss of vision	Subjective complaints; can count fingers at 6m	Can count fingers at 3m but not at 6m	Cannot count fingers at 3m	Blindness
Uncontrolled movements	Occasional clumsiness; mild coordination problems	tremors or dyskinesia or dysmetria or dysarthria; moderate impact on daily activity	Ataxia of upper or lower limbs or abnormal movements; impact on daily activity	Inability to stand, total dependency

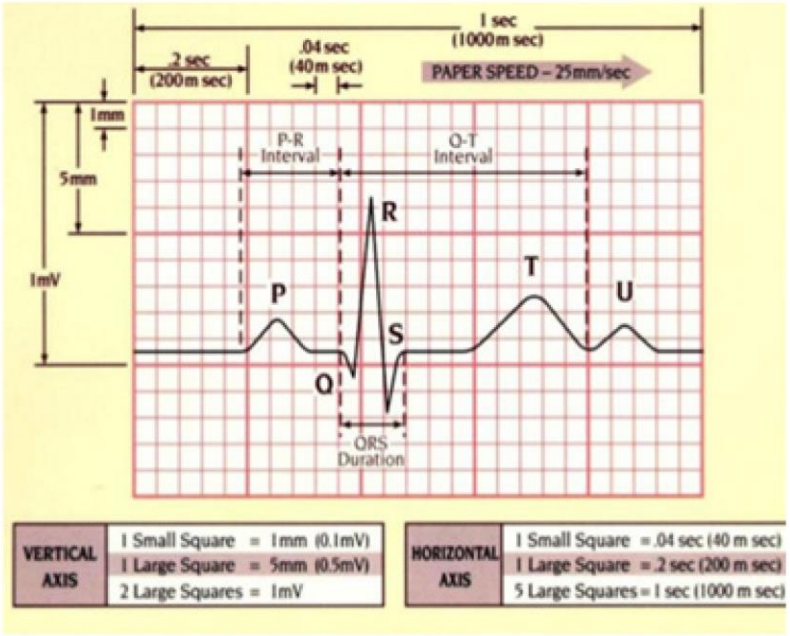
N = Normal value; N.A. = not applicable

ANNEX 3 CALCULATING THE QT INTERVAL

Note: The information below is about QTcF measurement and for management please see the relevant information in aDSM chapter

What Pathologies can ECG detect?

- Arrhythmias
- MI, IHD
- Cardiac Hypertrophy
- Electrolyte Disturbances(hypo-Hyperkalemia/calcemia
- Drug Toxicities, QT Interval- Digoxin, Bdq, Lzd, Mfx-Cfz etc



What is QT Interval and measuring QTc (Source: E. Burns 2017)

- QT Interval is the time measurement from the start of Q wave to the end of T wave
- It tells us the time taken for ventricular depolarization and ventricular repolarization- means ventricular contraction to relaxation
- QT interval is inversely proportional to Heart Rate, QT shortens at faster heart rate and QT lengthens at slower heart rate
- Abnormally prolonged QT wave is associated with sudden arrhythmias and leading to Torsade de pointes (Tdp)

Measuring QTc: Standardization

- The QT interval should be measured in long lead II, V5, V6
- Several successive beats should be measured with the maximum interval taken
- Large U waves (more than 1 mm) that are fuse to the T wave should be included in measurement
- Small U waves and those which are separate from T should be excluded
- The maximum slope intercept method is used to define the end of T wave

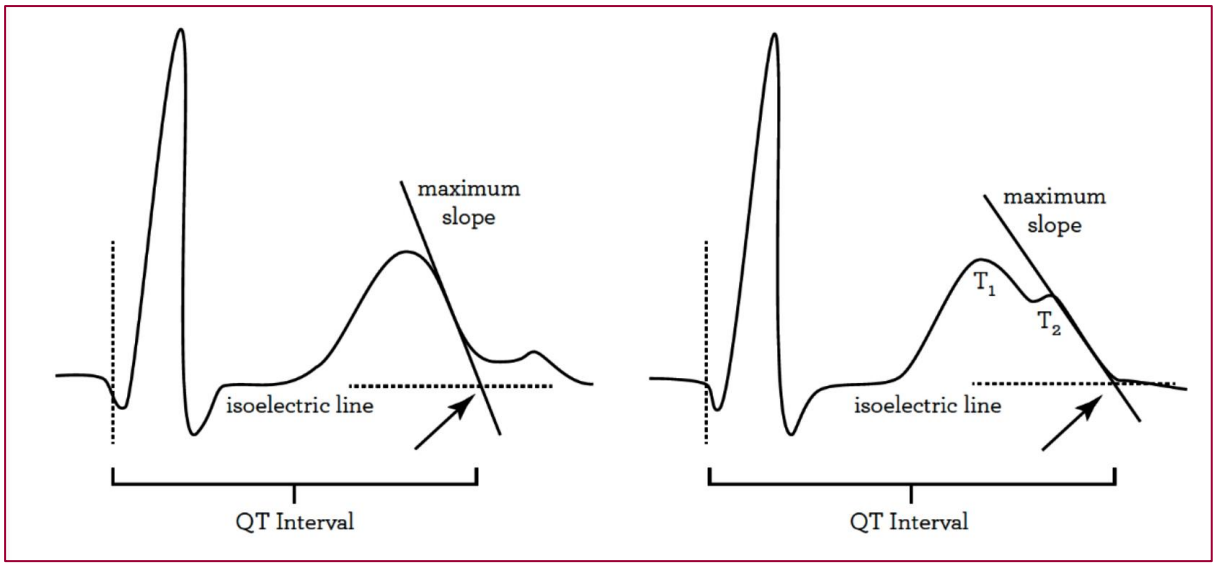


Figure: Maximum slope down of T wave

Corrected QT- is called QTc

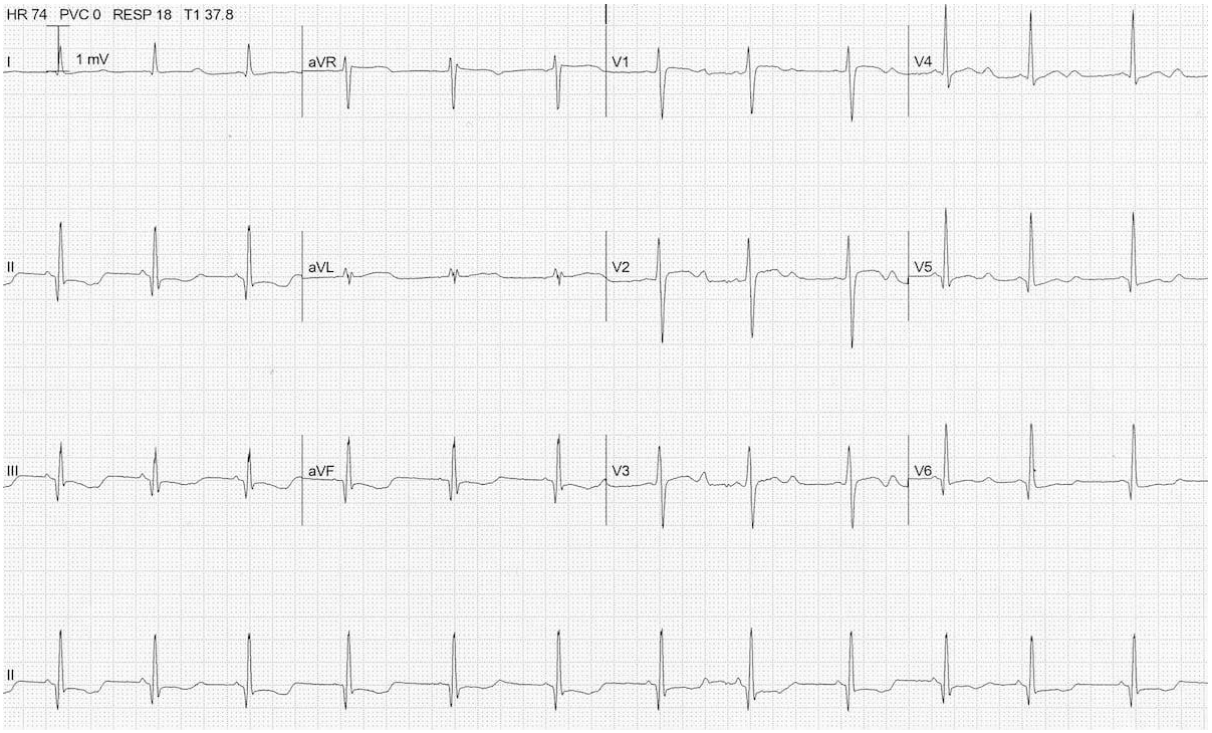
With Irregular Rhythms (such as Atrial Fibrillation) always note the general(average) ventricular rate (QRS's per 6-sec. strip × 10)

Rule of Thumb: Always remember

1. Use triplets' method quickly to estimate heart rate, one larger square is 300, 2 LSs = 150, 3LSs=100,4 LSs=75,5LSs =60 all per minute
2. The normal QT interval is between 7-11 small squares
3. The normal QT is less than half of the preceding RR interval

Prolonged QTC in Hypokalemia- Example

- ST depression and T wave inversion best noted in inferior leads
- Prominent U waves
- Long QU interval
- Hypokalemia- The serum K+ 1.9 mmol/L.



Source: https://litfl.com/hypokalaemia-ecg-library/

QTcF Nomogram

How to use the QTcF Nomogram?

1. Identify the patient's HR or RR interval on the top of the table.
2. Identify the measured QT (uncorrected) interval on the left of the table (below).
3. Find the corresponding calculated QTcF in the cell below the HR (or RR) and to the right of the QT interval.

	Heart rate (beats per minute)	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130	135	140	145	150
	R - R interval (sec)	1.33	1.20	1.09	1.00	0.92	0.86	0.80	0.75	0.71	0.67	0.63	0.60	0.57	0.55	0.52	0.50	0.48	0.46	0.44	0.43	0.41	0.40
QT interval (msec)	300	273	282	291	300	308	316	323	330	337	343	350	356	362	367	373	378	383	388	393	398	403	407
	310	282	292	301	310	318	326	334	341	348	355	361	368	374	379	385	391	396	401	406	411	416	421
	320	291	301	311	320	329	337	345	352	359	366	373	379	386	392	397	403	409	414	419	424	429	434
	330	300	311	321	330	339	347	355	363	371	378	385	391	398	404	410	416	421	427	432	438	443	448
	340	309	320	330	340	349	358	366	374	382	389	396	403	410	416	422	428	434	440	446	451	456	461
	350	318	329	340	350	359	368	377	385	393	401	408	415	422	428	435	441	447	453	459	464	470	475
	360	327	339	350	360	370	379	388	396	404	412	420	427	434	441	447	454	460	466	472	477	483	489
	370	336	348	359	370	380	390	399	407	416	424	431	439	446	453	460	466	473	479	485	491	497	502
	380	345	358	369	380	390	400	409	418	427	435	443	451	458	465	472	479	485	492	498	504	510	516
	390	354	367	379	390	401	411	420	429	438	446	455	462	470	477	484	491	498	505	511	517	523	529
	400	363	376	389	400	411	421	431	440	449	458	466	474	482	490	497	504	511	518	524	531	537	543
	410	373	386	398	410	421	432	442	451	460	469	478	486	494	502	509	517	524	531	537	544	550	556
	420	382	395	408	420	431	442	452	462	472	481	490	498	506	514	522	529	536	543	550	557	564	570
	430	391	405	418	430	442	453	463	473	483	492	501	510	518	526	534	542	549	556	563	570	577	584
	440	400	414	427	440	452	463	474	484	494	504	513	522	530	539	547	554	562	569	577	584	590	597
	450	409	423	437	450	462	474	485	495	505	515	524	534	542	551	559	567	575	582	590	597	604	611
	460	418	433	447	460	472	484	496	506	517	527	536	545	554	563	571	580	588	595	603	610	617	624
	470	427	442	457	470	483	495	506	517	528	538	548	557	566	575	584	592	600	608	616	623	631	638
	480	436	452	466	480	493	505	517	528	539	549	559	569	578	587	596	605	613	621	629	637	644	651
	490	445	461	476	490	503	516	528	539	550	561	571	581	590	600	609	617	626	634	642	650	658	665
	500	454	471	486	500	514	526	539	550	562	572	583	593	603	612	621	630	639	647	655	663	671	679
	510	463	480	495	519	524	537	549	561	573	584	594	605	615	624	634	643	651	660	668	676	684	692
	520	472	489	505	520	534	547	560	572	584	595	606	617	627	636	646	655	664	673	681	690	698	706
	530	482	499	515	530	544	558	571	583	595	607	618	628	639	649	658	668	677	686	694	703	711	719
	540	491	508	525	540	555	568	582	594	606	618	629	640	651	661	671	680	690	699	708	716	725	733
	550	500	518	534	550	565	579	592	605	618	630	641	652	663	673	683	693	702	712	721	729	738	746
	560	509	527	544	560	575	590	603	616	629	641	653	664	675	685	696	706	715	725	734	743	751	760
	570	518	536	554	570	585	600	614	627	640	652	664	676	687	698	708	718	728	738	747	756	765	774
	580	527	546	563	580	596	611	625	538	651	664	676	688	699	710	720	731	741	751	760	769	778	787
	590	536	555	573	590	606	621	636	649	663	675	688	700	711	722	733	743	754	763	773	783	792	801
	600	545	565	583	600	616	632	646	660	674	687	699	711	723	734	745	756	766	776	786	796	805	814

The Framingham Formula

Calculation of QTcF

QTF(s)= QT +0.154 [1-RR(s)]

QT: distance between start of QRS complex and end of T wave, in seconds (number of small squares x 0.04)

RR: distance between two R waves: R et R' in seconds (number of small squares x 0.04)

QTcF(sec) x 1000= QTcF(ms)

ANNEX 4 CALCULATING THE CREATININE CLEARANCE

The estimated creatinine clearance is calculated based on the Cockcroft-Gault equation and is expressed in ml/minute.

$$\textbf{Creatinine clearance (CreatClear)} = \textbf{constant} \times \frac{\textbf{140 - age}}{\textbf{Serum creatinine}} \times \left(\frac{\textbf{Weight}}{\textbf{72}}\right)$$

The constant is dependent on the sex: male = 1; female = 0.85
The serum creatinine should be expressed in mg/dl. If the laboratory gives the result in µmol/l, it can be converted into mg/dl by dividing the µmol/l by 88.4.
Example: 212µmol/l = 212/88.4 = 2.398 mg/l.
A calculator to convert a serum creatinine result expressed in µmol/L to mg/dL can be found on the internet: http://www.endmemo.com/medical/unitconvert/Creatinine.php
Example: a female patient (age = 46 years, weight = 50 kg) has serum creatinine = 212 µmol/l.

Create Clear = 0.85× (140-46)/2.398× (50/72) = 0.85×39.2×0.694 = 23.1 ml/min

A calculator to calculate the estimated creatinine clearance based on the Cockcroft-Gault equation can be found on the internet:

http://reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault
Normal values for creatinine clearance are:
Men: 97 to 137 ml/min
Women: 88 to 128 ml/min

ANNEX 5 PERIPHERAL NEUROPATHY DIAGNOSTICS

Note: Please use this with relevant chapter of aDSM to follow gradings and management
It is characterized by a decline and damage of nerve function leading to loss of sensation, ulceration, and subsequent amputation.

There is a common misconception that diabetic neuropathy is a phenomenon limited largely to the lower limbs, which is not true. About 40% of patients with neuropathy have upper limb involvement in addition and the associated symptoms could be positive with that of pain, paresthesias and dysesthesias, typically glove and stocking distribution.
There is probability that in some TB, HIV, Diabetic patients there is some level of pre-existing peripheral neuropathy and use of toxic drugs may further exacerbate the situation leading to grade 1 or grade 2 of PN, which limits the use of such toxic drugs (for example Lzd, Cs, high dose INH)

TABLE 5.1: Distal symmetrical Polyneuropathy, small fiber and large fiber neuropathy

	Small fiber neuropathy	Large fiber neuropathy
Fiber	C-fiber type	Delta type (Aδ)
Sensory loss	0 to + (Warm thermal perception) Pinprick hypoesthesia Light touch sensation ↓↓ Monofilament testing-1 and 50 g)	0 to +++ (touch, vibration perception)- checked with biothesiometer and tuning fork (128 Hz) ↓ position sense and muscle strength ↓ sharp-dull and two-point discrimination.
Prominent symptoms	Hyperalgesia-superficial pain (+ to +++) Constant burning Allodynia- ↓ sweating → dryness Severe hyperesthesia Shock-like sensations Hypoalgesia-late	Deep-seated, dull aching pain (+ to +++) Sensory ataxia → falls → minor trauma/ fractures → ulcers/amputation

Source: A Practical guide to DM,7th edition, © 2016, Jaypee Brothers Medical Publishers

ACTG Brief Peripheral Neuropathy Screening Tool

Source: NIAID Adult AIDS Clinical Trials Group

Following are the step wise approaches to detect peripheral neuropathy in patients. Please remember that this assessment is subjective and may lead to wrong scoring if not properly carried out. Therefore, it is imperative that doctors/nurses/health care workers should be appropriately trained to carry out below assessments.

1. Elicit Subjective Symptoms

Ask the subject to rate the severity of each symptom listed in Question 1 on a scale of 01 (mild) to 10 (most severe) for right and left feet and legs. Enter the score for each symptom in the columns marked R (right lower limb) and L (left lower limb). If a symptom has been present in the past, but not since the last visit, enter "00 - Currently Absent." If the symptom has never been present, enter "11 - Always Been Normal."

Always Been Normal	Currently Absent	Mild							Severe		
11	00	01	02	03	04	05	06	07	08	09	10

Symptoms	R	L
a. Pain, aching or burning in feet, legs		
b. “pins and needles” in feet, legs		
c. Numbness (lack of feeling) in feet, legs		

2. Grade Subjective Symptoms

Use the single highest severity score from Question 1 above to obtain a subjective sensory neuropathy score. If all severity scores are "00" or "11," the subjective sensory neuropathy score will equal "0."

Subjective Sensory Neuropathy Score (based on highest severity rating)

01- 03 = grade of 1
04- 06 = grade of 2
07- 10 = grade of 3
11 or 00 = grade of 0

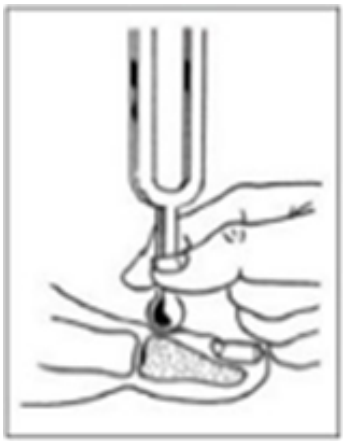
R	L

3. Evaluate Perception of Vibration

Compress the ends of a 128-Hz tuning fork just hard enough that the sides touch. Place the vibrating tuning fork on a bony prominence on the subject's wrist or hand to be sure that he/she can recognizes the vibration or "buzzing" quality of the tuning fork. Again, compress the ends of the tuning fork just hard enough that the sides touch. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint of one great toe and begin counting the seconds. Instruct the subject to tell you when the "buzzing" stops. Repeat for the other great toe.

Vibration perception

a. Great toe DIP joint perception of vibration in seconds
b. Vibration perception score
0 = felt >10 seconds (normal)
1 = felt 6-10 seconds (mild loss)
2 = felt <5 seconds (moderate loss) 3 = not felt (severe loss)
8 = unable to or did not assess



R	L

Vibration perception	Result	Score
Felt > 10 seconds	Normal	0
Felt 6-10 seconds	Mild loss	1
Felt <S seconds	Moderate loss	2
Not felt	Severe loss	3

4. Evaluate Deep Tendon Reflexes

With the subject seated, the examiner uses one hand to press upward on the ball of the foot, dorsiflexing the subject's ankle to 90 degrees. Using a reflex hammer, the examiner then strikes the Achilles tendon. The tendon reflex is felt by the examiner's hand as a plantar flexion of the foot, appearing after a slight delay from the time the Achilles tendon is struck. Use reinforcement by having the subject clench his/her fist before classifying the reflex as absent.

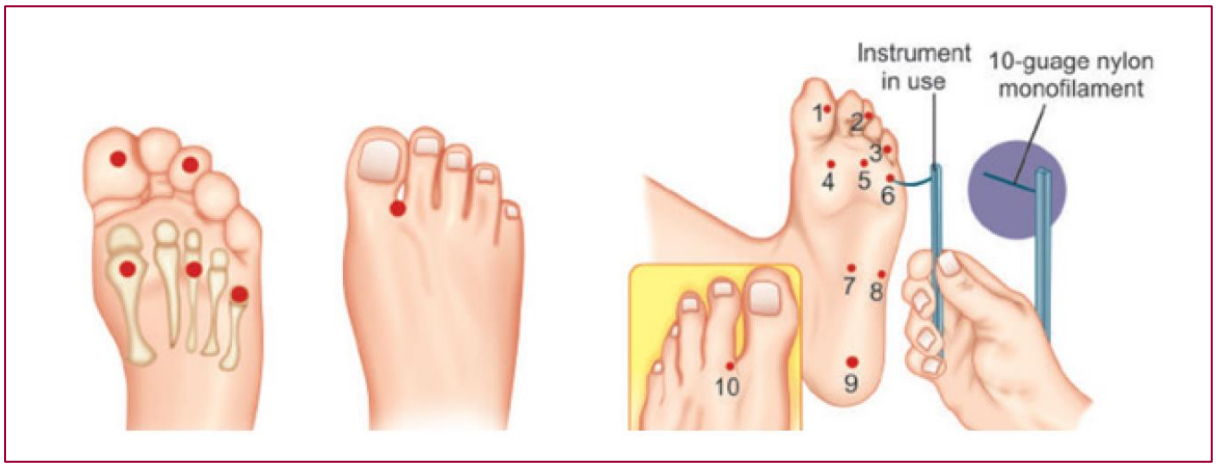
Ankle Reflexes Score

0 = absent
1 = hypoactive
2 = normal deep tendon reflexes 3 = hyperactive
4 = clonus
8 = unable to or did not assess

R	L

Nylon Monofilament Test

The Semmes-Weinstein monofilament: The standard American Diabetes Association (ADA) criteria will mention that it is only necessary to do a 2 g and a 10 g monofilament testing. In leprosy or TB, up to 300 g may be utilized.



Source: a practical guide to DM, 7th edition

Form to be completed on monthly visit while patient is on Lzd/Cs and or Diabetics: The Brief Peripheral Neuropathy Screen Tool.

Brief Peripheral Neuropathy Screening
NIAID ADULTS' AIDS CLINICAL TRIALS GROUPS

Patient number ☐☐☐☐☐☐☐☐ date of patient visit ☐☐☐☐☐☐

Protocol Number ☐☐☐☐☐☐ Institution Code ☐☐☐☐☐☐

Form week ☐☐☐ key operator code ☐☐☐

INSTRUCTIONS FOR RECORDING SUBJECTIVE ELICITED SYMPTOMS:

- Ask the subject to rate the severity of each symptom listed in question 2 (a-c) on a scale of 01 (m to 10 (most severe) for right and left feet, legs.
- Enter the score for each symptom in the column marked Presence/Severity.
- If a symptom has been present in the past, but not since the last visit, enter '00-Currently Absent
- If the symptom has never been present enter '11-Always Been Normal.'
- The use of "-1" is not acceptable as an answer to any question.

1. Was a subjective elicited peripheral neuropathy evaluation completed?.....(1-Yes, 2-No) ☐
   If Yes, go to question 2.
   If No, complete 'a' and go to question 4

   a. If not completed, indicate reason why: ……..……1 - Subject declined, specify ☐
   2 - Subject missed clinic visit
   9 - Other reason, specify

If '1-Subject declined' or '9-other reason',
specify [30]:

Always Been Normal	Currently Absent	Mild									Severe
11	00	01	02	03	04	05	06	07	08	09	10

2. SYMPTOMS PRESENCE/SEVERITY

	Right	Left
a. Pain, aching, or burning in feet, legs:	☐☐	☐☐
b. 'Pins and needles' in feet legs:	☐☐	☐☐
c. Numbness (lack of feeling) in feet, legs:	☐☐	☐☐

INSTRUCTIONS FOR GRADING SUBJECTIVE ELICITED SYMPTOMS:

Use the single highest severity score from 01-10 In question 2 (a-c) above to obtain a subjective peripheral neuropathy grade.

If all severity score is '00' or '11', the subjective peripheral neuropathy grade will equal '0.'

Presence/Severity score of:
01 – 03 = Grade of 1
04 – 06 = Grade of 2
07 – 10 = Grade 3
11 or 00 = Grade 0

3. Subjective peripheral neuropathy grade ……

Source: JH McArthur

ANNEX 6 JOB AID FOR PEDIATRIC GASTRIC ASPIRATE



ANNEX 7 DR-TB RECORDING AND REPORTING FORMS

HMIS 6.5B

नेपाल सरकार

स्वास्थ्य व्यवस्थापन सूचना प्रणाली

औषधी प्रतिरोधी क्षयरोग उपचार रजिस्टर

DR TUBERCULOSIS TREATMENT REGISTER

स्वास्थ्य संस्थाको नाम: _____

जिल्ला: .....नगरपालिका/गाउँ पालिका:

आर्थिक वर्ष:

परिमार्जित: २०७७/७८ Print FY: 2077/78

HMIS 6.5B

DR TB Treatment Register

DRTB Reg. No:	Registration Date: dd/mm/yyyy			Patient under CBDOT		Transfer IN Case
Patient Name:	Ethinic Code:	Age:	Sex: F M	Weight (kg):	Height:.....cm	Co-morbidity:
Province	District:	MRM:	Ward No/ Tole			
Guardian's Name:	Phone no:. Guardian/Patient					
No.of Household Member:	No.of <5 years children :.....			No.of HH members screened for TB:.....		
DOT Provider:						

DST Result	H	R	Z	E	Mfx	Cm	Lfx	Bdq	Lzd	Cs	Cfz	Am	Eto	Dlm	Pa			TB HIV Status		
Base line/ Date	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	HIV Infection	Patients on	
Follow up Date	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	1.Positive 2.Negative 3.Unknown	ART	CPT
Follow up Date	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S	R/S			

\$Type: *1. MDR/RR (Shorter) 2. MDR/RR (Longer) 3. PRE- XDR (Shorter) 4. PRE-XDR (Longer) 5. XDR*

Registration Category: 1. New 2. Relapse 3.1 TAF*(New_FLD) 3.2 TAF(Retreatment_FLD) 3.3 TAF(Ret_Hr TB) 3.4. TAF (2nd line) 4. TALF** 5. OPT*** 6. UPTH****

Type	Treatment Start (\$Type: .....) (Regimen@.....)			1. Shifted Treatment (\$Type: .....) (Regimen@.....)			2. Shifted Treatment (\$Type: .....) (Regimen@.....)			3. Shifted Treatment (\$Type: .....) (Regimen@.....)		
Month	Lab No/date	SR	CR	Lab No/date	SR	CR	Lab No/date	SR	CR	Lab No/date	SR	CR
Month												
Month												
Month												
Month												
Month												
Month												
Month												
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Month												
Month												
Month												
Month												
Month												
Month												
Month												

Outcome: 1.cured 2. Completed 3. Failed 4. Died 5. Loss to follow-up 6 Not Evaluated **Date:**

Group A: Lfx=Levofloxacin, Mfx=Moxifloxacin, Bdq=Bedaquiline, Lzd=Linezolid Group B: Cfz=Clofazimine, Cs=Cycloserine, Trd=Terizidone, Group C: E=Ethambutol, Dlm=Delamanid, Z=Pyrazinamide, Imp,Cln=Imipenem-cilastatin, Mpm=Meropenem, Am=Amikacin, S=Streptomycin, Eto=Ethionamide, Pa=Pretomanid

After Treatment Completion follow-up

6 Month	Lab No/date	SR	12 Month	Lab No/date	SR	18 Month	Lab No/date	SR	24 Month	Lab No/date	SR

*TAF = Treatment After Failure **TALF= Treatment After Loss to follow up ***OPT =Other Perviously Treatmentfollowup ****UPTH = Unknown Previous TB Treatment History

@ Regimen Used: BPaLM, BPaL, OSSTR-Lzd, OSSTR-Eto, LR1, LR2, LR3, Individualized Regimen

जाती कोड: १ दलित, २ जनजाती, ३ मधेशी, ४ मुस्लीम, ५ ब्राह्मण/क्षेत्री, ६अन्य

HMIS 6.4C

नेपाल सरकार

स्वास्थ्य व्यवस्थापन सूचना प्रणाली

औषधी प्रतिरोधी क्षयरोग उपचार व्यवस्थापन कार्ड

DR TUBERCULOSIS TREATMENT MANAGEMENT CARD

बिरामीको नाम:

स्वास्थ्य संस्थाको नाम:

जिल्ला: **.....नगरपालिका/गाउँ पालिका:** **वडा नं.:**

आर्थिक वर्ष:

परिमार्जित: २०७७/७८ Print FY: 2077/78

Section I: Treatment Card HMIS 6.4C

| | | |

DOT Compliance

HMIS 6.4C

Month/DAY	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	28	29	30	31	32	Weight in (KG)	Adverse Side Effect
Month																																	Yes No
Month																																	Yes No
Month																																	Yes No
Month																																	Yes No
Month																																	Yes No
Month																																	Yes No
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Month																																	Yes No
Month																																	Yes No
Month																																	Yes No
Month																																	Yes No
Month																																	Yes No

TREATMENT REGIMEN .....with dosages (mg or gm)

Months	Lfx	Mfx	Bdq	Lzd	Cfz	Cs	Trd	E	Dlm	Z	Imp,Cln	Mpm	Am	Eto	Pa	Other
Month																
Month																
Month																
Month																
Month																
Month																
Month																
Month																
Month																
Month																
Month																
Month																

Month	Lfx	Mfx	Bdq	Lzd	Cfz	Cs	Trd	E	Dlm	Z	Imp,Cln	Mpm	Am	Eto	Pa	Other
Month																
Month																
Month																
Month																
Month																
Month																
Month																
Month																
Month																
Month																
Month																
Month																

Group A: Lfx=Levofloxacin, Mfx=Moxifloxacin, Bdq=Bedaquiline, Lzd=Linezolid Group B: Cfz=Clofazimine, Cs=Cycloserine, Trd=Terizidone, Group C: E=Ethambutol, Dlm=Delamanid, Z=Pyrazinamide, Imp,Cln=Imipenem-cilastatin, Mpm=Meropenem, Am=Amikacin, S=Streptomycin, Eto=Ethionamide, Pa=Pretomanid

Revised FY 2076/77

Printed FY 2077/78

Section on ABC Smoking Cessation

HMIS 6.4C

At start of TB treatment then at follow-up examination visit:

Month of Treatment	Date	Ask				Brief advice given to patient (30 seconds-1 minute)		Cessation support provided to patient (1-3 minutes)	
		Do you smoke?* Yes / No							
			If Yes						
	DD/MM/YY	No	Have you smoked at all—even a puff—in the last 2 weeks?	How soon after you wake do you usually have your first cigarette? 1 – <30 min or 2 – >30 min	Does anyone smoke inside your home? Yes / No 1 – yes 2 – no	Yes / No 1 – yes 2 – no	*Comments*	Yes / No 1 – yes 2 – no	*Comments*
Months			S		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	
Months			S R Q		1 2	1 2		1 2	

*Definitions for status of smoking

S = current smoker: has smoked in the last 2 weeks before the visit and has not made any quit attempt since the last visit (quit attempt = patient tried to quit and succeeded for at least 24 hours).

R = relapsed smoker: has smoked in the last 2 weeks before the visit but has made at least one quit attempt of at least 24 hours since the last visit.

Q = quitter: has not smoked at all in the last 2 weeks before the visit, not even a puff

HMIS 6.4C

Section II: Treatment Managment Related

Investigations and Result

Investigations	Base line	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months
CBC .	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
Blood Glucose	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
ECG	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
LFT	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
RFT	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
Uric Acid	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
Hep B	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
Hep C	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
Audiometry	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
Peripherial Neuropathy	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
Visual Acuity	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
Pregnancy	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
Xray	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
Other	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
Other	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
Other	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result	Result
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date

Printed FY 2077/78

Follow-up of Site-affect

Side Effect	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months	F/U Months
Nausea/Vomiting	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Diarrhoea	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Arthralgia	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Dizziness/ Vertigo	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Hearing Disturbances	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Vision Problem	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Signs of Hypothyroidism	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Minor mood changes or insomnia	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Depression	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Suicidal thoughts	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Hallucinations/ Psychosis	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Urine Output	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Itchy skin	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Jaundice	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Seizures	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Anaemia	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Others	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Others	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Others	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Others	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No

Note: Based on the Side Effect Identified please fill the aDSM form (HMIS 6.10)

Signed at Treatment center	Signed at Treatment Sub-Center
Patient commitment I am aware that in order to be cured of this form of tuberculosis, I need to take anti-TB drugs daily till the end of my treatment. If I do not take these drugs daily, I am putting my own health at risk as well as the health of family and community members. I commit to taking these drugs at this health center (sub-center) till the end of my treatment. If I decide to leave this treatment, I understand the risk and consequences of this disease. Name: Address: Date: Signature: Treatment center DR-TB focal person commitment I have explained the importance of taking these drugs and potential difficulties during treatment. I will do my best to support him/her in completing a full course of treatment and ensuring cure/completion. I also commit to ensuring proper documentation and reporting as per NTP guidelines Name: Address: Date: Signature:	Sub-centre DR-TB focal person commitment I have explained the importance of taking these drugs and potential difficulties during treatment. I will do my best to support him/her in completing a full course of treatment and getting cured. I also commit to ensuring proper documentation and reporting as per NTP guidelines Name: Address: Date: Signature: Treatment provider Commitment I commit to supporting his/her in completing a full course of treatment. I will encourage him/her to comply with the treatment and commit to informing the treatment sub-center if I know that s/he has stopped taking drugs. Name: Address: Date: Signature:

HMIS 6.4 D

नेपाल सरकार
स्वास्थ्य व्यवस्थापन सूचना प्रणाली

.....

नगरपालिका/गाउँपालिका

औषधी प्रतिरोधी क्षयरोग उपचार कार्ड

बिरामीको नामः

फोटो

उमेरः लिंगः

ठेगानाः

सम्पर्क नं

तौल (के.जी):

क्षयरोग दर्ता नं दर्ता मितिः

दर्ता समूह

१ नयाँ (new) २ रोग बल्झेको (Relapse) ३.१ उपचार असफल नयाँ (TAF_New-FLD)

३.२ उपचार असफल पुन उपचार (TAF_Retreatment-FLD) ३.३ उपचार असफल Hr TB (TAF)

३.४ उपचार असफल पुन उपचार औषधी प्रतिरोधी (TAF_2nd Line)

४ उपचार पुरा नगरेको (TALFU) ५ पहिले उपचार गरेका अन्य (OPT)

६ यस अघिको उपचार अवस्था थाहा नभएको (UPTH)

क्षयरोगको किसिमः

MDR/RR(Shorter), MDR/RR (Longer), PRE-XDR(Shorter), PRE-XDR(Longer), XDR

क्षयरोग प्रभावित अंग

१ छाती २ छाती वाहेक अन्य अंग

दिइएको उपचार रेजिमनः

Shorter				Longer			
BPaLM	BPaL	OSSTR-Lzd	OSSTR-Eto.	LR1	LR2	LR3	Individualized Regimen

उचार सहयोगीको नाम

सम्पर्क नं

स्पुटम कल्चर फलोअप र तौल

Month	Lab No/date	SR	CR	Weight in KG
Month				
Month				
Month				
Month				
Month				
Month				
Month				
Month				
Month				
Month				
Month				
Month				
Month				
Month				
Month				
Month				
Month				
Month				
Month				
Month				

दिइएको औषधीको नाम र मात्राः

Months	Weight (KG)	Lfx	Mfx	Bdq	Lzd	Cfz	Cs	Trd	E	Dlm	Z	Imp,Cln	Mpm	Am	Eto	Pa	Other
Month																	
Month																	
Month																	
Month																	
Month																	
Month																	
Month																	
Month																	
Month																	
Month																	

Months	Weight (KG)	Lfx	Mfx	Bdq	Lzd	Cfz	Cs	Trd	E	Dlm	Z	Imp,Cln	Mpm	Am	Eto	Pa	Other
Month																	
Month																	
Month																	
Month																	
Month																	
Month																	
Month																	
Month																	
Month																	
Month																	

DRUG COMPLINE DETAIL

Month/DAY	01	02	03	04	05	06	07	08	09	10	11	12	13	14
Month														
Month														
Month														
Month														
Month														
Month														
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15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32

उपचार नतिजा विवरण

१ निको भएको Cured: मिति

२ उपचार पुरा गरेको Complete :

३ उपचार असफल Failure:

४ मृत्यू भएको Died:

५ उपचार पुरा नगरेको Loss to follow up:

६ मूल्यांकन नभएका Not Evaluated:

प्रेषण/स्थानान्तरण भएको संस्था

क्षयरोग एक सरूवा रोग हो । आखाले देख्न नसकिने सुक्ष्म कीटाणु -*Mycobacterium Tuberculosis*_ ले क्षयरोग हुन्छ । यो एक व्यक्तिवाट अर्को व्यक्तिमा हावाको माध्यमबाट सर्दछ ।

क्षयरोग सर्ने तरिका:

क्षयरोग फोक्सोमा लाग्ने र फोक्सो वाहेक शरीरको अन्य भागमा लाग्ने गरी २ प्रकार हुन्छन । फोक्सोको क्षयरोग भएका बिरामीले खोक्दा, हाछ्यू गर्दा वा थुक्दा क्षयरोगका कीटाणु बाहिर वातावरणमा फैलिन्छन र स्वस्थ्य मानिसमा श्वास प्रश्वासको माध्यामबाट फोक्सोमा पुग्न सक्दछन । क्षयरोगको संक्रमण भएका सवै व्यक्तिलाई क्षयरोग हुदैन रोग प्रतिरोध क्षमता कमजोर भएका व्यक्ति (कुपोषित, मधूमेह, एच आइ भी एड्रस भएका आदि) मा यो रोगले छिटो आक्रमण गर्दछ

क्षयरोगका लक्षणहरू:

- *२ हप्ता वा सो भन्दा बढी अवधी खोकी लागि रहनु*
- *शरीरको तौल घटदै जानु*
- *छाती दुख्नु*
- *खकारमा रगत देखिनु*
- *साझपख वा राती ज्वरो आउनु*

औषधी प्रतिरोधी क्षयरोग (DRTB)

क्षयरोगको उपचारमा प्रयोग हुने कुनै पनि औषधीमा कीटाणु Resistant भएको अवस्थानै Drug Resistance हो ।

औषधी प्रतिरोधी क्षयरोग हुने सक्ने कारणहरू

- बीचैमा औषधी खान छाडेमा वा अनियमितरूपमा औषधी सेवन गरेमा
- कम गुणस्तरको औषधी सेवन गरेमा
- औषधीको मात्रा पर्याप्त नभएमा
- उपयुक्त उपचार पद्धति प्रयोग नएमा
- एन्टिवायोटिक्सको अनुचित प्रयोग

क्षयरोगका बिरामीको छिटोभन्दा छिटो निदान गरी सही उपचार पध्दतिबाट उपचार गर्नु नै क्षयरोग नियन्त्रणको मुख्य उपाय हो

क्षयरोगको औषधी स्वास्थ्य संस्थामा निःशुल्क पाइन्छ,
स्वास्थ्यकर्मी/चिकित्सकको सल्लाह बमोजिम नियमित औषधी सेवन गरे
क्षयरोग पूर्णरूपमा निको हुन्छ।

DR-TB Reporting Format

DRTB Reporting Format

Block 1 : Case Registration		New		Relapse		TAF* (New_FLD)		TAF* (Retreatment_FLD)		TAF* (Retreatment_Hr TB)		TAF* (2nd line)		TALFU**		OPT***		UPTH****	
		F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
MDR/RR (Shorter)	Pulmonary																		
	Extra Pulmonary																		
MDR/RR (Longer)	Pulmonary																		
	Extra Pulmonary																		
PRE-XDR (Shorter)	Pulmonary																		
	Extra Pulmonary																		
PRE-XDR (Longer)	Pulmonary																		
	Extra Pulmonary																		
XDR	Pulmonary																		
	Extra Pulmonary																		

BLOCK 2: Age Group [2]	0-4 Years		5-14 Years		15-24 Years		25-34 Years		35-44 Years		45-54 Years		55-64 Years		≥ 65 Years	
	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
1	2	4	5	5	6	7	8	9	10	11	12	13	14	15	16	17
MDR/RR (Shorter)																
MDR/RR (Longer)																
PRE-XDR (Shorter)																
PRE-XDR (Longer)																
XDR																

Block 3 :Registration by Treatment Regimen [3]

Sex of Patient	Shorter				Longer			
	BPaLM	BPaL	OSSTR-Lzd	OSSTR-Eto.	LR1	LR2	LR3	Individualized Regimen
1	2	3	4	5	6	7	8	9
Female								
Male								

Block 4:TB HIV status

Patients Tested for HIV	Total HIV Positive	HIV +ve TB Patients on	
		ART	CPT
1	2	3	4

Block 5:Contact Investigation

1	Total Number of Close Contacts	
2	Total Number Investigated (Examined)	
3	Total Number diagnosed with DS/DRTB	
4	Total Number linked to DS/DRTB treatment and Care	

Block 6:Treatment Outcome

Types of DR TB	Registered		Cured		Treatment Completed		Died		Lost to Follow up		Not Evaluated		Switched to							
													MDR/RR (Longer)		PRE-XDR (Shorter)		PRE-XDR (Longer)		XDR	
	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
1	2	3	4	5	6	7	8	9	10	11	10	13	14	15	16	17	18	19	20	21
MDR/RR (Shorter)- *Cases Reg 16 Month Ago*																				
MDR/RR (Longer)- *Cases Reg 24 Month Ago*																				
PRE-XDR (Shorter)- *Cases Reg 16 Month Ago*																				
Pre-XDR (Longer)- *Cases Reg 24 Month Ago*																				
XDR- *Cases Reg 24 Month Ago*																				

**TAF= Treatment After Failure, **TALF= Treatment After Loss to Follow-up, ***OPT= Other Previously Treated, ****UPTH- Unknown Previous Treatment History*

HMIS 6.10

Government of Nepal

Health Management Information System

aDSM Adverse Event Recording/Reporting Form

A. Patient and Health Facility Information

Name/Patient ID number (as DRTB Register:			Treatment Centre:	
Date of Birth (or Age):			Province:	
Sex:	☐ Male	☐ Female		
HIV status:	☐ Non-reactive	☐ Reactive		
Pregnancy:	☐ No	☐ Yes	Trimester:	
Weight (kg):			Height (cm):	BMI:

B. Adverse events experienced by patient (including abnormal investigations)

Adverse event	Onset date	End date	Severity grade	Seriousness *	Outcome §

* Please select: *D died* *LT life threatening* *HA caused or prolonged hospital admission* *PD permanent disability* *OS other medically serious* *CA congenital abnormality* *NS not serious*

§ Please select: *A recovered* *B recovering* *C recovered with residual effects* *D died* *E not recovered* *F unknown*

Detailed description of adverse event(s):

Was treatment of adverse event required? ☐ No ☐ Yes (please specify):

C. Laboratory assessment: Results of tests and procedures

Test performed	Test date	Result	Unit	Reference range

D. Medicines: DR-TB Regimen and other concomitant medicines, vaccines, traditional / herbal medicines and dietary supplements

☑ *Tick if medicine suspected of causing adverse event*

Medicine	Dose	Frequency	Route	Start date	Stop date	Reason for use	Action taken †	Response ‡
☐								
☐								
☐								
☐								
☐								

† *Action taken in response to AE:* *DW drug withdrawn* *DR dose reduced* *DI dose increased* *DNC dose not changed* *UK unknown* *NA not applicable*

‡ *Response to action taken:* *RA recovered* *NE no effect on AE* *FA fatal AE* *UN unknown* *NA not applicable*

E. Re-challenge information

List any medicines that were restarted and indicate effect on adverse event

Medicine	adverse event recurred	adverse event did not recur	unknown
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

F. Other relevant information e.g. medical history, concurrent illnesses, smoking, alcohol use and Hospital Management

HMIS 6.10

Government of Nepal
Health Management Information System

aDSM Adverse Event Recording/Reporting Form

G. Causality Assessment at Treatment Center Level

1. Certain 2. Probable 3. Possible 4. Unlikely 5. Unassessed 6. Un-assessable

Comments:

H. Final AE/SAE Summary

Adverse Events Description:

Event Start date

Event End date

Severity Grading

Event classified: 1. Serious 2. Not – Serious (Based on Annex 2)

Narrative / Additional information (Final Result):

G. Reporter Information

Name:			Phone number:	
Email:				
Occupation:	☐ Doctor	☐ Nurse	☐ Paramedics	☐ Other (please specify):
Signature:			Date	

Submit form to:

Email to: M&E Unit, NTCC: aDSMNTCC@gmail.com

NTC Use Only:

Date received by NTCC:						
Causality assessment:	☐ Certain	☐ Probable	☐ Possible	☐ Unlikely	☐ Unassessed	☐ Un-assessable
Comment:						

Reported to DDA:	☐ No	☐ Yes	Date reported to DDA:

Sample forms for Core Package of aDSM

11.1 Clinical and laboratory testing schedule for aDSM

To be adapted to the treatment regimen and national policy[1]

	M0	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23	M24
Date																									
Clinical screen																									
Visual acuity																									
Simple hearing test																									
Audiogram																									
Neuro & psychiatric investigations																									
Serum creatinine																									
ALT (SGPT)																									
AST (SGOT)																									
Bilirubin																									
Alkaline phospatase																									
γGT																									
ECG																									
Lipase																									
Amylase																									
Potassium																									
Magnesium																									
Calcium																									
Albumin																									
CBC																									
Blood glucose																									
Thyroid tests: TSH																									

[1] *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* (WHO/HTM/TB/2014.11). Geneva, World Health Organization. 2014

Shade cells for the months when the test will not be done.

Notation for marking the cells: 0= screen/test not done 1=screen/test done; result pending 2=screen/test done; no SAE 3=screen/test done; SAE detected

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic-oxaloacetic transaminase);

CBC=complete blood count; ECG=electrocardiogram; γGT=gamma glutamyl transferase; TSH=thyroid stimulating hormone.

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TECHNICAL SUPPORT BY:

World Health Organization
Nepal