REPUBLIC OF ZAMBIA

THE NATIONAL TUBERCULOSIS AND LEPROSY CONTROL PROGRAM

GUIDELINES

FOR THE PROGRAMMATIC MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS IN ZAMBIA

UNITE TO END TB

THIRD EDITION - 2017

Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis in Zambia

Third edition

October 2017

FOREWORD

The Ministry of Health through the National Tuberculosis and Leprosy Programme (NTLP) has launched an ambitious National Strategic Plan (NSP) 2017–2021 for TB prevention, care, and elimination in Zambia with the theme "Towards TB Elimination". The publication of the third edition of the drug-resistant TB (DR-TB) guidelines complements the NSP 2017–2021. These guidelines provide the latest guidance for all aspects of the programmatic and clinical management of DR-TB at all levels of the health care system, as well as clinical guidance on the use of the multidrug-resistant TB (MDR-TB) shorter regimen and new DR-TB drugs in line with the international standards. These updated guidelines have introduced novel approaches for detecting and treating patients with MDR-TB.

MDR-TB is a national health threat. Currently, only 10% of the estimated MDR-TB cases are detected. Out of the few identified MDR-TB patients, more than 25% are not put on the second-line anti-TB drugs. Further, only 51% of patients commenced on MDR-TB treatment are successfully treated. These guidelines have introduced the MDR-TB shorter regimen requiring patients to be treated with a nine months' MDR-TB regimen as opposed to a more prolonged treatment regimen that used to last for more than two years. These guidelines also provide guidance on increasing MDR-TB treatment initiation and clinical follow-up centres from only two centres to all provincial and district hospitals countrywide. This means patients will for the first time be accessing DR-TB services close to their homes.

In line with the National Health Strategic Plan (2017–2021) that prioritizes the primary health care approach as a strategy to improve access to health services, these guidelines have introduced a community care model of MDR-TB management. MDR-TB patients who are not acutely ill no longer require hospital admission. This approach in addition to the introduction of a shorter MDR-TB regimen will significantly improve adherence to MDR-TB treatment, thus supporting the country in achieving high cure and treatment success rates.

Drug-resistant TB is a notifiable disease per the Public Health Act, Chapter 295 of the laws of Zambia; therefore, all care providers managing DR-TB clients both in public and private sectors are expected to ensure that all DR-TB cases are notified in line with the government policies and guidelines.

I urge all health care workers in both public and private institutions and the community to efficiently use these guidelines to avoid DR-TB becoming a major public health problem in Zambia. The guidelines will continue to be updated as new knowledge becomes available.

HON. DR. CHITALU CHILUFYA, MP
MINISTER OF HEALTH

ACKNOWLEDGEMENTS

The development of these guidelines was a result of collaborative efforts of various organizations, institutions, clinicians, individuals, and the civil society organizations. The Ministry of Health applauds the Department of Public Health and Research and the National Tuberculosis and Leprosy Control Programme Unit for their stewardship and coordination roles they played throughout the process of developing these guidelines. The United States Agency for International Development (USAID) through the Challenge TB and Eradicate TB projects, the Resident TB Technical Advisor, the Stop TB Partnership Consultant, KNCV, and the Global Fund to Fight AIDS, Tuberculosis and Malaria should be acknowledged for their financial and technical support toward the development of this document.

DR. JABBIN MULWANDA
PERMANENT SECRETARY-TECHNICAL SERVICES

Table of Contents

ABBREVIATIONS

ACSM	Advocacy, communication, and social mobilization
ADR	Adverse drug reaction
aDSM	Active drug safety monitoring and management
AE	Adverse event
AFB	Acid fast bacilli
AIDS	Acquired Immune Deficiency Syndrome
ALAT	Alanine aminotransferase
Am	Amikacin
Amx/Clv	Amoxicillin/clavulanate
ART	Antiretroviral therapy
ASAT	Aspartate aminotransferase
ATV/r	Atanazavir/ritonavir
Bdq	Bedaquiline
BMI	Body mass index
CA CDL	Causality assessment Chest Diseases Laboratory
CEC	Clinical expert committee
Cfz	Clofazimine
Clv	Clavulanate
Cm	Capreomycin
CNS CMV CPT	Central nervous system Cytomegalovirus Cotrimoxazole preventive therapy
CrCl	Creatinine clearance
Cs	Cycloserine
CSF	Cerebrospinal fluid
CTB	Challenge TB
Dlm	Delamanid
DM	Diabetes mellitus
DOT	Directly observed therapy
DRS	Drug resistance survey
DR-TB	Drug-resistant tuberculosis
DST	Drug-susceptibility testing
DS-TB	Drug-susceptible tuberculosis
DTLO	District tuberculosis and leprosy officers
E or EMB	Ethambutol
ECG	Electrocardiogram
EFV	Efavirenz
EPTB	Extra-pulmonary tuberculosis
Eto	Ethionamide

FLD FL LPA	First-line drug First-line line probe assay
FQ	Fluoroquinolone
GDF	Global Drug Facility
GLC	Green Light Committee
GLI	Global Laboratory Initiative
H or INH	Isoniazid
H^{HD}	Isoniazid high dose
HIV	Human Immunodeficiency Virus
Imp/Cln INH	Imipenem/cilastatin isoniazid
IRIS	Immune reconstitution inflammatory syndrome
Km	Kanamycin
LF-LAM LFT	Lateral flow lipoarabinomannan assay Liver function test
Lfx	Levofloxacin
LJ	Lowenstein Jensen
LPA	Line probe assay
LPV/r	Lopinavir/ritonavir
LTFU	Lost to follow-up
Lzd	Linezolid
M&E	Monitoring and evaluation
MDR-TB	Multidrug-resistant tuberculosis
Mfx	Moxifloxacin
MGIT	Mycobacterial growth indicator tube
MIC	Minimum inhibitory concentration
Mpm	Meropenem
MTB	Mycobacterium tuberculosis
ND	New drugs
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRL	National TB Reference Laboratory
NRTI	Nucleoside reverse transcriptase inhibitor
NTH	Ndola Teaching Hospital
NTLP	National Tuberculosis and Leprosy Control Program
NTM	Nontuberculous mycobacteria
NVP	Nevirapine
Ofx	Ofloxacin
PAS	Para-aminosalicylic acid
pDST	Phenotypic drug-susceptibility testing
PI	Protease inhibitor
PK	Pharmacokinetics
PLHIV	People living with HIV

PMDT	Programmatic management of drug-resistant tuberculosis
Pre-XDR-TB	Pre-extensively drug-resistant tuberculosis
PTB	Pulmonary tuberculosis
Pto	Prothionamide
QTc QTcF R or RIF	corrected QT interval corrected QT interval by Fredericia Rifampicin
RR	Rifampicin resistance
RR-TB	Rifampicin resistant tuberculosis
SAE	Serious adverse event
SL LPA	Second-line line probe assay
SLD	Second-line drug
SLI Sm	Second-line injectable Streptomycin
SOP	Standard operating procedure
STR	Shorter DR-TB treatment regimen
T	Thioacetazone
TB	Tuberculosis
TB IC	Tuberculosis infection control
TDRC	Tropical Diseases Research Centre
TSH	Thyroid stimulating hormone
ULN	Upper limits of normal
UMC UTH	Uppsala Monitoring Centre University Teaching Hospital
WHO	World Health Organization
WRD	WHO recommended rapid diagnostics
XDR-TB	Extensively drug-resistant tuberculosis
Xpert MTB/RIF	GeneXpert MTB/RIF
Z or PZA	Pyrazinamide
ZAMRA	Zambia Medicines Regulatory Authority

CHAPTER 1. INTRODUCTION AND OVERVIEW

In 2015, 10.4 million people globally developed tuberculosis (TB) and 1.4 million died, with TB remaining one of the top 10 causes of death [1]. Of the estimated 580,000 people newly eligible for multidrug-resistant TB (MDR-TB) treatment, only 125,000 (20%) were enrolled on treatment. The approach currently used for MDR-TB management requires a lengthy treatment period of at least 20 months; has multiple toxicities and adverse events; is less effective when compared to first-line regimens; is costly, both for patients and TB programmes; and requires health care worker expertise. MDR-TB treatment success rates remain unacceptably low at 52% overall [1].

Despite fairly good treatment success rates for drug-susceptible TB (DS-TB), MDR-TB is a growing problem in Zambia. The World Health Organization (WHO) Global Tuberculosis Report 2016 estimated there were 1,500 MDR/rifampicin resistant TB (RR-TB) patients among notified pulmonary TB patients in Zambia in 2015; in the same year, only 196 patients were bacteriologically confirmed with MDR/RR-TB, and 99 patients were started on treatment [1]. The estimated MDR/RR-TB prevalence among new and previously treated TB patients was 1.1% and 18% respectively. With reference to the above findings, WHO projects the burden of MDR-TB and RR-TB in Zambia by 2021 to be 1,610 and 2,415 respectively [1].

In May 2011, WHO produced policy guidance recommending GeneXpert MTB/RIF (Xpert MTB/RIF) as the preferred rapid molecular diagnostic test for rifampicin resistance (RR) for all patients with signs and symptoms of TB [2]. Laboratory support is essential for improving the capacity to diagnose DR-TB and to support the implementation of the shorter regimen and new DR-TB drugs in Zambia. In 2012, the National Tuberculosis and Leprosy Programme (NTLP) endorsed the WHO recommendations and introduced diagnostic algorithms recommending Xpert MTB/RIF as the primary diagnostic tool for high-risk presumptive TB patients. In this guideline update, Xpert MTB/RIF is now recommended as the universal test for all presumptive TB patients regardless of risk factors, and there is an ongoing effort to improve access by placing Xpert MTB/RIF machines as close as possible to patients in their communities. To further improve DR-TB diagnosis, second-line line probe assay (SL LPA) is available for the early detection of resistance to key second-line DR-TB drugs; one national and two regional TB reference laboratories have incorporated SL LPA technology and are in the process of implementation, including the Chest Diseases Laboratory (CDL) and University Teaching Hospital (UTH) in Lusaka and the Tropical Diseases Research Centre (TDRC) in Ndola. Resistance testing to additional second-line drugs, including new and repurposed drugs for DR-TB, will be considered in the future as testing methods are validated and become more widely available.

WHO produced guidance on the use of two new agents to improve DR-TB treatment outcomes—bedaquiline and delamanid—in 2013 and 2014 respectively [3,4]. In May 2016, WHO issued recommendations on the use of a shorter DR-TB treatment regimen [5] for uncomplicated DR-TB treatment. This updated version of the national Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis (PMDT) describes the steps necessary to

implement the shorter regimen and individualized regimens containing new drugs for DR-TB treatment in Zambia, including the organization and management of DR-TB control; detection and diagnosis of DR-TB; bacteriological confirmation of drug resistance; DR-TB treatment regimen design; DR-TB in special populations; identification and management of close contacts; monitoring and management of adverse events as part of active drug safety monitoring and management (aDSM); promoting adherence to DR-TB treatment; DR-TB infection control; and programmatic monitoring and evaluation.

CHAPTER 2.
THE ORGANIZATION AND MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS CONTROL

2.1 PMDT structure

The management of DR-TB in Zambia follows a multidisciplinary framework which includes the following specialties: clinicians, laboratory personnel, pharmacists, programme managers, community health care workers, monitoring and evaluation managers, supporting partners, procurement and supply chain managers, regulatory authorities, civil society, and DR-TB patients. The programmatic management of drug-resistant tuberculosis (PMDT) management structure spans national and sub-national (provincial, district, and facility) levels. At the national level, the TB Technical Working Group provides oversight of provincial PMDT committees, guideline development, and programmatic evaluation; the Technical Working Group should meet quarterly with reports from the chairperson to the NTLP manager. Provincial PMDT committees should meet at least quarterly, and they should have representation from the specialties listed above. Lastly, a national-level clinical expert committee (CEC) should meet monthly to provide oversight to CECs from each provincial hospital; the composition of the National CEC should consist of clinicians (physicians, pediatricians, obstetricians, amongst others) and pharmacists with DR-TB experience from throughout the country. The main role of each provincial CEC is to provide clinical guidance on the management of complex DR-TB patients, including all patients started on the shorter regimen or individualized regimens containing new drugs. Annexure 1 provides a sample terms of reference for clinical expert committees, as well as outlines the roles and responsibilities of the DR-TB clinical care team (Figure 6).

2.2 Diagnosis of DR-TB

There are 187 Xpert MTB/RIF machines at diagnostic centres spread across the country. In Zambia, there is one National TB Reference Laboratory (CDL in Lusaka) and two Regional TB Reference Laboratories (UTH in Lusaka and TDRC in Ndola). The three facilities can perform culture and first-line phenotypic drug-susceptibility testing (DST), and they have the capacity to perform first- and second-line genotypic DST via line probe assay (LPA). District and provincial facilities should refer specimens for LPA, culture, and DST to the aforementioned laboratories and be responsible for the follow-up of results.

2.3 Initiation of DR-TB treatment

The main centres initiating DR-TB treatment are located at provincial hospitals in the country. Two of them, the University Teaching Hospital (UTH) and Ndola Teaching Hospital (NTH), are the referral centres with the capacity to manage pre-extensively drug-resistant TB (pre-XDR-TB) and extensively drug-resistant TB (XDR-TB) patients and other patients that require individualized regimens containing new drugs. As part of the decentralization process, capacity is being built at additional provincial hospitals to initiate and manage patients with pre-XDR-TB and XDR-TB as well as additional district locations for standard DR-TB treatment initiation.

Each DR-TB treatment initiation site should ensure that before commencing therapy all the drugs in the regimen are available, appropriate monitoring equipment is in place, staff have received DR-TB training, and a guaranteed chain of supply of drugs and other health product consumables is in place from start to completion of treatment. Provincial PMDT committees should ensure that a new DR-TB treatment initiation site meets the above criteria prior to initiation of DR-TB treatment at the site.

2.4 Follow-up of patients on DR-TB treatment

Stable patients may be down referred from DR-TB treatment initiation sites to district hospitals or primary health facilities, provided inpatients meet discharge criteria (see Section 2.6) and all patients are referred to facilities providing DR-TB directly observed therapy (DOT). Primary care DOT centres are responsible for the daily follow-up of patients as well as administration of drugs for those on ambulatory care. At the community level, trained community health care workers can provide DOT as well as help with tracing contacts of DR-TB patients and patients who are lost to follow-up. Ideally, a home visit should be done for all DR-TB patients starting DR-TB treatment, in order to educate the patient's family on DR-TB; assess infection control measures in the home; identify and screen all contacts; and promote support from the family for the patient's adherence to treatment. All DR-TB patients should have monthly clinical follow-ups with a DR-TB doctor, either from clinical teams that travel to DOT centres or grouped district locations; trained clinical staff at primary care DOT centres; or by sending patients back to centralized sites at the district or provincial level for clinical monitoring and management.

2.5 Organization of DR-TB care

Patients with DR-TB may need both inpatient and outpatient care at different times during DR-TB treatment. It is not required to hospitalize patients to initiate DR-TB treatment if they are stable and have uncomplicated disease. Regardless of the location where patients receive DR-TB management, infection control is critical and should be observed at all levels of care: hospitals, primary health centres, and in the community. Infection prevention measures must be adhered to by clinical staff and patients in order to prevent transmission of disease and contain the burden of DR-TB (see Chapter 13, Infection Control).

Ambulatory (outpatient) model of care: Zambia has adopted a patient-centred approach to DR-TB care that includes ambulatory care in decentralized settings to treat DR-TB patients that do not have acute medical conditions. This is in line with the Ministry of Health's mission statement to take TB health services as close to the family and community as possible to improve service delivery and treatment outcomes. The following ambulatory treatment options are considered:

- **Ambulatory care throughout DR-TB treatment**: DR-TB treatment, including the shorter regimen or an individualized regimen with new drugs, is initiated on an ambulatory basis with no hospitalization unless there is an acute medical condition. The QT prolongation that may occur in patients receiving bedaquiline or delamanid can be monitored in the outpatient setting. There is no reason to admit stable patients to initiate bedaquiline or delamanid; delamanid takes 8 weeks to reach its peak concentration, and bedaquiline up to 16 weeks.

- **Ambulatory care after stabilization**: Seriously ill patients are hospitalized to initiate DR-TB treatment and/or address comorbidities and complications, and then they are discharged to ambulatory care once their clinical condition has stabilized and major symptoms have been controlled.
- **Inpatient model of care:** Hospitalization of patients starting treatment (or at any time on treatment) should be considered for the following indications or reasons:
    - The patient is too ill (clinically or psychologically) to commence DR-TB treatment on an ambulatory basis.
    - DOT and adherence support are not guaranteed.
    - The patient experiences a severe adverse drug reaction.
    - Implementation of adequate infection control measures are not feasible at home or the place of employment.
    - Patient monitoring cannot be implemented on an outpatient basis.

      Hospitalization should not be for the entire course of treatment; after stabilization and management of the adverse drug reaction, or in certain cases sputum conversion, the patient should be discharged and managed on an ambulatory basis.
    - Hospital infection control policies and procedures are in place and isolation rooms are available.

2.6 Discharge criteria

Patients who meet the following criteria can be discharged to ambulatory care:

- Patients whose clinical status has improved to the extent that he/she can be managed on ambulatory basis.
- Measures to ensure full implementation of DOT, adherence support, and regular follow-up have been put in place (including transport).
- The inpatient medical team has educated the family or relatives on DOT options, adherence support, and infection control measures in the home.
- The social worker has certified that the home environment facilitates adherence to treatment.
- The health facility team has conducted contact tracing and investigation.
- Adequate nutritional and social patient support is available to the patient.
- The receiving facility has been oriented and mentored on the patient's management.
- At least a 3-month supply of DR-TB medications (and usually the entire course of treatment), including drugs for the shorter regimen or the complete 6-month course of bedaquiline or delamanid, should be sent to the receiving facility.
- The receiving facility should order additional supplies, including ancillary drugs for side effect management.

CHAPTER 3.
DETECTION AND DIAGNOSIS OF DRUG-RESISTANT TUBERCULOSIS

3.1 DR-TB patient detection

The diagnosis and treatment of persons with DR-TB starts with identification of a presumptive DR-TB patient. All health care workers in all parts of the health care system (not only NTLP affiliated facilities or staff involved in TB care) should receive training to be alert to and know how to ask patients about TB symptoms and refer them for TB diagnostic testing. TB screening should be well established for patients accessing care at all primary care centres and hospitals; actively asking all patients about cough (including those who do not mention cough spontaneously) can yield identification of a substantial additional number of patients.

Sputum samples from all presumptive TB patients should be sent for Xpert MTB/RIF rapid diagnostic testing, and a chest X-ray should be obtained for patients when the diagnosis of TB is uncertain. Every effort should be undertaken to confirm the diagnosis of RR-TB/MDR-TB with Xpert MTB/RIF, especially for patients in the following risk categories:

- A close contact of a person diagnosed with DR-TB, especially if the person is not on treatment, is failing treatment, or has recently died from DR-TB disease.
- Someone who has a history of TB treatment failure, lost to follow-up from DS-TB or DR-TB treatment, or could be considered to have early relapse from a previously treated DS-TB or DR-TB (successfully treated less than two years previously).
- HIV co-infected patients with severe immunosuppression: bacteriologic confirmation may be difficult so a history of contacts and risk factors is important.
- Persons recently from facilities with high rates of DR-TB: the risk of nosocomial infection is high for health care workers, miners, prisoners, and patients admitted for prolonged periods, especially in the absence of appropriate infection control measures.
- DS-TB patients who remain smear positive ≥ 2 months on first-line drug treatment, as this may indicate the presence of drug resistance.

3.2. Diagnosis of drug-resistant tuberculosis

3.2.1 Clinical presentation

- The clinical features of DR-TB are not different from those of drug-susceptible TB (both pulmonary and extra-pulmonary TB).
- DR-TB is by definition a bacteriological diagnosis. However, in patients where bacteriological confirmation is difficult, such as children, HIV-positive patients, or those with extra-pulmonary TB, and those who are also close contacts of known DR-TB patients, a clinical diagnosis of DR-TB can be made. Such patients should be discussed with the clinical expert committee (CEC).

3.2.2 Bacteriologic confirmation

Xpert MTB/RIF has been recommended as the primary diagnostic test in all adults and children with signs and symptoms of TB where available (See Figure 1) [2,6].

Rapid molecular tests such as Xpert MTB/RIF and LPA (FL and SL) are being scaled up to increase access to the prompt diagnosis of resistance to rifampicin (Xpert MTB/RIF); rifampicin plus isoniazid (FL LPA); and key second-line drugs such as the fluoroquinolones and second-line injectables (SL LPA) (see Table 1).

- The diagnosis of DR-TB is done by Xpert MTB/RIF, line probe assay (first- and second-line LPA), culture, and phenotypic drug-susceptibility testing (pDST).
- In facilities where Xpert MTB/RIF is not yet available, samples should be referred to the nearest facility where the test is available, especially for individuals with risk factors of DR-TB (Section 3.1).
- **Patients who require TB re-treatment based on history should NOT get the category II regimen** (the standard DS-TB regimen plus streptomycin). Instead, patients should get drug-susceptibility testing with rapid molecular testing (Xpert MTB/RIF, FL and SL LPA) to inform the choice of treatment. WHO no longer recommends the use of the category II regimen [7].
- For all patients with rifampicin resistance detected on Xpert MTB/RIF, samples should be sent for FL and SL LPA, culture, and phenotypic DST; **for those eligible, the shorter DR-TB treatment regimen should be started while awaiting results from LPA and/or culture/DST.**
- The turnaround time (specimen collection until receipt of results) for LPA and culture/DST results varies on when the test becomes positive and the type of media used (e.g. liquid or solid media for culture):
    - Line probe assay results should take between 3–14 days (turnaround time of LPA within the processing lab should be 48 hours).
    - Liquid culture (mycobacterial growth indicator tube [MGIT]): positive results at 4–14 days, negative result by 42 days.
    - Solid culture (Lowenstein Jensen [LJ]): positive results at 28–56 days, negative result by 60 days.
    - Phenotypic DST results (from the date culture was positive): MGIT 14 days, LJ 30 days.
- Phenotypic DST (pDST) is reliable and reproducible for rifampicin (RIF), isoniazid (INH), kanamycin (Km), amikacin (Am), ofloxacin (Ofx), and levofloxacin (Lfx).
    - Moxifloxacin (Mfx): There is a need for critical concentrations to be re-evaluated.
    - Ethambutol (EMB), streptomycin (Sm), capreomycin (Cm), ethionamide (Eto)/Prothionamide (Pto), cycloserine (Cs), pyrazinamide (PZA), para-aminosalicylic acid (PAS): pDST is not reliable.
    - New and repurposed drugs bedaquiline (Bdq), delamanid (Dlm), clofazimine (Cfz), and linezolid (Lzd): pDST needs validation and is not widely available outside of research settings.

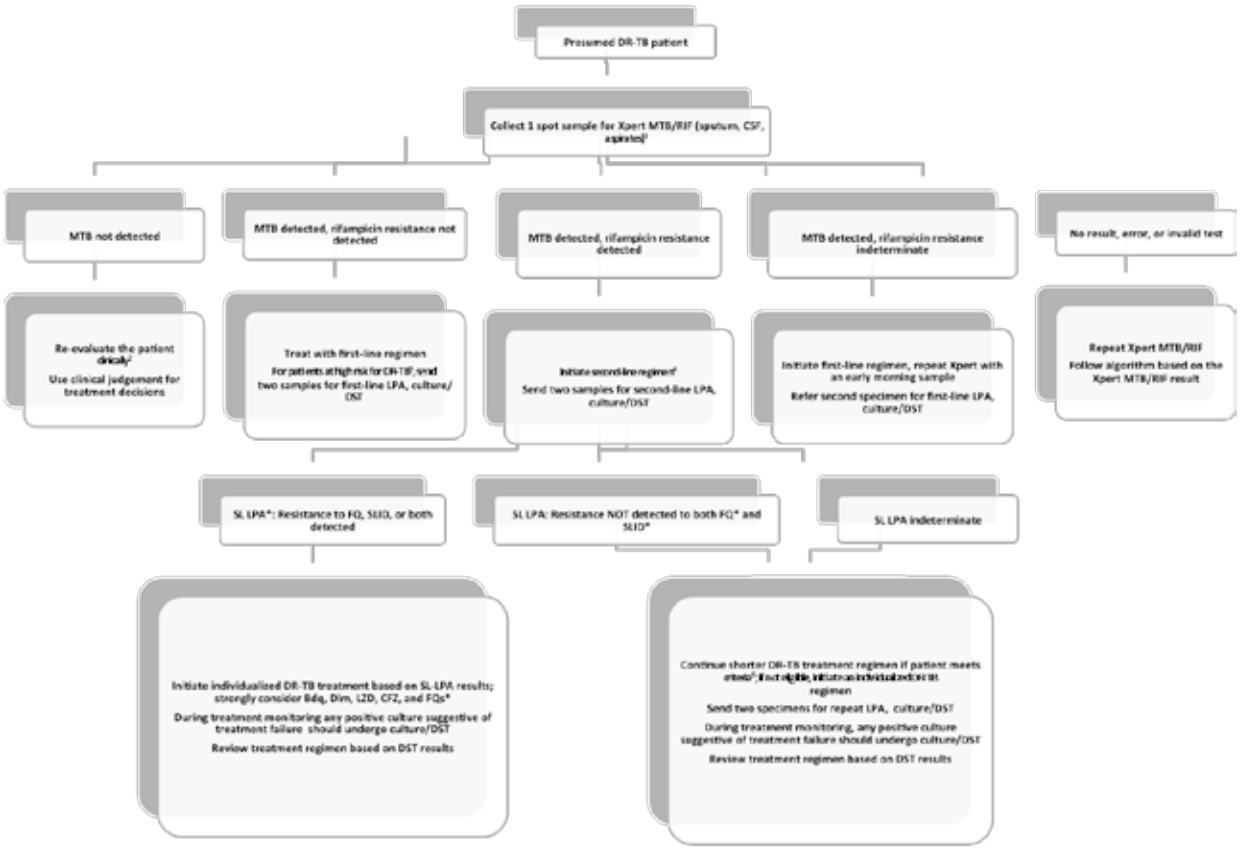
Table 1: Description of different diagnostic tests for drug-resistant tuberculosis

Method	Principle	What is detected	Indication	Detection of living mycobacteria	Advantages	Disadvantages
Microscopy	Staining	AFB	(Initial test if Xpert MTB/RIF is not available) Monitoring treatment	No	Fast (<1 hour), cheap, widely available	Low sensitivity, no speciation
Xpert MTB/RIF	Molecular genotypic test, real time PCR based	MTB, rifampicin resistance	Initial test of choice for all presumptive TB patients	No	Fast (2 hours), high sensitivity and specificity	Relatively expensive, specific settings, maintenance and supply logistics Only resistance to RIF
LPA **FL:** Hain MTBDR plus **SL:** Hain MTBDRsl v2	Molecular genotypic test, line probe assay (PCR + hybridization)	MTB, resistance to RIF and INH (FL) and FQ and SLI (SL)	FL LPA: detection of resistance to RIF and INH; use for RIF sensitive, MTB positive Xpert results SL LPA: use for SL resistance testing in all patients diagnosed with RR on Xpert	No	Relatively fast (1 day), confirms MTB and detects resistance to FLD and SLD by recognition of mutations	Relatively expensive, Biosafety level 2 & 3, Highly skilled staff, FL LPA only performed in smear positive samples, SL LPA performed regardless of smear positivity, but SL LPA on smear negative samples can give uninterpretable result

Method	Principle	What is detected	Indication	Detection of living mycobacteria	Advantages	Disadvantages
Culture	Incubation of bacteria on liquid (MGIT) or solid (LJ) media	MTB species	Test for all presumptive and RR positive DR-TB patients Monitoring treatment	**Yes**	Detects live mycobacteria, high sensitivity, relatively fast on liquid media (70% culture positive between 4–14 days)	Relatively expensive, Biosafety level 2 & 3, Highly skilled staff, slow growth on solid media (up to 2 months), relatively slow on liquid media (⩽ 42 days)
Phenotypic DST	Phenotypic test, based on incubation of mycobacteria in presence of antibiotics	Resistance to **FLD: R, H** (EZ); **SLD: FQ/SLD** (+/- Eto, Cs, Cfz, Lzd, PAS, Bdq, Dlm)	Baseline for all DR-TB patients; during treatment if suspect failure or smear or culture positive after ⩾ 4 months	**Yes**	Can catch resistant strains overlooked by genotypic methods	Relatively expensive, Require culture to be completed and confirmed, Relatively slow (14 days for liquid and 30 days for solid after culture positivity)

3.2.3 Diagnostic algorithms

Figure 1: Diagnostic testing and management of presumptive TB patients



*DST=Drug-susceptibility testing; SL LPA=Second-line line probe assay; FL=first-line; FQ=Fluoroquinolone; SLID=Second-line injectable drugs; Bdq=bedaquiline; Dlm=delamanid; LZD=linezolid; CFZ=clofazamine

[1] Broncoalveolar lavage, gastric lavage, and gastric aspirate specimens have a low yield of bacteria hence a negative result does not always rule out TB. Data are limited for the sensitivity of Xpert MTB/RIF with other samples such as nasopharyngeal aspirates, string test samples, stool samples, and other extra-pulmonary tuberculosis samples.

[2] Further investigations may include chest X-rays, additional clinical assessments, other biological specimens (tissue aspirates and biopsies), clinical response following treatment with broad spectrum anti-microbial agents and repeat Xpert MTB/RIF testing. For patients being evaluated for TB who are HIV-positive and have a CD4 count of less than 100 cells/µl or are seriously ill, perform urine LF-LAM TB test according to national guidelines.

[3] For patients at high risk of DR-TB, a sample should be sent for Xpert and culture/pDST: known DR-TB contacts; previously treated TB patients, including lost to follow-up, relapse, and treatment failure; smear positive at ≥ 2 months of first-line TB treatment; health care workers; miners and prisoners; and HIV co-infected patients, especially those with severe immunosuppression.

[4] Patients may be initiated on the shorter DR-TB regimen if the patient is assessed as being at low risk of having resistance to FQs and to SLIDs and meets the eligibility requirements (Figure 2). In patients at high risk of resistance, design of the treatment regimen to initiate may be guided by SL LPA if the results can be obtained rapidly.

[5] The shorter DR-TB regimen may be used in DR-TB patients who do not have confirmed resistance or suspected ineffectiveness to second-line drugs. The specific eligibility criteria for the shorter DR-TB regimen are: 1) no confirmed resistance to fluoroquinolones (FQ) and/or a second-line injectable (SLI); 2) no contact with a patient that has resistance to FQ and/or SLI; 3) no exposure to SLD for ≥ 1 month; 4) no known intolerance to drugs in the shorter regimen; 5) not pregnant; 6) no form of extra-pulmonary TB; and no other risk of an unfavorable outcome. Please see Chapter 4 for more detail on treatment regimen choice.

3.2.4 Approach to discordant drug-susceptibility testing (DST) results

Discordance in drug-susceptibility testing (DST) results may happen, usually when comparing culture-based results (phenotypic DST) with molecular results (genotypic DST). Each individual case of discordant results will need to be investigated in collaboration with laboratory personnel, and treatment regimen decisions should be discussed with the clinical expert committee (CEC). As a general rule, the patient should be treated according to the positive result and highest resistance pattern. DNA sequencing of the TB genome can solve the dilemma when it potentially becomes available in the future.

Different possibilities for potential discordant results are as follows [8]:

1. **Xpert MTB/RIF MTB detected, culture negative:** Treat the patient according to the Xpert MTB/RIF detected result (submit another sample for culture).

Possible reasons for negative cultures in persons with pulmonary TB:

- Patient is being treated for TB.
- Transport or processing problems that inactivates the tubercle bacilli.
- Inadequate testing volume.
- Laboratory or clerical error.

2. **Xpert MTB/RIF MTB not detected, culture positive:** Treat the patient based on the positive culture result.

- The positive culture result should be considered as bacteriological confirmation of TB (compared with culture, Xpert MTB/RIF can detect the presence of M. tuberculosis bacteria weeks before culture for 72%–98%—higher for smear positives—of patients suspected to have pulmonary TB whose TB is ultimately confirmed by culture [8]).
- Xpert MTB/RIF sensitivity is lower in people living with HIV (PLHIV), children, and other specimen types such as cerebrospinal fluid.
- False positive culture results are very rare due to laboratory errors such as cross contamination and sample labeling problems.

3. **Xpert MTB/RIF MTB detected, rifampicin resistance detected; rifampicin susceptible by phenotypic DST:** Treat the patient according to the Xpert MTB/RIF resistant result and repeat culture and phenotypic DST using solid media.

- Certain mutations are known to generate this discordant result, particularly in the BACTEC™ MGIT™ system (e.g. a false-susceptible phenotypic result).
- In some low DR-TB prevalence settings, silent mutations have been observed that generate a false resistant MTB/RIF result, but these tend to be very rare.

4. **Xpert MTB/RIF MTB detected, rifampicin resistance not detected (susceptible); rifampicin resistance by phenotypic DST:** Treatment decisions should be based on the culture phenotypic DST rifampicin resistant result.

- False rifampicin-susceptible Xpert MTB/RIF results are rare but have been observed in 1%–5% of TB cases tested in various epidemiologic settings.
- Mutations in the region of the rpoB gene sampled by the Xpert MTB/RIF tests have been shown to account for 95%–99% of rifampicin resistance. The remainder of rifampicin resistance arises from mutations outside the sampled region, which produce an Xpert MTB/RIF result of rifampicin resistance not detected.

5. **Xpert MTB/RIF MTB detected rifampicin not detected (susceptible); FL LPA rifampicin detected (resistant):** Treat the patient based on FL LPA (rifampicin resistant).

- This discordance is rare, due to hetero-resistant strains. Different populations of bacteria are co-existing with varying susceptibility to TB drugs (some are resistant and some sensitive).
- Depending on the treatment and "fitness" of the bacteria, different DST results from different samples may occur (especially if an interval has elapsed).
- Rifampicin hetero-resistance can be detected in FL LPA (detect absence of wild type and mutations) but not always in Xpert MTB/RIF (detects resistance by absence of wild type and single copy target of rpoB).
- Culture results can vary too, according to the prevalent population.

CHAPTER 4
TREATMENT OF DR-TB

4.1 Principles and goals of DR-TB treatment

The major goals of treatment for DR-TB disease are to:

- Cure DR-TB disease and prevent relapse in individual patients.
- Minimize the risk of death and disability in DR-TB patients.
- Detect DR-TB patients as early as possible.
- Promptly initiate appropriate therapy for patients with DR-TB.
- Reduce infectiousness and transmission of DR-TB strains to other people.
- Select medicines and regimens for the treatment of DR-TB in a manner that prevents emergence of further resistance.

In order to improve DR-TB treatment outcomes, adherence to treatment, and quality of life for DR-TB patients, the NTLP has adopted the WHO recommended shorter regimen (9 to 11 months) in patients without resistance or intolerance to key second-line drugs, including the fluoroquinolones (FQ) and/or second-line injectables (SLIs**). RR-TB patients should be evaluated to assess the risk of resistance or intolerance to FQ and/or SLI following the eligibility criteria for the shorter DR-TB regimen (Figure 3)**. After two sputum samples are collected and sent for SL LPA and culture/pDST, patients should be commenced on the shorter regimen until the results are available. **It is essential for clinicians to follow up on results of all samples sent for LPA and culture/pDST in order to modify the DR-TB regimen as indicated from resistance patterns.** For patients that are not eligible for the shorter regimen, an individualized treatment regimen should be designed containing new drugs such as bedaquiline (Bdq) and delamanid (Dlm) and repurposed drugs like linezolid (Lzd) and clofazimine (Cfz); Annexure 2 provides further detail on the new and repurposed drugs.

Summary of preparatory activities before initiating a patient on DR-TB treatment:

- Classification and registration including details of the patient's address and contact person.
- Initial clinical evaluation by history taking and physical examination.
- Collection of baseline samples for second-line LPA, culture, and DST.
- HIV testing and counseling (if positive, CD4 count; if on antiretroviral therapy (ART), viral load and CD4).
- Baseline laboratory evaluations (Chapter 8).
- Baseline radiological investigations, audiometry, and electrocardiogram (ECG).
- Patient education, adherence counseling, choosing a treatment supporter, and inviting family members to support the patient on treatment.
- Contact investigation.
- Confirm the availability of all second-line drugs in the treatment regimen.
- Register the patient according to standardized DR-TB patient definitions and create a treatment card (Chapter 12).

4.2.1 Patient education and information to be provided to each DR-TB patient:

- Nature of his/her illness (TB and DR-TB).
- Mechanism of transmission, the need to evaluate contacts, and prevention of further spread.
- Implication if there is concomitant HIV infection and importance of HIV testing.
- Medications and duration of treatment.
- Expected follow-up visits including necessary laboratory and radiological monitoring.
- Information not to share medications and appropriate storage of medications.
- All services related to the treatment of his/her illness (DR-TB) are free.
- Importance of adherence to treatment until completion.
- Expected adverse drug reactions and their manifestations; availability of treatment to treat side effects and whom to report when such manifestations occur.
- Expected treatment outcomes.
- Responsibilities of the patient including providing information on accurate contact details.
- Rights and responsibilities of the patient in relation to his/her treatment.
- Who to contact for psychosocial assistance during and after DR-TB treatment.
- Implications of pregnancy and contraception for women of childbearing age.

4.2.2 Initial patient evaluation

Before enrolling a patient, detailed history taking is necessary and should include the following:

1. Demographic data and patient classification:
   a. Name, age, sex.
   b. Address and contact details of the patient's family members.
   c. Patient classification: new, previously treated (failure, treatment after interruption, relapse, or transfer in), pulmonary/extra-pulmonary tuberculosis (EPTB).
2. TB history:
   a. Date of initial diagnosis.
   b. Start and end date of all previous treatments; adherence to treatment regimens; outcomes.
   c. Smear microscopy, Xpert MTB/RIF, FL/SL LPA, culture, and DST results.
   d. Adverse drug reactions, intolerance, and allergies.
   e. Surgical treatments (resections, chest tubes).

a. Complications (pneumothorax, empyema, massive hemoptysis).

3. Past medical and social history:
   a. Chronic medical conditions, including HIV, diabetes, renal insufficiency, chronic liver disease, chronic heart disease.
   b. Prior psychiatric history.
   c. Current medications not associated with TB.
   d. Allergies.
   e. Alcohol, drugs, and tobacco use.
   f. Incarceration history.
   g. Last menstrual period and method of contraception.

4. Documented or presumptive DR-TB contacts:
    a. Treatment history of contacts.
    b. Current status.
    c. DST data.
    d. Assessment of how closely the patient interacted with the contact.
5. Review of symptoms: cough, sputum production, fever, night sweats, weight loss (include previous weight when healthy, with date), dyspnea, chest pain, appetite, abdominal pain, nausea, vomiting, diarrhea, constipation, headache, peripheral neuropathy (leg pain, paresthesia), hearing loss, depression, anxiety.

- The initial evaluation serves to establish a baseline and may identify patients who are at increased risk of adverse drug reactions or poor treatment outcomes.
- Treatment monitoring and management of adverse events may need to be more intensive in patients with pre-existing conditions identified at the initial evaluation. This include conditions such as diabetes mellitus, renal insufficiency, acute or chronic liver disease, thyroid disease, mental illness, drug or alcohol dependence, HIV infection, and pregnancy/breastfeeding. In addition, it is essential that contraceptive methods during treatment for women of childbearing age be discussed (Depo-Provera or intrauterine device are preferred).
- Symptoms like nausea and vomiting need to be adequately treated before the initiation of treatment.
- Provider-initiated testing and counseling should be offered routinely if the HIV status is not already known; HIV treatment for all DR-TB patients diagnosed as HIV-positive should follow the national ART guidelines.
- Routine laboratory investigations such as full blood count and liver and kidney function tests should be done at baseline to aid treatment monitoring (Chapter 8); other investigations should be done based on preexisting comorbidities or as need arises.

4.3 Classification of DR-TB medicines

Medicines used in the shorter regimen and in the design of individualized regimens have been re-grouped by WHO [5] based on emerging evidence on their effectiveness and safety. Table 2 is adapted from the new WHO classification.

Table 2: Medicines recommended for the individualized treatment of RR-TB and MDR-TB[1]

Group A. Fluoroquinolones[2]		Levofloxacin Moxifloxacin	Lfx Mfx
Group B. Second-line injectable agents		Amikacin Capreomycin Kanamycin	Am Cm Km
Group C. Other core second-line agents[2]		Ethionamide/prothionamide Cycloserine/terizidone Linezolid Clofazimine[3]	Eto/Pto Cs/Trd Lzd Cfz
Group D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide High-dose isoniazid Ethambutol	Z H^{HD} E
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	Para-aminosalicylic acid Imipenem/cilastatin Meropenem + amoxicillin-clavulanate[4] (Thioacetazone)[5]	PAS Ipm Mpm + Amx-Clv (T)

[1]This regrouping is intended to guide the design of individualized regimens; for shorter regimens lasting 9–12 months, the composition is usually standardized.

[2]Medicines in Groups A and C are shown by decreasing order of usual preference for use.

[3]Clofazimine is a medicine commonly used for the treatment of leprosy.

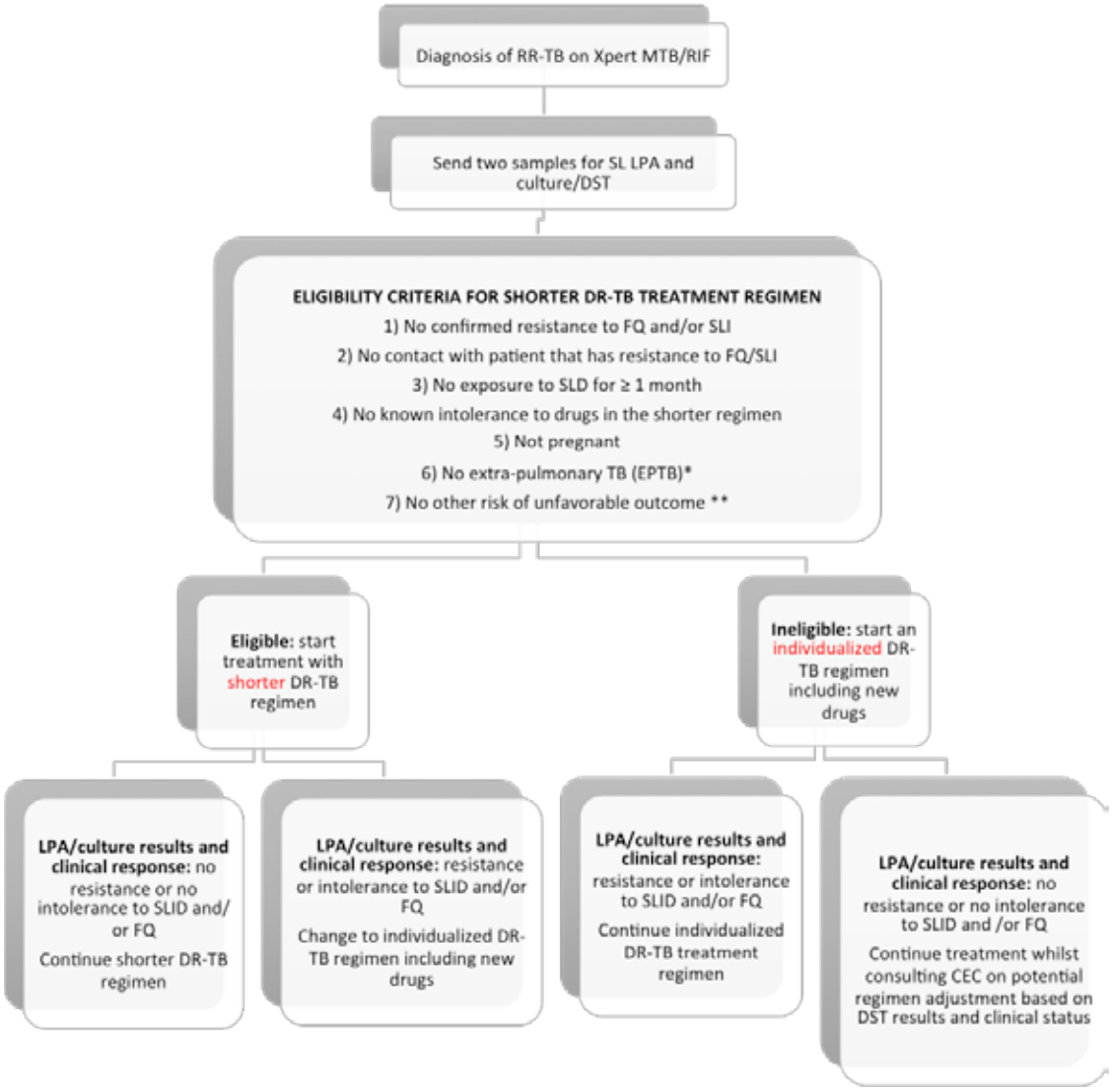
[4]Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin.

[5]The use of thioacetazone is strongly contraindicated in HIV-positive patients because it can cause severe (sometimes fatal) skin reactions. In addition, there is no advantage to using thioacetazone if the regimen used already contains ethambutol.

4.4 Selecting the appropriate DR-TB treatment regimen

For patients with confirmed RR-TB, a systematic approach must be followed to determine if the patient should be treated with the shorter or an individualized DR-TB regimen (Figure 2). Before starting treatment, collect **two sputum samples and send** for SL LPA, culture, and phenotypic FL/SL DST. Once sputum is collected, treatment initiation should **not be delayed** until LPA or DST results are known. However, it is essential to follow up on LPA and DST results; once the results are available, the initial regimen should be adjusted appropriately (Figure 2).

Figure 2: Algorithm of regimen choice for patients diagnosed with RR-TB



* Non-severe forms of EPTB can be eligible for the shorter DR-TB regimen, including TB pleural effusion (adults and children) and TB lymphadenitis (children).
**Patients to consider as high risk for an unfavorable outcome are patients with extensive parenchymal damage, poorly controlled diabetics, and HIV co-infected patients with severe immunosuppression.

4.4.1 Shorter DR-TB treatment regimen (STR)

The shorter DR-TB regimen represents a new standardized approach to managing the majority of DR-TB patients, with reduced costs, less toxicity, and potential for improved adherence and treatment outcomes. However, RR-/MDR-TB patients should be carefully selected for the shorter regimen based on eligibility criteria (Figure 2).

4.4.1.1 Patients eligible for the shorter DR-TB treatment regimen

- Patients with DR-TB who have not been previously treated with second-line drugs.
- Patients with low risk for resistance to FQs and/or SLI or with DST results excluding resistance to FQ and/or SLI.
- Children ⩽ 8 years of age, HIV-infected patients, or patients with non-severe forms of EPTB who:
  - Have not been previously treated with SLD.
  - Have a low risk of resistance to FQ and/or SLI.
  - In the absence of bacteriologic confirmation of DR-TB, who are clinically diagnosed with DR-TB based on risk factors (e.g. close contact of a known DR-TB patient).

4.4.1.2 Patients not eligible for the shorter DR-TB treatment regimen

- Patients with confirmed resistance or suspected ineffectiveness to FQ or SLI (the DST for other drugs of the shorter regimen are not available or reliable; INH resistance testing is reliable, and if resistance to INH is known, it is excluded from the shorter regimen).
- Patients with suspected resistance to FQ or SLI based on contact with patient with this resistance pattern or other risk factor.
- Patients with exposure to SLD for > 1 month (e.g. patients already on treatment with a conventional DR-TB treatment regimen for more than a month or patients with history of previous DR-TB treatment).
- Patients with intolerance to any of the medicines in the shorter treatment regimen.
- Pregnant women.
- Patients with extra-pulmonary TB; (an exception be made for patients with TB pleural effusion and children with TB lymphadenitis, who may be considered for the shorter treatment regimen).
- Patients with higher risk of treatment failure, such as extensive TB disease (patients with severely low body mass index [BMI] can be offered the shorter regimen with strong nutritional support and follow-up).

Presence of any of the above disqualifies a DR-TB patient from the shorter treatment regimen.

4.4.1.3 Regimen design for the shorter DR-TB treatment regimen

Standardized shorter DR-TB regimen
4–6 Km-Mfx-Cfz-Eto-Z-E-H^{HD} / 5 Mfx-Cfz-E-Z
Add vitamin B6 100 mg/day in intensive phase

The shorter DR-TB regimen is given as a standardized regimen; the provincial CEC should be consulted if any substitutions or customization are being considered.

- The intensive phase consists of Km, high dose Mfx, Cfz, Eto, Z, E, and H^{HD} daily for 4 months (see dosages in Table 3):

- Cm (or less ideally, Am) is an acceptable alternative to Km when there is documented Km resistance; however, in the case of ototoxicity, patients should be switched to an individualized regimen.
- In children < 14 kg, levofloxacin is an alternative due to the poor palatability of Mfx.
- Pto can be used as an alternative to Eto.

- If culture conversion is not achieved at month 4 on treatment, the intensive phase should be extended for 2 more months to a maximum total duration of 6 months; **it is critical in this case that repeat drug-susceptibility testing be done through both LPA and culture/phenotypic DST for the possibility that the patient will require a switch to an individualized regimen.**
- If the patient remains culture positive at 6 months, he or she should be considered as MDR treatment failure and switched to an individualized regimen.
- **Patients should be switched to continuation phase of the shorter regimen based on culture results**; ideally, there should be documentation of at least one negative culture. If there are no culture results available, patients may be switched to continuation phase based on smear conversion and clinical improvement (including X-ray if appropriate). All attempts should be made to send monthly samples for culture and trace results.
- It is essential to have SL LPA, culture, and SL phenotypic DST results available to appropriately choose between the shorter regimen or an individualized regimen.
- Continuation phase for the shorter regimen consists of high dose Mfx, Cfz, E, and Z for a fixed duration of 5 months.

Table 3: Short course regimen drug dosages for adults and adolescents > 30 kg

Drug	Weight group		
	30–33 kg	33–50 kg	> 50 kg
Kanamycin* (1 gm vial)	15 mg/kg	15 mg/kg	1 gm**
Moxifloxacin (400 mg tablet)	400 mg (1 tablet)	600 mg (1 and ½ tablet)	800 mg (2 tablets)
Clofazimine (50 and 100 mg capsules)	50 mg (1 capsule 50 mg)	100 mg (1 capsule 100 mg)	100 mg (1 capsule 100 mg)
thionamide (250 mg tablet)	250 mg (1 tablet)	500 mg (1 morning + 1 evening tablet)	750 mg (2 morning +1 evening tablets)
Isoniazid—High dose (300 mg tablet)	300 mg (1 tablet)	400 mg (1 and ½ tablets)	600 mg (2 tablets)
Ethambutol (400 mg tablet)	800 mg (2 tablets)	800 mg (2 tablets)	1200 mg (3 tablets)
Pyrazinamide (400 mg tablet)	1,000 mg (3 and ½ tablets)	1,600 mg (4 tablets)	2,000 mg (5 tablets)
Pyridoxine (vitamin B6) to be given at 100 mg			

*In case of extension of intensive phase after month 4, kanamycin will be given three times per week.

**Patient aged > 49 years old will receive a maximum of 750 mg per day.

4.4.1.4 Criteria to change from the shorter regimen to an individualized regimen

- Lack of response to treatment (e.g. no culture conversion by 6 months or deterioration of clinical condition despite treatment).
- Culture reversion in the continuation phase after conversion to negative.
- Evidence of resistance to an FQ or SLI.
- Adverse drug reaction requiring discontinuation of ≥ 1 drug in the shorter regimen (aside from INH).
- A patient becomes pregnant during the intensive phase of the shorter regimen (second-line injectable agents are contraindicated in pregnancy)—every effort should be made to counsel women diagnosed with DR-TB on contraception use to prevent unintended pregnancies during DR-TB treatment.

4.4.2 Individualized DR-TB treatment regimen

Patients who are not eligible for the shorter DR-TB regimen should be initiated on an individualized DR-TB regimen (Figure 2 above), including patients with MDR-TB treatment failure, pre-XDR-TB, and XDR-TB. The design of the individualized regimen will include new and repurposed drugs such as Bdq, Dlm, Lzd, and Cfz. For treatment in special conditions such as pregnancy and breastfeeding refer to Chapter 5 (5.1 and 5.2 respectively).

Each patient requiring an individualized regimen for DR-TB treatment, including regimens with new and repurposed drugs, must be discussed with the clinical expert committee.

4.4.2.1 Principles for designing individualized DR-TB treatment regimens

- The standard duration of the intensive phase should be at least 8 months, and duration of the continuation phase should be at least 12 months (though the transition from intensive and continuation phase might not be clear if there is no injectable agent and will depend on drug tolerability and DST results).
- The regimen should be designed based on the patient's most recent DST results and history of previous drug use and/or exposure (see Table 4 below).
- Never add Bdq, Dlm, Cfz, or Lzd as a single drug to a failing regimen.
- If the patient is culture negative and the new drugs are being SUBSTITUTED for toxicity reasons, a single drug substitution can be made [9].
- The regimen should consist of at least four drugs in the intensive phase never used before and likely to be effective, plus pyrazinamide (Table 4). In the continuation phase, at least three effective drugs should remain. Table 5 lists recommended dosing for drugs in individualized regimens.

- The backbone regimen usually consists of a new drug (Bdq, Dlm, or both), Lzd, Cfz, and PZA [9].
- There have been no studies comparing Bdq and Dlm; if one drug has been used in the past, or there is documented drug allergy, then the other drug should be chosen.

- Dlm should be the new drug of choice for HIV co-infected patients, due to the lack of drug-drug interactions with antiretroviral therapy.
- For patients with limited treatment options (MDR treatment failure, pre-XDR, and XDR-TB), a regimen combining Bdq and Dlm should be designed and approved by the clinical expert committee [10]. Ensure closer monitoring of the QT interval by performing an ECG at baseline, 2 weeks, and monthly until the end of treatment with Bdq or Dlm.
- Bdq or Dlm should be initially given for 6 months; the use of Bdq or Dlm can be extended by the clinical expert committee in patients with highly resistant forms of DR-TB where the remaining regimen is insufficient (fewer than three effective drugs) without Bdq or Dlm and the drug is well tolerated [10].
- For patients enrolled for treatment with regimens containing new drugs (Bdq or Dlm), informed consent policies should follow local practice for DR-TB in general [11].
- For HIV-infected patients, antiretroviral therapy (ART) should be prescribed within 2–8 weeks of DR-TB treatment initiation, and as soon as possible after DR-TB treatment is tolerated. See Chapter 6 for the treatment of DR-TB/HIV co-infection.
- The QT prolongation that may occur in patients receiving Bdq or Dlm can be monitored in the outpatient setting. There is no reason to admit stable patients to initiate Bdq or Dlm only for cardiac monitoring; Dlm takes 8 weeks to reach its peak concentration, and Bdq up to 16 weeks.
- Dlm is recommended for use in children ⩾ 6 years old [5], and it is being tested for pharmacokinetics and safety in children aged 5 years and under. There may be individual children less than 6 years of age requiring Dlm due to highly resistant forms of DR-TB (often the resistance pattern of the adult index patient). Regimen design for these children must be discussed and approved by the National CEC.
- Although Bdq is recommended for patients over the age of 18, there may be a need to use Bdq in DR-TB patients less than 18 years of age; each of these individual patients must be referred to the National CEC for approval of Bdq in this age category.

- **All children less than 18 years of age need to be referred to the National Clinical Expert Committee (CEC) for guidance and approval of DR-TB treatment regimen design, whether a shorter regimen or an individualized regimen with new drugs is used**.

Table 4: Regimen design steps for RR-TB patients who are not eligible for the shorter DR-TB regimen and require an individualized regimen

Step 1: Choose either bedaquiline or delamanid (Group D2). Patients with MDR-TB treatment failure, intolerance to ≥ 1 drug in the shorter regimen, pre-XDR, or XDR-TB should have either Bdq, Dlm, or both in their regimen. The choice of which drug (or potentially both drugs) is outlined in Section 4.4.2.2 on "Additional Considerations" below.
Step 2: Choose a fluoroquinolone (Group A—Mfx or Lfx). If only ofloxacin resistance from DST is known, Mfx or Lfx high dose (Lfx is preferred due to less QT prolongation than Mfx) can still be added to the regimen, but it should not be counted as one of the effective drugs. Treatment with a later generation FQ (Mfx or Lfx) significantly improves RR-TB treatment outcomes; they should therefore always be included unless there is an absolute contra-indication for their use or confirmed high level of resistance by LPA or phenotypic DST.
Step 3: Choose an injectable (Group B—Km, Cm, Am). If clinical history or DST suggests resistance to all SLI drugs, or in case of a serious adverse event (hearing loss, nephrotoxicity), the injectable should not be used or should be promptly discontinued. If the patient's strain is still susceptible to one of the injectable drugs, it can be included in the regimen only if consistent monitoring for adverse events is assured. In children with mild forms of DR-TB disease, the harms associated with an injectable may outweigh potential benefits and therefore injectable agents may be excluded in this group.
Step 4: Choose at least two or more Group C drugs (Lzd, Cfz, Eto, Cs) thought to be effective as additional core second-line drugs. If efficacy is uncertain, the drug can be added to the regimen, but it should not be counted as an effective drug.
Step 5: Choose D1 drugs (PZA, INH_{hd}, EMB) as add-on agents. PZA is routinely added to most regimens. High dose INH may further strengthen the regimen if DST shows INH sensitivity (e.g. inhA mutation alone), or INH resistance is unknown. Do not use INH if the katG mutation is present. D1 drugs are usually added to the core second-line drugs, unless the risks from confirmed resistance, pill burden, intolerance, or drug-drug interaction outweigh potential benefits.
Step 6: Only choose D3 drugs (PAS, imipenem, or meropenem + amoxicillin/clavulanic acid) if there are no other treatment options available due to highly resistant forms of DR-TB or multiple intolerances to other DR-TB drugs.
The final individualized DR-TB regimen will consist of at least five drugs with confirmed or high likelihood of susceptibility from the following list: Bdq or Dlm, Lfx or Mfx, Km (Am, Cm), Lzd, Cfz, Eto, Cs, Z, H^{HD}, E.

4.4.2.2 Additional considerations on choice of new drug use (Bdq or Dlm) in individualized regimens:

- Bedaquiline, delamanid, the fluoroquinolones (Mfx more than Lfx), and clofazamine can all cause prolongation of the QT interval (Annexure 3). Patients with DR-TB regimens that contain one of the new drugs, especially when used with additional QT prolonging drugs, should be carefully monitored for clinical signs of an irregular heartbeat, as well as checking regular ECGs.

- Bdq had drug-drug interactions with ART: efavirenz (EFV) lowers Bdq serum levels; lopinavir/ritonavir (LPV/r) increases Bdq levels. See Chapter 6 for the treatment of DR-TB/HIV co-infection.
- When starting Bdq or Dlm, serum electrolytes should be checked and corrected when feasible to reduce the risk of cardiac arrhythmias. Since Dlm is metabolized by albumin, patients with a low BMI and/or a low serum albumin should be provided with high protein dietary foods.
- There is potential cross resistance between Bdq and Cfz; use Dlm if there is a history of prior Cfz use > 2 months for DR-TB (Bdq can be used if there is history of prior Cfz use for leprosy).
- Bdq has a prolonged terminal elimination half-life of 5 months; if considering the use of Dlm after completion of Bdq (e.g. Bdq treatment failure), patients should be monitored closely given the theoretical risk that the patient will be on "combination" with both drugs.
- It is not recommended to dose reduce either Bdq or Dlm in the event of adverse events; linezolid, however, may be reduced from 600 mg daily to 300 mg daily if there are serious adverse events at the 600-mg dose (pyridoxine 50 mg should be added as well).
- Patients that are highly likely to have second-line drug (SLD) resistance—those failing MDR-TB treatment, symptomatic close contacts of DR-TB patients with SLD resistance, or patients that have received SLDs for ≥ 1 month in the past—can be started on Bdq or Dlm in the absence of confirmed DST by LPA or culture.

Table 5: Weight-based daily dosages of DR-TB drugs for patients ≥ 30 kg

DRUGS	DAILY DOSE	30–35 KG	36–45 KG	46–55 KG	56–70 KG	>70 KG
Isoniazid	4–6 mg/kg once daily	150 mg	200 mg	300 mg	300 mg	300 mg
Rifampicin	8–12 mg/kg once daily	300 mg	450 mg	450 mg	600 mg	600 mg
Pyrazinamide	20–30 mg/kg once daily	800 mg	1000 mg	1200 mg	1600 mg	2000 mg
Ethambutol	15–25 mg/kg once daily	600 mg	800 mg	1000 mg	1200 mg	1200 mg
Rifabutin	5–10 mg/kg once daily	300 mg	300 mg	300 mg	300 mg	300 mg
Levofloxacin	750–1000 mg once daily	750 mg	750 mg	1000 mg	1000 mg	1000 mg
Moxifloxacin	400 mg once daily	400 mg	400 mg	400 mg	400 mg	400 mg
Ethionamide	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Prothionamide	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Cycloserine	500–750 mg/day in 2 divided doses	500 mg	500 mg	500 mg	750 mg	750 mg
***p*-aminosalicylic acid**[a]	8 g/day in 2 divided doses	8 g	8 g	8 g	8 g	8–12 g
Bedaquiline	400 mg once daily for 2 weeks then 200 mg 3 times per week					
Delamanid	100 mg twice daily (total daily dose = 200 mg)					
Clofazimine	200–300 mg daily (2 first months) then reduce to 100 mg daily (alternative dosing 100 mg daily)					
Linezolid	600 mg once daily	600 mg	600 mg	600 mg	600 mg	600 mg

DRUGS	DAILY DOSE	30–33 KG	34–40 KG	41–45 KG	46–50 KG	51–70 KG	>70 KG
Streptomycin	12–18 mg/kg once daily	500 mg	600 mg	700 mg	800 mg	900 mg	1000 mg
Kanamycin	15–20 mg/kg once daily	500 mg	625 mg	750 mg	875 mg	1000 mg	1000 mg
Amikacin	15–20 mg/kg once daily	500 mg	625 mg	750 mg	875 mg	1000 mg	1000 mg
Capreomycin	15–20 mg/kg once daily	500 mg	600 mg	750 mg	800 mg	1000 mg	1000 mg

Notes:
*High dose INH is 10–15 mg/kg daily, maximum 600 mg daily.
*High dose Lfx is 1,000–1,500 mg once daily.
*High dose Mfx for the shorter regimen is 600 mg once daily.
*Clofazimine in the shorter regimen is given 100 mg daily from the start of treatment.
*Linezolid can be reduced to 300 mg daily in the event of toxicity at 600 mg daily.
*Meropenem dosing is 1,000 mg three times daily (alternative dosing is 2,000 mg twice daily).
*Imipenem/cilastatin dosing is 1,000 mg imipenem/1,000 mg cilastatin twice daily.
*Meropenem and imipenem should be given with clavulanic acid available as amoxicillin/clavulanic (625 mg 1 tablet 30 minutes before the infusion).

4.5 Treating mono- and poly-drug-resistant TB

First-line line probe assay only provides results for rifampicin and isoniazid resistance. If the isolate is RIF sensitive and INH resistant, the patient can have either INH mono- or INH poly-resistant DR-TB. The diagnosis of INH mono-resistance should be confirmed with phenotypic DST.

Care should be taken to evaluate the medical history for possible amplification of resistance which may have developed but may not be apparent from the laboratory results. As such, treatment for mono- and poly-drug-resistant TB should never rely solely on DST results.

It is important to assess history of previous TB treatment, contact history, risk of amplification of resistance, extension of disease, and the patient's condition. Though there is clear guidance to treat all rifampicin mono-resistant or poly-resistant patients with MDR-TB treatment regimens, there is no updated international recommendation on the treatment of isoniazid mono- and poly-resistant DR-TB. **If a patient has mono- or poly-resistant DR-TB on laboratory results, further resistance should be suspected and it is essential to follow up on second-line LPA and culture/DST.**

Table 6: Suggested treatment for mono- and poly-drug-resistant DR-TB

DRUG RESISTANCE PATTERN	SUGGESTED REGIMEN	COMMENTS
RIF mono- or poly-drug resistance	DR-TB regimen	The patient should be started on either a shorter or individualized DR-TB regimen depending on eligibility criteria.
INH poly-drug resistance susceptible to RIF (e.g. INH + EMB and/or S resistance)	DR-TB regimen	Treat as DR-TB. Caution should be taken when interpreting these DST results, as many patients with DST results suggesting poly-drug resistance actually have MDR-TB. Determine the patient's treatment history. If any doubt, consult with the clinical expert committee.

INH mono-resistance Note: Should be diagnosed by full phenotypic DST, if available, and not only by FL LPA	Consult CEC for regimen selection	Patient with no previous treatment of TB, no risk of amplification of resistance, and no risk of unfavorable outcome: consider treatment with levofloxacin + REZ for 6 months (+/-INH^{HD}).
		Patient with history of previous TB treatment, risk of amplification of resistance, or risk of unfavorable outcome (extensive disease) treat with an individualized treatment regimen.

4.6 Extra-pulmonary DR-TB

In general, extra-pulmonary DR-TB is treated with the same strategy as pulmonary DR-TB, although there has been much less experience with the use of the shorter regimen for patients with extra-pulmonary disease. Adults and children diagnosed with an isolated DR-TB pleural effusion and children with DR-TB lymphadenitis may be considered for the shorter regimen; all other patients, especially patients with TB meningitis, DR-TB pericarditis, or osteoarticular DR-TB should be treated with an individualized DR-TB regimen.

4.7 Adjuvant therapy during DR-TB treatment

- Vitamin B6 (pyridoxine) preventive therapy at doses of 50–150 mg/day (maximum dose of 150 mg/day) should be given to all patients receiving isoniazid, cycloserine, or linezolid to minimize peripheral neuropathy, neurological side effects, and myelosuppression.
- Corticosteroids (prednisolone 1 mg/kg and gradually decreasing by 10 mg per week when a long course is indicated) may be used in the following conditions:
    - TB meningitis (and other central nervous system compromise).
    - TB pericarditis.
    - Immune reconstitution inflammatory syndrome (IRIS).

4.8 Role of surgery in the management of DR-TB

The World Health Organization recommends that for patients with DR-TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended DR-TB regimen [5]. Patients with DR-TB and all of the following should be considered for surgical intervention:

- Patients who remain smear positive, while on fully monitored treatment for more than 6 months, and
- Have resistance to a large number of medicines, and
- Have localized pulmonary disease.

The most common operative procedure in patients with pulmonary DR-TB is resection surgery. Generally, at least two months of therapy should be given prior to resection surgery to decrease the bacterial load in the surrounding lung tissue. Even with successful resection, an additional 12–24 months of DR-TB treatment should still be given.

CHAPTER 5
TREATMENT OF DR-TB IN SPECIAL POPULATIONS

5.1 DR-TB diagnosis and treatment during pregnancy

- **Ideally pregnancy should be avoided during DR-TB treatment**. A baseline pregnancy test at the start of DR-TB treatment is mandatory, and effective use of contraceptives (preferably an injectable contraceptive or intrauterine device) throughout DR-TB treatment should be considered an essential component of patient education.
- If pregnancy is confirmed in a patient with DR-TB, she is not eligible for the shorter regimen and **an individualized regimen with four effective oral drugs plus pyrazinamide** should be designed based on Xpert MTB/RIF, LPA, and culture/DST. The National CEC should be consulted for every pregnant patient started on DR-TB treatment with an individualized regimen.
- Pregnant patients should be started on DR-TB treatment as soon as the diagnosis is made, and not delayed until after the first trimester of pregnancy.
- Delamanid and bedaquiline are pregnancy category B, meaning they can be used with caution in pregnancy; this applies to several other DR-TB drugs as well (many of which are in a lower, or less safe, category than Bdq and Dlm).
- The injectable agents and ethionamide are contraindicated during pregnancy, thus the use of delamanid or bedaquiline to construct an effective DR-TB treatment regimen should be strongly considered for the benefit of the pregnant woman. Aminoglycosides can be toxic to the developing fetal ear, and Eto can increase the risk of nausea and vomiting associated with pregnancy (teratogenic effects have also been observed in animal studies).
- As a last resort, the injectable agent can be given to strengthen a treatment regimen for 3–6 months postpartum even in the middle of treatment. However, if the patient is doing well and past the normal intensive phase period for the injectable agent, there is no need of adding it. These cases should be discussed with the National CEC.
- There is no evidence of safety for clofazimine (Cfz) in pregnancy or lactation, thus it should be avoided unless absolutely necessary.
- If a woman becomes pregnant while on the shorter DR-TB regimen, the decision about continuing the shorter regimen will depend on whether the patient has culture converted, the number of months the patient has been on treatment, and whether the patient is receiving the injectable and ethionamide. If culture converted and completed at least 4 months of intensive phase, the patient can be switched to continuation phase of the shorter regimen; if neither of these criteria are met, the patient should be switched to an individualized regimen with new drugs (in consultation with the National CEC).
- If a woman becomes pregnant on an individualized regimen containing an injectable, the injectable should be discontinued and the National CEC should be consulted to safely substitute other oral second-line drug(s), including Bdq or Dlm.

5.2 DR-TB diagnosis and treatment during breastfeeding

- Second-line DR-TB drugs are not contraindicated in breastfeeding patients. The general recommendation is that women can breastfeed while they are on DR-TB treatment, although formula feeding is an option if safe and feasible (AFASS criteria for the choice of formula feeding are affordable, feasible, accessible, sustainable, and safe).
- Most DR-TB drugs are passed to the infant through breastmilk, but the concentrations are sub-therapeutic (very low).
- The notable exceptions are clofazimine and bedaquiline, both of which accumulate in the fatty tissues of the breast and are excreted in the milk (the baby can have coloration of the skin due to clofazimine).
- If the mother has bacteriologically confirmed DR-TB, either of the following precautionary measures can be taken:
    - Recommend that the infant be placed under the care of a family member.
    - The mother uses a surgical mask, especially while breastfeeding, until culture conversion.

  Each breastfeeding patient should be considered individually, with a multidisciplinary approach that includes social workers, treatment supporters, nursing staff, and the management team. What will work for one mother-child pair will not work for another.
- It is essential to closely monitor the infant, as well as other children in the household, for signs and symptoms of TB while managing DR-TB in the mother.

5.3 DR-TB diagnosis and treatment and liver disease

- Note that many of the first- and second-line drugs for TB are associated with liver toxicity.
- DR-TB patients can be treated with SLDs provided there is no clinical evidence of chronic liver disease, hepatitis, or excess consumption of alcohol. The clinician should anticipate hepatotoxic adverse effects in these patients since they occur frequently.
- No dose adjustment is necessary for Bdq or Dlm in patients with mild or moderate hepatic impairment. Bdq has not been studied in patients with severe hepatic impairment and should be used with caution in these patients and only when the benefits outweigh the risks. Dlm is not recommended in patients with moderate to severe hepatic impairment.
- Pyrazinamide should not be given to patients with chronic liver disease.
- Eto, H^{HD}, PAS, and Bdq might be hepatotoxic; use with caution in chronic stable liver disease with close monitoring.
- If drug-resistant TB is to be treated concurrently with acute hepatitis, a combination of four non-hepatotoxic drugs should be used.
- Check the ALT (SGPT) at baseline; if the ALT is less than five times the upper limit of normal, commence DR-TB treatment; if the ALT is greater than five times the upper limit of normal, consult with the provincial CEC, investigate the cause, and recheck the ALT in one week.
- Screen for hepatitis B at baseline by performing an HBsAg; if HBsAg is positive, investigate for active hepatitis B by consulting with the provincial CEC for additional investigations.
- Monitor ALT monthly if the ALT (SGPT) is elevated at baseline. Stop all drugs if the ALT (SGPT) is more than five times the upper limit, and investigate accordingly.

- Avoid other potentially hepatotoxic drugs in patients with underlying chronic liver disease.
- No formal studies of drug-drug interactions between the hepatitis C protease inhibitors and the second-line tuberculosis drugs have been done; if a patient has stable liver function, treatment of DR-TB should be initiated first.
- Alcohol use might substantially exacerbate liver disease in some settings, although studies have found no increased risk of hepatic adverse events in DR-TB patients.

5.4 DR-TB diagnosis and treatment and renal disease

- Renal insufficiency can be caused by longstanding TB or previous aminoglycoside use (e.g. patients that received streptomycin as part of category II re-treatment).
- The frequency and dosage of first- and second-line TB drugs should be adjusted if the creatinine clearance is below 30 mL/min (Annexure 4); patients with renal insufficiency should be monitored carefully on DR-TB treatment.
- Bdq or Dlm can be used to substitute second-line injectable drugs in patients with significant pre-existing or aminoglycoside-related renal dysfunction.
- No dose adjustment of Bdq or Dlm is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end stage renal disease requiring hemodialysis or peritoneal dialysis, Bdq can be used but with caution (Bdq should be taken after hemodialysis). There are no data on the use of Dlm in patients with severe renal impairment and its use is not recommended.

5.5 DR-TB diagnosis and treatment and diabetes mellitus

- Diabetes mellitus (DM) increases the risk of poor outcomes and can potentiate adverse events during DR-TB treatment such as renal dysfunction, peripheral neuropathy, and vision changes/retinopathy.
- Prompt diagnosis and initiation of effective DR-TB treatment is crucial in patients with diabetes; no DR-TB drug is contraindicated in diabetic patients.
- If a patient's diabetes is well controlled and they meet eligibility criteria, they should be initiated on DR-TB treatment using the shorter DR-TB regimen (Figure 2); patients with chronic poor glycemic control may be at risk of an unfavorable DR-TB treatment outcome and should be considered for an individualized treatment regimen including either Bdq or Dlm.
- DM must be monitored closely throughout the treatment of drug-resistant TB using fasting blood sugar; creatinine and potassium levels should be monitored frequently, often weekly for the first month and then at least monthly thereafter.
- Oral hypoglycaemics are not contraindicated but dosages may need to be increased during DR-TB treatment.
- Eto/Pto tend to make insulin control in diabetes more difficult and can result in hypoglycaemia and poor glucose regulation.

5.6 DR-TB diagnosis and treatment and seizure disorders

- Cycloserine (Cs) should be avoided in patients with poorly controlled seizure disorders. However, in patients where Cs is a crucial component of the treatment regimen, it can be given and the anti-seizure medication adjusted as needed to control the seizure disorder.

- Seizures that present for the first time during anti-TB therapy are likely to be the result of an adverse event of one of the anti-TB medicines, particularly cycloserine, isoniazid, or imipenem.
- The use of isoniazid and rifampicin may interfere with some commonly used anti-seizure medications; drug-drug interactions should always be checked prior to use of RIF or INH in patients on seizure medications. The provincial or National CEC can be consulted when needed.

5.7 DR-TB diagnosis and treatment and psychiatric disorders

- Patients with a history of overt psychiatric illness should be evaluated by a psychiatrist at the start of DR-TB treatment and at any point if severe symptoms re-appear.
- There is a high baseline incidence of depression and anxiety in patients with DR-TB, often related to the chronicity of the condition and socioeconomic stress factors associated with the disease.
- Medical treatment, individual counseling and/or group therapy may be necessary to manage the patient suffering from a psychiatric condition or an adverse psychiatric event caused by DR-TB medication. Group therapy provides a supportive environment for DR-TB patients and should be provided for all patients, including those without psychiatric conditions. Every facility that treats DR-TB patients is encouraged to conduct regular support group sessions for patients.
- Psychiatric adverse events from cycloserine or high dose isoniazid may be more prevalent in the psychiatric patient; close monitoring is recommended if either drug is used in patients with psychiatric disorders.
- All facilities treating DR-TB should have an organized system for psychiatric emergencies (e.g. psychosis or suicidal tendencies); atypical antipsychotics should be used for DR-TB patients on multiple QT prolonging DR-TB drugs since haloperidol significantly prolongs the QTc interval and has been associated with torsades de pointes.
- Avoid serotonin reuptake inhibitors and tricyclic antidepressants with linezolid, as there is a risk of serotonin syndrome.

5.8 DR-TB diagnosis and treatment and substance abuse

- Patients with substance dependence disorders, including alcohol dependence, should be offered treatment for their addiction. Consultation with social workers, psychiatrists, and/or drug rehabilitation centres is encouraged to formulate the treatment plan.
- Complete abstinence from alcohol or other substances should be strongly encouraged, although active consumption is not a contraindication to DR-TB treatment.
- If DR-TB treatment is repeatedly interrupted because of the patient's dependence to alcohol or psychoactive substances, DR-TB treatment may be suspended until measures to increase adherence support have been established.
- Good directly observed therapy (DOT) gives the patient an opportunity to interact with and get support from health care providers, which often allows treatment completion even in patients with substance dependence.
- Cycloserine will have a higher incidence of adverse effects in patients who are dependent on alcohol or other substances, and predisposes to seizures. However, if cycloserine is considered essential to the regimen, it should be used and the patient closely observed for adverse events.

CHAPTER 6
HIV AND DRUG-RESISTANT TUBERCULOSIS

6.1 General considerations in the management of DR-TB/HIV co-infection

- HIV testing is an essential component in the management all presumptive DR-TB patients.
- Prompt initiation of both DR-TB and antiretroviral therapy (ART) is crucial to successful treatment; close clinical monitoring is required for DR-TB/HIV co-infected patients due to overlapping toxicities and drug-drug interactions (Table 7). It is important to aggressively diagnose and manage adverse events.
- Patients who are not on ART, but are HIV-positive, at the time of DR-TB diagnosis should start DR-TB treatment prior to ART initiation. ART should be initiated for all DR-TB/HIV co-infected patients regardless of CD4 count. ART should be started approximately two weeks after DR-TB treatment initiation, or within 2–8 weeks and as soon as the patient is tolerating DR-TB treatment.
- If the patient is already on ART, **request a CD4 and viral load** for early detection of ART failure. If the patient is failing, he or she needs to be switched to second-line ART without delays.
- Be aware of opportunistic infections, especially at lower CD4 counts, and immune reconstitution inflammatory syndrome (IRIS) (both unmasking IRIS and paradoxical IRIS) when starting ART in ART naïve HIV-positive patients.
- Provide additional nutritional support and assess functional status for co-infected patients.
- Commence cotrimoxazole preventive therapy (CPT) immediately for all HIV-positive patients irrespective of CD4 cell count.
- Currently there is no preventive therapy for close contacts of patients diagnosed with DR-TB. However, all contacts of an index case should be identified, screened, and investigated for the presence of TB disease or infection. Those found to be asymptomatic for TB should be educated to report the development of any symptoms and followed up with at the health care facility for two years.
- For patients who are not eligible for the shorter regimen, delamanid is the preferred new drug for individualized regimens, since there are no significant drug-drug interactions between delamanid and ART. If delamanid is not available, then bedaquiline can be used.
- Since delamanid is metabolized by albumin, patients with low BMIs and/or a low serum albumin should be provided with high protein dietary foods.
- Bedaquiline and ART:
    - Bdq should not be used with any dose of efavirenz (EFV) (400 mg or 600 mg), as EFV reduces Bdq levels.
    - Nevirapine (NVP) can be used safely with Bdq in HIV-infected patients as there are no drug-drug interactions between the two drugs.

- Lopinavir/ritonavir (LPV/r) has been shown to increase Bdq plasma concentrations hence it should be used with caution and there should be frequent monitoring of ECGs and liver function tests; if integrase inhibitors are available (e.g. dolutegravir or raltegravir), they can be used instead of protease inhibitors.

6.2 HIV-positive patients not on ART at the time of DR-TB diagnosis

- ART naïve patients on a bedaquiline containing regimen should start on a NVP based regimen (with a loading dose for the first 14 days) within 2–8 weeks of starting DR-TB treatment; use caution when initiating ART with NVP at higher CD4 counts, as there is increased risk of liver toxicity.
- If there are concerns starting NVP, especially if the baseline ALT is elevated, the patient should be initiated on a protease inhibitor (PI) regimen with LPV/r.
- After completion of bedaquiline, patients may be switched from an NVP ART regimen to an EFV regimen.
- ART naïve patients on a delamanid containing regimen may initiate ART with an EFV containing fixed dose combination.

6.3 HIV-positive patients already on ART at the time of DR-TB diagnosis

- If the patient is already on ART with EFV for ≥ 6 months and there are no viral load results within 3 months, assess the viral load:
  - If the viral load is undetectable, the patient can be switched from EFV to NVP (without the initial loading dose) while he or she is on Bdq and then put back on EFV as soon as Bdq is completed.
  - If the viral load is detectable (defined as a VL ≥ 1,000), the patient should undergo adherence counseling and be switched from EFV to lopinavir/ritonavir with careful monitoring of ECGs/liver function tests.
- If the patient is already on second-line ART for ≥ 6 months containing lopinavir/ritonavir, then a viral load should be assessed:
  - If the viral load is undetectable, continue with lopinavir/ritonavir with close monitoring.
  - If the viral load is detectable, the patient should undergo adherence counseling and be evaluated for third-line ART per HIV guidelines.

Table 7: Overlapping drug toxicities in the treatment of DR-TB and HIV co-infection

TOXICITY	DR-TB DRUG	ANTIRETROVIRAL AGENT	COMMENTS
Gastrointestinal (nausea, vomiting)	Eto/Pto, PAS, Cfz, H, Z, Bdq, Dlm	Stavudine, didanosine, nevirapine, ritonavir	If diarrhea is chronic, consider opportunistic infections, especially with low CD4 counts. Persistent vomiting may be due to other causes (hepatitis, lactic acidosis, meningitis, or pregnancy).
Abdominal pain	Eto/Pto, PAS, Cfz, Lzd	All antiretroviral therapy	Abdominal pain may be an early symptom of severe side effects such as hepatitis, pancreatitis, or lactic acidosis.
Dermatologic (skin rash)	H, R, E, Z, FQ, Eto/Pto, Cfz	Abacavir, nevirapine, efavirenz	Do not rechallenge abacavir if thought to be the cause of rash, as it can result in life-threatening anaphylaxis. Do not rechallenge with any agent that may have caused Stevens-Johnson syndrome. Also consider cotrimoxazole as cause of skin rash.
CNS toxicity and/or psychiatric adverse event (depression, psychosis)	Cs, H^{HD}, FQ, Eto/Pto, imipenem, meropenem	efavirenz (EFV)	EFV CNS side effects often resolve after the first 2–4 weeks of treatment, thus other causes need to be ruled out.
Headache	Cs, Bdq	Zidovudine, EFV	Rule out more serious causes of headache such as meningitis, toxoplasma, etc.
Peripheral neuropathy	H^{HD}, Lzd (less frequent: FQ, SLI, Cs, Eto/Pto, E)	Stavudine (d4T), didanosine (ddI)	Patient receiving H^{HD}, Cs, and/or Lzd should receive prophylaxis with pyridoxine (B6). Avoid use of d4T and ddI with Cs and Lzd. If Lzd is the cause and is grade ⩾ 2, stop and do not reintroduce.
Renal insufficiency hypokalemia	SLI (Am, Km, Cm)	Tenofovir (TDF)	Avoid concomitant use of TDF and SLI if possible. Even without the concomitant use of TDF, PLHIV have an increased risk of renal toxicity secondary to SLI. Frequent creatinine and electrolytes monitoring is recommended. Adjust doses if clearance < 30 mL/min (see Annexure 4).
Hematological (bone marrow toxicity)	Lzd	Zidovudine (AZT)	Monitor full blood count monthly when using Lzd. All patients with Lzd should receive pyridoxine (Vit B6) 100 mg. Consider other causes such as cotrimoxazole, HIV infection, and opportunistic infections.
Hepatotoxicity	PZA, H^{HD}, Eto/Pto, PAS, Bdq	NVP, EFV, all NRTIs, all PIs	If ALT/LFTs elevated > 5 times stop both ART and DR-TB drugs, then restart the DR-TB drugs first (see Chapter 9). Rule out other causes such as viral hepatitis (A, B, C, and CMV).

TOXICITY	DR-TB DRUG	ANTIRETROVIRAL AGENT	COMMENTS
Pancreatitis	Lzd	d4T, ddI	Avoid the use of these agents together. If an agent caused pancreatitis, suspend it permanently. Also consider other causes as gallstones or excessive alcohol use.
Lactic acidosis	Lzd	d4T, ddI, AZT	If an agent has caused high lactate or lactic acidosis, replace it.
Optic neuritis	E, Lzd	ddI	Permanently suspend the agent that caused optic neuritis and replace it.
Hypothyroidism	Eto/Pto, PAS	d4T	Monitor thyroid stimulating hormone (TSH) and replace with levothyroxine when necessary.
Dysglycaemia	Gfx, Eto/Pto	Protease inhibitors (PIs)	Eto/Pto can make insulin control in diabetic patients more difficult (hypoglycemia and poor glucose regulation). PIs can cause insulin resistance and hyperglycemia.
Arthralgia	Z, Bdq	Protease inhibitors (PI)	Arthralgia is very common with Z; also reported with Bdq and PIs.
QT prolongation	Bdq, Dlm, Mxf, Gfx, Cfz (less frequent Lfx)	ART has been associated with QT prolongation	Unknown data on additive effects of combining ART with prolonging QTc second-line anti-TB drugs. If the QTcF is prolonged > 500 ms stop DR-TB QTcF prolonging drugs but do not stop ART.

CHAPTER 7.
PEDIATRIC DRUG-RESISTANT TUBERCULOSIS

7.1 General considerations for DR-TB diagnosis in children

The clinical presentation of DR-TB is similar to drug-susceptible TB in children (pulmonary tuberculosis [PTB] and extra-pulmonary tuberculosis [EPTB]), though symptoms can be non-specific. Bacteriological confirmation is not always possible due to paucibacillary disease and difficulties in sample collection (gastric aspirate or sputum induction). The diagnosis is often made on clinical and radiological grounds, taking into account all close contacts of the child and the drug resistance pattern of close contacts that have been diagnosed with DR-TB (Figure 3).

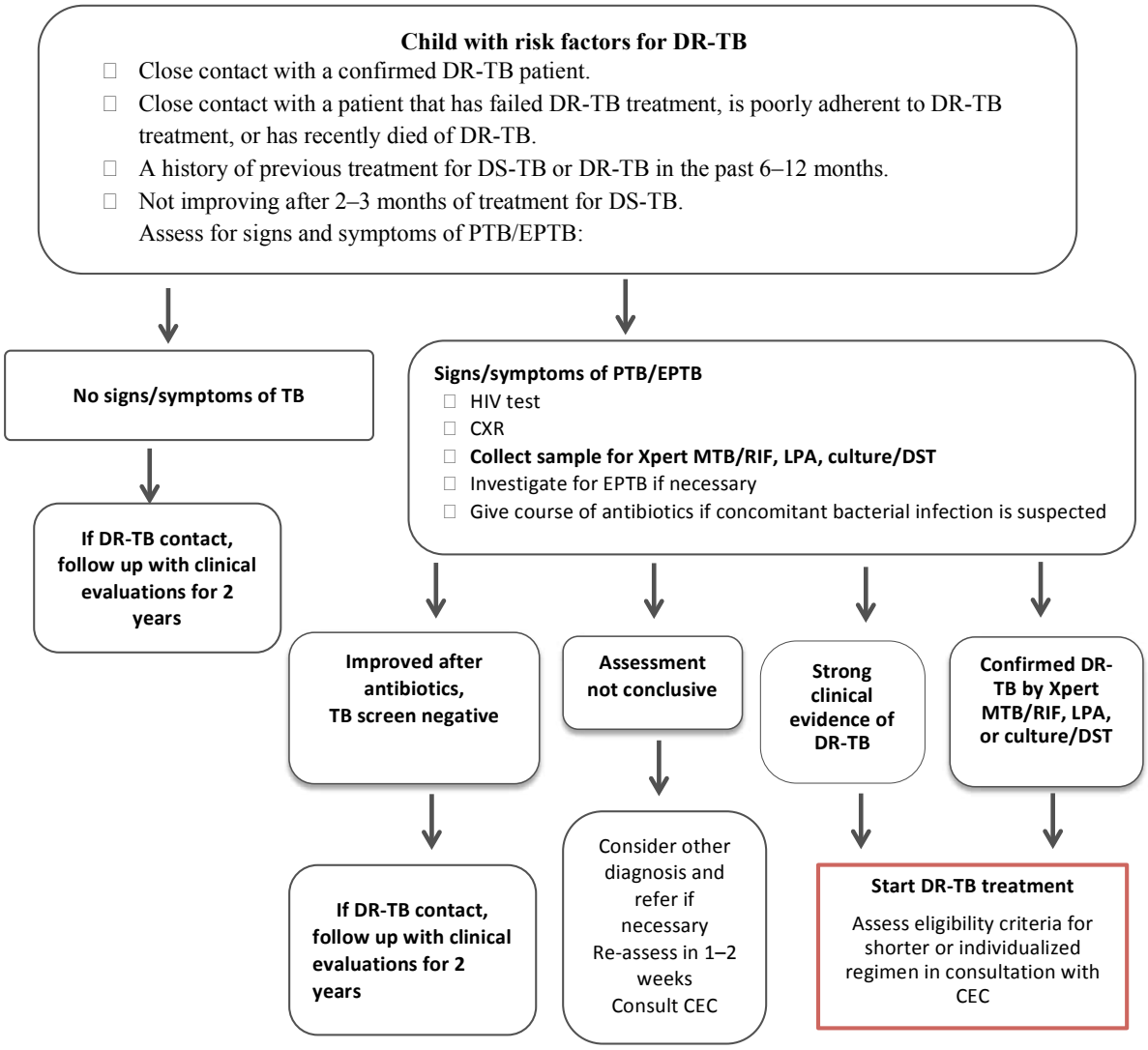
The most common radiologic manifestation of DR-TB in children is enlarged hilar lymph nodes; cavitation tends to occur in older children. Other chest X-ray abnormalities are often non-specific and may be similar to other lower respiratory tract infections like bacterial pneumonia, pneumocystis jiroveci pneumonia (PJP), and lymphoid interstitial pneumonia (LIP). In some children, the chest X-ray can also be normal. The use of X-ray in children may be useful to diagnose EPTB, such as pleural, miliary, pericardial, or spinal DR-TB.

Risk factors for DR-TB in children include:

- Close contact with a confirmed DR-TB patient.
- Close contact with a patient that has failed DR-TB treatment, is poorly adherent to DR-TB treatment, or has recently died of DR-TB.
- A history of previous treatment for DS-TB or DR-TB in the past 6–12 months.
- Not improving after 2–3 months of treatment for DS-TB.

When DR-TB is presumed, it is critical to make every effort to get samples for bacteriological confirmation by Xpert MTB/RIF and culture/DST. Xpert MTB/RIF is the recommended first-line diagnostic test in children, though it may be only positive in less than one third of children with TB. Culture/DST is more sensitive but is only positive in < 30%–40% of symptomatic children. A negative result of either Xpert MTB/RIF or culture/DST does not exclude the diagnosis of DR-TB. Each child or adolescent with presumptive DR-TB should be discussed with the National CEC for optimal management. Treatment should be started without waiting for bacteriological confirmation (based on the DST of the index patient if available). Early detection and initiation with appropriate DR-TB treatment is essential to ensure favourable outcomes in children.

Figure 3: Algorithm for the diagnosis of DR-TB in children



7.2 Treatment of DR-TB in children

7.2.1 DR-TB treatment regimens in children

- The same inclusion criteria for adults should be applied for children and adolescents being considered for the shorter regimen or individualized regimen, although documentation of fluoroquinolone or injectable resistance, as well as history of prior treatment with second-line medications, may be taken from the adult index patient/ close contact.
- Every effort should be undertaken to collect sputum for bacteriologic confirmation of a DR-TB diagnosis, especially in older children and adolescents. If sputum cannot be obtained, DR-TB treatment decisions for children can be based on the DST of a known DR-TB close contact.
- Clinicians should consult with the National CEC for each pediatric and adolescent patient receiving the shorter regimen or individualized regimens with new drugs.
- **The WHO now recommends that in children with mild forms of DR-TB disease, the harms associated with second-line injectable agents outweigh potential benefits and therefore injectable agents may be excluded in this group of children [5].**
- Monitoring children for visual changes should be done monthly on the shorter DR-TB regimen to assess for visual changes with EMB use.
- Monthly weights should be taken and dosage adjustment of medications should take place based on weight. Dosing of DR-TB drugs in pediatric and adolescents are given in Annexure 5, Tables 17 and 18.
- There should be special attention to adherence and psychosocial support for adolescents on DR-TB treatment regardless of regimen selection.
- Decisions on treatment duration in children, if unable to be determined from bacteriologic results, should be based on clinical improvement or standard durations.

7.2.1.1 Shorter treatment regimen in children

- The WHO recommends the shorter regimen for children and adolescents that have uncomplicated DR-TB.
- If a child or adolescent symptomatic for DR-TB is a known close household contact of a patient with pre-XDR or XDR-TB, the child should **not** be considered for the shorter regimen.
- The shorter regimen recommended for children and adolescents is the same as in adults:

  4–6 Km-Mfx-Cfz-Eto-Z-E-H^{HD} / 5 Mfx-Cfz-E-Z

  Add vitamin B6 1–2 mg/kg/day in intensive phase

- The following adaptations should be considered:

  Moxifloxacin:

  - The pediatric equivalent dose of high dose moxifloxacin is not known and the tablets are bitter and difficult to tolerate when crushed.

- In children under 14 kg, levofloxacin at a dose of 15–20 mg/kg/day can be used.
- In children over 14 kg, standard dose of moxifloxacin at 10 mg/kg/day can be used.
- In adolescents over 14 years old consider adult dosing of moxifloxacin (600 mg for the shorter regimen).

Clofazimine:

- There is no pediatric friendly formulation (capsules of 50 mg are should be made available).
- The recommended dose is 2–3 mg/kg/day; some experts increase to 5 mg/kg/day if necessary due to dosing or formulation restrictions. The maximum dose should not exceed 100 mg per day.
- To achieve the average dose, the medication may be given every other day or even every third day. (Cfz capsules are very difficult to open, they color the hands, and can only be diluted in sunflower vegetable oil.)

All children starting the shorter regimen should be discussed with the National CEC.

7.2.1.2 Individualized treatment regimen in children

The regimen should be designed following the same principles as adults (Table 4). Some considerations regarding the use of new and repurposed drugs in children and adolescents include the following:

- Bedaquiline (Bdq) is recommended by WHO for adolescents above 18 years old (same dose than adults). Bdq pharmacokinetics (PK) and safety have not been formally evaluated in younger children, although there is emerging data on the safe use of Bdq in children as young as 12 years old.
- Delamanid (Dlm) is recommended by WHO for children above 6 years old (weight more than 20 kg) and adolescents that are not eligible for short regimen.
- Linezolid: Vitamin B6 (pyridoxine) preventive therapy should be given to children receiving linezolid to minimize peripheral neuropathy, neurological side effects, and myelosuppression. The optimal prophylactic dose of pyridoxine for children has not been established; 1–2 mg/kg/day has been recommended in some reports, with a usual range of 10–50 mg/day for pediatric patients at risk for neurologic sequelae.

All children starting an individualized regimen should be discussed with the National CEC.

Infants and children below 6 years old (or less than 20 kg) that need an individualized DR-TB regimen with new drugs should be referred to international experts for consensus regarding regimen design in addition to the National CEC.

7.2.2 Considerations for DR-TB drug dosages and administration in children

- For children, all drugs including the fluoroquinolones should be dosed at the higher end of recommended ranges (with exception of ethambutol, which should be dosed at the lower range of 15 mg/kg).
- DS-TB and DR-TB drugs should be dosed according to the child's weight and adjusted

based on regular (at least monthly) weight checks (Annexure 5).

- Most second-line TB drugs do not have pediatric liquid or tablet formulations, so it may be necessary to split pills in order to approximate the correct dose; caregivers will need intensive support to ensure they are using the correct doses if caring for a child with DR-TB in an outpatient setting.
- Doses of most DR-TB drugs have not been established for children below 5 kg; in such cases, the child should be dosed as close to the middle of the mg/kg range as possible.
- Ideally the dose of the injectable is between 18–20 mg/kg/day—this is within WHO recommendations for range of dosage.
- Ensure that once treatment starts, it must be completed; adherence to the full course of treatment for children and adolescents should be emphasized and reinforced.
- Identify a caregiver as the DOT supporter for all ages including adolescents; health care workers are responsible for ensuring DOT.
- Provide adequate nutritional support for all malnourished children (ready to use therapeutic food, therapeutic milk when necessary).

7.3 DR-TB/HIV Co-infection in children

The management principles are the same as in adults (see Chapter 6):

- Give cotrimoxazole preventive therapy (CPT).
- Commence antiretroviral therapy (ART) within 2–8 weeks after starting DR-TB treatment.
- Address disclosure of the child's HIV status as soon as possible for children above 6 years old, with the help of a trained social worker or counselor.
- Comorbidities, overlapping toxicities, and IRIS should be closely managed.
- HIV-positive DR-TB patients less than 18 years of age: if the child or adolescent is on an LPV/r based regimen, no change in ART is necessary when starting DR-TB treatment; if the child or adolescent is on EFV, the non-nucleoside reverse transcriptase inhibitor (NNRTI) should be switched to LPV/r or other ART regimen (ATV/r) based on weight and national pediatric HIV guidelines.

CHAPTER 8.
MONITORING OF DR-TB TREATMENT

Treatment of DR-TB is associated with adverse drug reactions, which if not detected early can lead to patient deterioration and permanent disability (e.g. hearing loss). For this reason, patients should be closely monitored for adverse events and potential treatment failure (Tables 8 and 9).

- Treatment should be monitored through history, physical examination, bacteriological tests, chest radiography, laboratory tests, audiometry, and functional status.
- Weight should be monitored monthly and drug dosages should be adjusted accordingly, especially in children.
- For patients on individualized regimens, additional monitoring is required:
  - ECG (Dlm, Bdq).
  - Serum albumin, especially for patients with low BMI (Dlm).
  - Visual chart testing and monthly full blood count (Lzd).
  - Amylase/lipase only if symptoms of persistent nausea, vomiting, abdominal pain (Bdq/Lzd).

  Annexure 6 provides templates of clinical and laboratory monitoring schedules for patients on treatment that can be printed and placed in individual patient files to track completion of monitoring tests (based on Tables 8 and 9).

8.1 Clinical monitoring

Patients should be asked about their TB symptoms and their weight should be recorded at every encounter. Persistent fever, weight loss, or recurrence of any of the classic symptoms of TB should prompt investigation of treatment failure or untreated comorbidities (bacterial pneumonia is very frequent in patients with lung damaged due to TB). Patients should be routinely screened for adverse drug reactions (ADRs) at least weekly during the first month of intensive phase, and monthly for the entire duration of the treatment.

DOT providers should be trained to screen patients regularly for symptoms of common ADRs: rash, gastrointestinal disturbances (e.g. nausea, vomiting, and diarrhea), psychiatric symptoms (e.g. depression, anxiety, and suicidal ideation, behavior change), jaundice, ototoxicity, peripheral neuropathy, and symptoms of electrolyte wasting (e.g. muscle cramping, palpitations). DOT providers should also be trained in simple adverse event management and when to refer patients to a nurse or doctor.

8.2 Psychosocial consultation and patient education

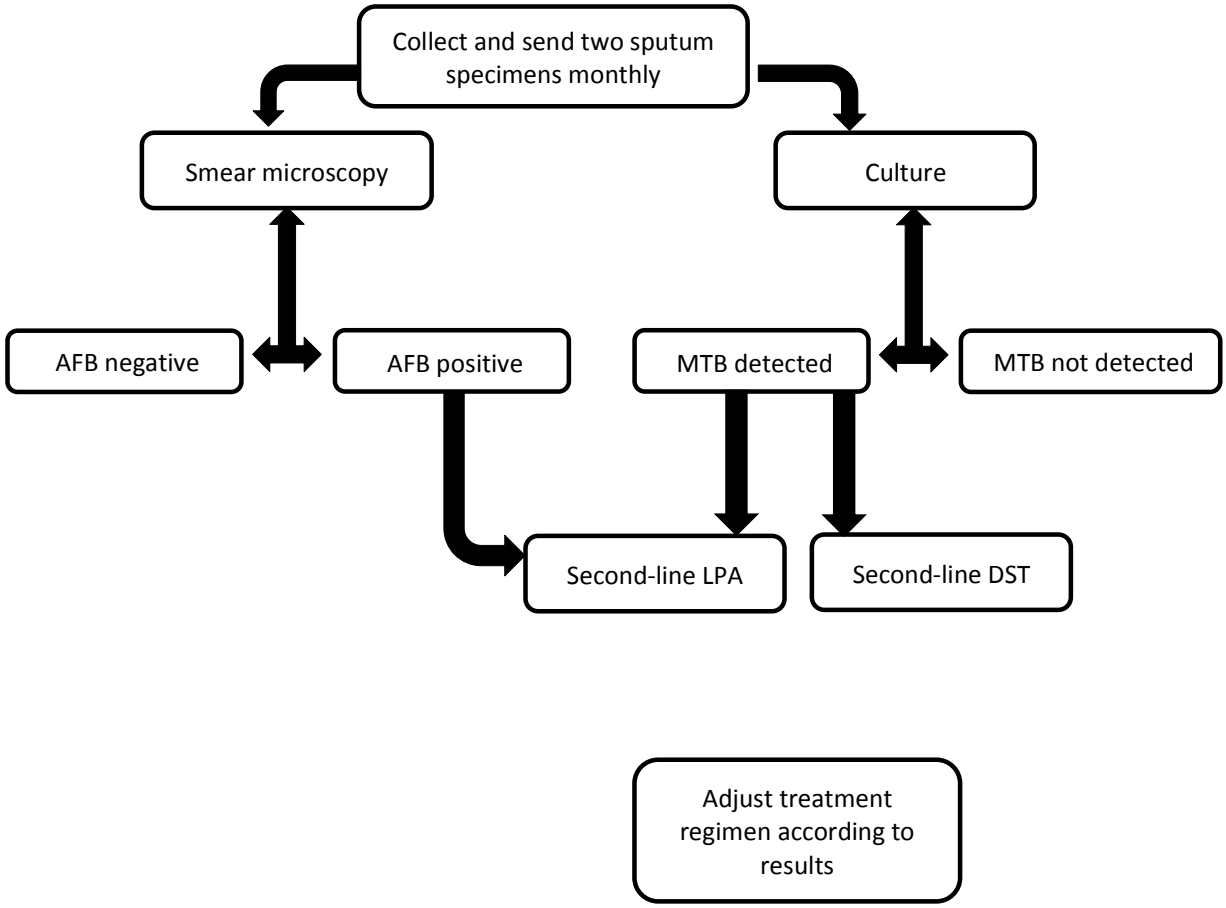
Psychosocial consultation and patient education should be done at baseline and monthly by trained personnel. Patient education should include clear information about adverse drug reactions (e.g. symptoms, importance of prompt consultation, basic management).

8.3 Bacteriological monitoring

- For monitoring the patient's response to treatment, monthly smear microscopy and culture should be performed. **Molecular tests (Xpert MTB/RIF) are not recommended for treatment monitoring as they may give false positive results.**
- For patients who remain culture positive after more than four months of treatment or there is suspicion of treatment failure, second-line LPA and phenotypic DST should be repeated (Figure 4).
- **After completion of DR-TB treatment**: Patients on both the shorter regimen and individualized regimens should be followed every 3 months during the first year (symptom screen and sputum for smear/culture) and every 6 months in the second year after treatment completion.

Figure 4: Bacteriologic monitoring for patients on DR-TB treatment [12]

Bacteriologic monitoring for patients on DR-TB treatment [12]



8.4 Radiological monitoring

- Chest radiographs should be taken at baseline, every 6 months, and at the end of the treatment to document progress and to use for comparison if the patient's clinical condition changes.
- Chest radiographs are also done when a surgical intervention is being considered, or whenever the patient's clinical situation has worsened.

8.5 Laboratory monitoring

For laboratory monitoring refer to Tables 8 and 9.

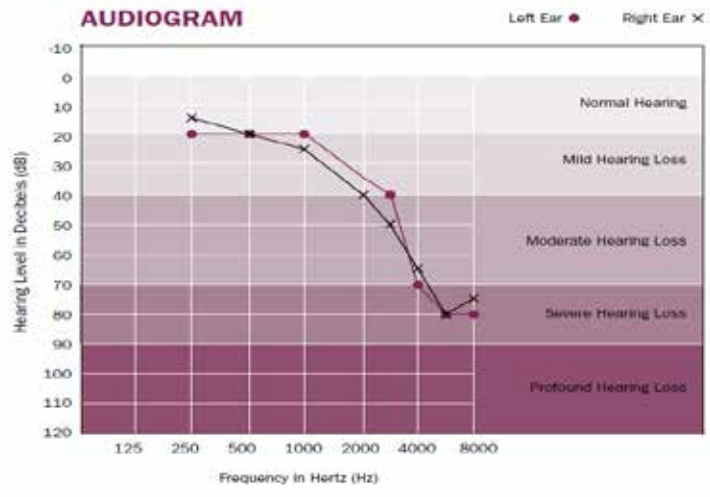
8.6 ECG monitoring

Bedaquiline, delamanid, moxifloxacin, and clofazimine all have the potential to cause prolongation of the QTcF interval (which may increase the risk of arrhythmias). For patients on an individualized regimen with either Bdq or Dlm (or both), the ECG should be performed at baseline, at 2 weeks on treatment, and then monthly with a standard 12-lead ECG machine (Annexure 3).

8.7 Audiometry monitoring

Audiometric examination should be performed at baseline and at least monthly while the patient is receiving the second-line injectable. In addition to a physical examination of the ears with an otoscope, an audiogram is charted for each audiometric measurement, denoting the hearing intensity threshold (in decibels [dB], shown on the vertical axis) for each ear at various frequencies (in hertz [Hz], shown on the horizontal axis). The threshold on the right ear is usually plotted as an O whereas that for the left ear is plotted as an X (Figure 5). Normal hearing threshold ranges from 0dB to 26dB hearing level.

Figure 5: Routine audiogram results showing charting of audiometric measurements and severe bilateral high frequency hearing loss



Source: Auditory neuroscience: making sense of sound. (http://auditoryneuroscience.com/acoustics/clinical_audiograms, accessed 30 June 2013)

8.8 Vision test charts

For patients on long-term ethambutol or linezolid, perform a visual acuity test with Snellen charts and color vision test (Ishiara) at baseline (as a small percentage of the population has color blindness). Repeat the test if any change in acuity or color vision is suspected.

8.9 Monitoring schedules for shorter and individualized regimens

Table 8: DR-TB treatment monitoring schedule for the shorter DR-TB regimen

*Prompt action on abnormal clinical or laboratory findings is essential **Circle each test completed												
Patient name: DR-TB registration number: Age: Sex: Height:												
Month/Year												
Examination	Baseline	1	2	3	4	5	6	7	8	9	10	11
Clinical exam	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Psychosocial, functional status	X	X	X	X	X	X	X	X	X	X	X	X
Weight/body mass index (wt/ht^2)	X	X	X	X	X	X	X	X	X	X	X	X
Xpert MTB/RIF	X											
SL LPA	X	Repeat if smear or culture positive or suspect failure										
Smear	X	X	X	X	X	X	X	X	X	X	X	X
Culture	X	X	X	X	X	X	X	X	X	X	X	X
Phenotypic DST	X	Repeat if smear or culture positive or suspect failure										
X-ray	X						X					X
Full blood count[1]	X						X					
Creatinine, potassium[2]	X	X	X	X	X	X	X	X				
Liver function tests (ALT/AST)	X			X			X			X		
TSH	X			X			X					
Fasting blood sugar	X											
Vision test charts[3]	X											
Audiometry[2]	X	X	X	X	X	X	X					
HIV test[4]	X			X								
Hepatitis B (HBsAg)	X											
Pregnancy test[5]	X											
CD4 count (HIV-positive patients)	X						X					
Viral load (HIV-positive patients)	X						X					

1. Repeat full blood count (FBC) as necessary if HIV-infected (especial care in patient with AZT) or if basal result is low.
2. Creatinine, potassium, and audiometry should be done monthly while on injectable.
3. Repeat vision testing if any change/complaint in acuity or color vision.
4. If HIV-negative at baseline, HIV testing should be repeated at month 3 and then every 6 months.
5. Pregnancy test: At baseline, then offer use of effective contraceptives (Depo-Provera or intrauterine device [IUD]).

Table 9: DR-TB treatment monitoring schedule for individualized DR-TB regimens

*Prompt action on abnormal clinical or laboratory findings is essential **Circle each test completed																					
Patient Name: DR-TB registration number: Age: Sex: Height:																					
Month/Year																					
Examination	Base-line	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Clinical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Psychosocial, functional status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/BMI (wt/ht^2)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Xpert MTB/RIF	X																				
SL LPA	X	Repeat if smear or culture positive presumption of failure																			
Smear	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Culture[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phenotypic DST	X	Repeat if smear or culture positive presumption of failure																			
X-ray	X						X						X						X		
Full blood count (monthly if on Lzd)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Creatinine, po-tassium[1]	X	X	X	X	X	X	X														
LFTs (ALT/AST)	X			X			X			X			X			X			X		
TSH[2]	X						X			X			X						X		
Fasting blood sugar	X																				
Serum albumin[3]	X																				
Serum amylase/ Lypase[4]	X																				
ECG[5]	X week 2	X	X	X	X	X	X		Continue monthly ECGs if Bdq/Dlm given > 6 months												
Vision test charts[6] (monthly if on Lzd)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Audiometry[1]	X	X	X	X	X	X	X														
HIV test[7]	X			X						X									X		
Hepatitis B (HBsAg)	X																				
Pregnancy test[8]	X																				
HIV-positive patients																					
CD4 count	X						X						X						X		
Viral load	X						X						X						X		

1. Creatinine, potassium, and audiometry should be done monthly while on injectable. Continue monthly creatinine monitoring for patients at risk of renal failure (HIV-positive patients, diabetics, patients receiving other nephrotoxic drugs). If any ECG abnormality, check potassium (and magnesium, calcium if available).

2. TSH: Only if on Eto/ Pto or PAS. If levotiroxine replacemen is needed, monitor every 30–45 days to adjust the dosage.

3. Serum albumin: If patient is on Dlm at baseline. If low (< 3,4 g/dL), provide high protein diet, repeat albumin at month 3, and follow ECG. If albumin < 2.8g/dL, Dlm is contraindicated.

4. Amylase/lipase: At baseline if patient on Bdq and Lzd. Then assess when clinically indicated (persistent nausea, vomiting, abdominal pain).

5. **ECG** is mandatory for patients on Bdq and or Dlm at baseline, week 2, and monthly while on either drug. ECG may be done more frequently in patients with low albumin (< 3.4 g/dl), low electrolytes, hypothyroidism, or heart conditions.

6. Visual test: If patient on linezolid, perform monthly visual acuity test (Snellen charts) and color vision test (Ishiara).

7. If HIV-negative at baseline, HIV testing should be repeated at month 3 and then every 6 months.

8. Pregnancy test: At baseline, then offer use of effective contraceptives (Depo-Provera or intrauterine device [IUD]).

9. Patient is not declared cured until culture tests negative at the end of treatment period.

CHAPTER 9
MANAGEMENT OF ADVERSE EVENTS

9.1 Principles in the management of adverse events

Most of the drugs used in the conventional 20-month DR-TB have been used by clinicians and TB programmes for decades, thus the adverse events associated with conventional DR-TB treatment are generally well known. It is also recognized that patients on DR-TB treatment nearly universally experience at least one adverse event during the course of treatment, as most of the drugs used have many potential toxicities; some of these adverse events can be severe and cause serious harm to the patient (Tables 10 and 11). With the introduction of both the shorter regimen and the individualized regimen, clinical staff treating patients will need to familiarize themselves with adverse events seen with the new and repurposed drugs used in both regimens. Additionally, there may be adverse events that occur with greater frequency in certain regions or countries due to demographic, genetic, or environmental patterns. For all of these reasons, every health care worker taking care of patients on DR-TB treatment should be able to promptly monitor, recognize, and manage the most common adverse events (AE) to second-line drugs (Table 12).

Management of AEs should take patient safety and treatment need into consideration. For minor AEs, reassurance to enhance adherence is needed. For AEs that need additional evaluation and/or medical treatment, treatment decisions should involve the whole health care team (DOT provider, nursing staff, and doctors), and additional tests and ancillary medicines should be available and accessible free of charge. Patients should always be informed at the beginning of treatment about the possibility of adverse events and what to do if they develop; psychosocial support is also important, and DOT providers should educate patients about adverse events and encourage them to continue treatment in the case of minor adverse events. Preventive therapy should be offered where necessary, such as pyridoxine for patients receiving cycloserine, INH, or linezolid.

If drug(s) thought to cause the AE need to be removed from the regimen, replacement is likely necessary, especially in the intensive phase when the bacillary load is high. Replacement of drugs should take the clinical condition and bacteriological status of patients into account. Ensure that the regimen contains at least four medicines with known effective drugs. Any decision must be made on the basis of careful patient review (if necessary consult the provincial or National CEC for guidance). Systematic monitoring to inform clinical practice helps to improve patient outcomes and promote patient confidence in their health care providers.

9.2 Grading and management of adverse events

Table 10: Severity grading scale of adverse events [13,14]

Grade	Description
GRADE 1: Mild	Mild or transient discomfort without limitation of normal daily activities*. No medical intervention or corrective treatment required.
GRADE 2: Moderate	Moderate limitation of normal daily activities*. Minimal medical intervention or corrective treatment required.
GRADE 3: Severe	Marked limitation of normal daily activities*. Medical intervention, therapy, or stopping or reduction of the offending drug is required. Possible hospitalization.
GRADE 4: Life-threatening or permanently disabling	Severe limitation of normal daily activities*. Medical intervention and corrective treatment required almost always in a hospital setting.

*The term "activity" covers basic self-care functions such as bathing, dressing, toileting, transfer/movement, continence, and feeding, as well as usual social and functional activities or adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby.

Table 11: Severity grading scale of main laboratory parameters [13,14]

	Hb (g/dL)	Platelets (/mm³)	Neutrophils (/mm³)	AST (UI/L)	ALT (UI/L)	Creatinine (µmol/L)	K+ (mEq/L) / (mmol/L)
Normal values	> 12	>150,000	> 1,500	*	*	*	3.5–5.0
Grade 1	10–11.9	100,000-149,999	1,000–1,500	1.5–2.5 x ULN	1.5–2.5 x ULN	1.1–1.5 x ULN	3.2–3.4
Grade 2	8–9.9	50,000-99,999	750–999	2.6–5.0 x ULN	2.6–5.0 x ULN	1.6–3 x ULN	2.8–3.1
Grade 3	6–8	20,000-49,999	500–749	5.1–10 x ULN	5.1–10 x ULN	3–6 x ULN	2.5–2.7
Grade 4	< 6	< 20,000	< 500	> 10 x ULN	> 10 x ULN	> 6 x ULN	< 2.5

*Normal values vary from laboratory to laboratory and might be slightly different in men, women, and children (check normal parameters for local laboratory).

ULN = upper limit of normal

Table 12: Management of adverse events associated with DR-TB treatment

Prolonged QT interval **Possible DR-TB drug causes: Bdq, Dlm, Mxf, Cfz**				
Normal Values (msecs)	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Male: ⩽ 430 **Female: ⩽ 450**	**Borderline:** Male: 430–450 Female: 450–470	**Prolonged:** Male: > 450–<500 Female: > 470–< 500	**Pathological:** > 500 or ⩾ 60 above baseline	**Life-threatening consequences:** QTcF ⩾ 500 or > 60 ms change from baseline and torsade de pointes or other associated serious ventricular dysrhythmia.
Action	Monitor ECG frequently.	Monitor more closely; at least weekly ECG until QTcF has returned to Grade 1 or less. Check electrolytes and replete as necessary.	Confirm with two additional 12-lead ECG (15–30 min apart). Stop the suspected causative drug. Hospitalize and replete electrolytes as necessary. Check TSH.	Stop the suspected causative drug. Hospitalize and replete electrolytes as necessary. Check TSH.
Suggestions and precautions: • Close follow-up of patients at high risk who take several medicines that prolong the QT. • Follow-up of potassium in high-risk patients. • Be careful in case of diarrhea, vomiting, use of diuretics, alcohol. • Stop the medicine if QTc persists over 500 ms even if the patient is asymptomatic. • Think of arrhythmia when the patient suffers vertigo, syncope, palpitations. If QTcF is prolonged ⩾ 500 ms (confirmed with two additional 12-lead ECG 15–30 minutes apart): • Stop all QT prolonging drugs immediately. ART is usually not stopped unless the patient is severely unstable. • Hospitalize (if symptomatic or other risk factors). Frequent ECG monitoring. • Check electrolytes and manage accordingly. (If low potassium: urgent management with replacement and frequent monitoring). Give magnesium sulfate supplements (orally or IV) and calcium. • Check a TSH and treat any hypothyroidism found. • Check albumin if on delamanid. Once stable (QTcF < 450 and normal electrolytes), critical prolonging QT drugs can be added back: • If the patient was on Mfx consider using Lfx instead. • If the patient was on Cfz consider suspending it permanently (if not critical to the regimen). If the patient is on Bdq (or Dlm) and it is critical to the regimen, add it back while suspending all other QT prolonging drugs (with the exception of stopping ART, which should not normally be suspended in the management of QT prolongation).				
Hypokalemia **Possible DR-TB drug causes: Am, Km, Cm, S**				
Normal value (mmol/L)	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
3.5–5.0	3.4–3.2	3.1–2.8	2.7–2.5	< 2.5

Action	Continue injectable. Start oral potassium. **slow K* 600 mg = 8 mEq: 1 tab twice daily.** **Monitor K monthly**	Continue injectable. Start oral potassium. **slow K* 600 mg = 8 mEq: 2 tabs twice daily.** Oral magnesium gluconate: 1,000 mg twice daily. **Monitor K every 2 weeks** and adjust the slow K dose accordingly.	Continue injectable. Oral potassium: **Slow K* 600 mg = 8 mEq: 2 tabs thrice daily.** Oral magnesium gluconate: 1,000 mg twice daily. **Monitor K every 1–2 days** and adjust dose accordingly.	Stop injectable temporarily. Hospitalization**.** Start IV potassium in addition to oral. Replace magnesium and other electrolytes. **Monitor K 1 hour after replacement and repeat till K is > 2.8 mmol/L.**

* The formulations of oral potassium chloride varies by manufacturer and countries. Slow-release versions are common in low-resources settings. One slow K 600 mg tab contains 8 mEq of potassium. Adjust the number of pills according to the formulation available.

Oral potassium and magnesium should be administered either 2 hours before or 4 to 6 hours after fluoroquinolones as they can interfere with fluoroquinolone absorption**.**

Replacing serum electrolytes

- Replacement of 40 mEq of potassium increase 1 mEq/L the potassium.
- Oral replacement: The replacement varies 40 mEq to 80 mEq day. Usually patients don't tolerate more than six tabs of slow K (diarrhea, nausea). Doses should be divided to two or three times a day (no more than 20 mEq per dose).
- Hypokalemia may be refractory if concurrent hypomagnesemia is not also corrected.
- If unable to check serum magnesium, give empiric replacement therapy in all cases of hypokalemia with oral magnesium gluconate 1,000 mg twice daily.
- In refractory cases can be given spironolactone 25 mg/ day or amiloride 5–10 mg/day orally (decrease of potassium and magnesium wasting).

FOR HOSPITALIZED PATIENTS:

If severe hypokalemia (K ⩽ 2.5 mmol/L or symptomatic hypokalemia): give intravenous potassium concurrently with oral potassium replacement.
Dosing: 10–15 mEq /h IV and 80 mEq orally every 6 to 8 hours. Recheck serum potassium 1 hour after infusion. Repeat IV replacement every 6 to 8 hours until serum potassium is ⩾ 2.8 mmol/L.
The normal preparation of a potassium chloride infusion is 40 mEq in 200 mL of normal saline over 2–4 hrs. Do not exceed an infusion rate of 20 mEq/hr (100 mL/hr).

Magnesium replacement:
Dosing: 2,000 mg/day. If Mg can be measured and is less than 1.0, increase the dose up to 3,000 mg–6,000 mg if Mg IV (doses greater than 2,000 mg are usually given IV). Magnesium IV: The normal preparation is magnesium sulfate 2 g in 100 mL or 4 g in 250 mL of 5% dextrose or normal saline. Do not exceed an infusion rate of 150 mg/min (2 g in 100 mL administered over 1 to 2 hours, 4 g in 250 mL administered over 2 to 4 hours). Repeat until serum K is > 2.8 mmol/L.

Other considerations:

- Check an ECG in patients with significant serum electrolyte disturbances.
- Electrolyte abnormalities are reversible upon discontinuation of the injectable. Even after suspending the injectable, it may take weeks or months for this syndrome to disappear, so electrolyte replacement therapy should continue for several months after completion of the injectable phase of DR-TB treatment.

Nephrotoxicity [15] **Possible DR-TB drug causes: Am, Km, Cm, S**				
	Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Creatinine	1.1–1.5 x ULN	1.6–3.0 x ULN	3.1–6 x ULN	> 6 x ULN or dialysis required
Creatinine clearance* Normal value Cr Cl grading [13] Male: 97–137 mL/min Female: 88–128 mL/min	> 90 mL/min	60–89 mL/min	30–59 mL/min	15–29 mL/min Note: < 15 mL/min is Grade 5 and requires dialysis.
Action	Continue monitoring.	Reduce injectable to 3 times a week dosing at 12–15 mg/kg.**	Reduce injectable to 2 times a week dosing at 12 mg/kg.**	Stop injectable.** Monitor creatinine and electrolytes weekly till creatinine returns to normal. Adjust other drug dosages (Annexure 4).
**Suspend the injectable permanently if the nephrotoxicity recurs despite intermittent dosing, and transition the patient to an individualized regimen with new drugs (bedaquiline, delamanid, or linezolid).				
Consider other causes of renal insufficiency (pre-renal, renal, and post-renal). Consider other contributing etiologies (pre-renal, intrinsic renal, and post-renal). ***Creatinine clearance formula:** **Weight (Kg) x (140 – Age) x (constant)** **Serum creatinine µmol/L** **Constant: 1.23 for men and 1.04 for woman** **If creatinine is reported in mg/dL, multiply by 88.4 to convert to µmol/L.**				
Hearing loss (ANRS scale) **Possible DR-TB drug causes: Am, Km, Cm, S**				
AUDIOMETRY TEST: Exclude causes of conductive hearing loss: ear wax, otitis media, tympanic perforation *Attain a baseline record of the hearing status of a person prior to treatment initiation. Perform a monthly audiogram that includes speech frequencies (500–4,000 Hz) and higher up to 8,000 Hz. Calculate the average hearing loss (AHL) for each ear: sum the loss in dB at each frequencies of 500-1,000-2,000-4000 Hz (if a frequency is not perceived consider a loss of 120 dB) and divide by 4. You have the average of the best ear and the bad ear. Then calculate the weighted average hearing loss (WAHL) for both ears: WAHL= (Average of the best ear multiplied by 7) + (Average of the worst ear multiplied by 3), and divide the total by 10.				
Normal Values	**Grade 1** **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Profound**

0–20 dB	**21–40 dB** Speech perceived if voice is normal; difficulties arise if voice is low-pitched or distant from the subject. Most of the daily life noises are perceived.	**41–70 dB** Speech is perceived if the voice is loud. The subject understands better what is being said if he can see his/her interlocutor.	**71–90 dB** Speech is perceived if the voice is loud and close to the ear. Loud noises are perceived.	**> 90 dB** Speech is not perceived at all. Only very loud noises are perceived.
Action: Confirm results on repeated test in the same visit before any change in the treatment. Before reducing or stopping a drug, discuss with provincial CEC. If detected early it may be possible to reduce or to stop the dose of the injectable to prevent progression of hearing loss. **If vestibular disorder (vertigo, dizziness, imbalance, disequilibrium, nausea, and vision problems) injectable should be stopped**.				
Patient with no hearing loss at baseline:				
Injectable	Continue injectable but consider reducing the frequency to 3 times per week and perform more frequent audiometry.	Stop the injectable and replace by new drugs Bdq, Dlm, or Lzd. Refer to audiologist.	Stop the injectable and replace by new drugs Bdq, Dlm, or Lzd. Refer to audiologist.	Stop the injectable and replace by new drugs Bdq, Dlm, or Lzd. Refer to audiologist.
Patients with hearing loss at baseline: Consider reducing frequency or stopping the injectable if there is a worsening of 1 grade of hearing loss compared with baseline.				
Hearing aid	Counseling.	Hearing aids usually recommended.	Hearing aids are needed. If not available, lip-reading and signing should be taught.	Hearing aids may help understanding words but additional rehabilitation needed and lip-reading and sometimes signing essential.

- *Five percent of the world's population has disabling hearing loss (> 40 dB in better ear in adults and > 30 dB in children). This includes one third of those 65 years old. Hence, it is important to attain a baseline record of the hearing status of a person prior to treatment initiation.
- The toxicity to the eight-cranial nerve concerns the vestibule (dizziness) and the cochlea (hearing loss), and it is irreversible.
- The frequencies between 500 Hz and 4,000 Hz are considered to be those of a normal conversation.
- The higher frequencies (4,000–8,000 Hz) are the first to be affected; the frequencies of the human voice come next.
- Hearing loss becomes perceptible for patients at a frequency < 4,000 Hz when it reaches 25–30 dB (Brumett 1989). When patients mention hearing loss, there is already a severe degree of loss.
- Children: Above 4 years can perform pure tone audiometry. Below 4 years refer to audiologist.
- Patient at higher risk of ototoxicity: previous use of aminoglycoside, elderly, renal insufficiency, preexisting hearing problems, receiving other ototoxic medications.
- Hearing loss should always be compared to baseline measurements and ototoxicity is defined as any of:
  (a) 20 dB decrease at any one frequency.
  (b) 10 dB decrease at any two adjacent frequencies.
  (c) Loss of response at three consecutive test frequencies where responses were previously obtained.

Hepatotoxicity
Possible DR-TB drug causes: Z, H, Pto, Lzd, Cfz, Bdq, Mfx

	Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
ALT (SGPT)	1.5–2.5 x ULN	2.6–5.0 x ULN	5.1–10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25–2.5 x ULN	2.6–5.0 x ULN	5.1–10.0 x ULN	> 10.0 x ULN
Action	Continue treatment. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Continue treatment. Patients should be followed until resolution (return to baseline). If JAUNDICE: Stop all anti-TB drugs until resolution.	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.

Consider other potential causes of hepatitis: viral (hepatitis B and C), HIV, alcohol.
Avoid potentially hepatotoxic non-tuberculosis drugs.
Reintroduction of anti-TB drugs:

- Check ALT/AST once a week. Reintroduce anti-TB drugs once liver enzymes return to at least Grade 2.
- Anti-TB drugs should be reintroduced in serial fashion. The least hepatotoxic drugs should be added first: Km-E-Cfz-Mfx. Then introduce the more hepatotoxic one by one every three days: Pto-H-Z while monitoring liver function tests after each one to identify the responsible drug.
- If reintroduction leads to signs of hepatotoxicity, stop the suspected drug and replace it by another if it is essential for the treatment. If the drug stopped is H or Z, there is no need to replace by another agent. Follow transaminases monthly.

If patient is on ART and experienced nevirapine (NVP) hepatotoxicity, the patient should not be re-challenged with NVP.

Peripheral neuropathy
Possible DR-TB drug causes: Lzd, Cs, H, S, Km, Cm, H, FQ, Pto/Eto, E
Possible other causes: Diabetes mellitus, alcohol, HIV infection, vitamin B deficiency, hypothyroidism, and other drugs

	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social and functional activities.	Sensory alteration or paresthesia causing greater than minimal interference with usual social and functional activities.	Sensory alteration or paresthesia causing inability to perform usual social and functional activities.	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions.
Action	Stop offending drugs (Lzd, High dose INH). If symptoms improve after 2 weeks consider restarting Lzd at a lower dose (300 mg).	Stop Lzd. Do not reintroduce Lzd.	Stop Lzd. Do not reintroduce Lzd.	Stop Lzd. Do not reintroduce Lzd.

Suggested management strategy

- All patients taking high dose INH and linezolid should receive 100 mg of pyridoxine (vitamin B6) day.
- The neuropathy associated with linezolid is common after prolonged use and often extremely painful and irreversible. For this reason, linezolid should be immediately stopped and not reintroduced when symptomatic neuropathy develops (Grade 2 and above).
- Symptomatic relief:
  - Increase pyridoxine (vitamin B6) to a maximum of 150 mg.
  - Nonsteroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms.
  - Tricyclic antidepressants have also been used successfully. Start amitriptyline 25 mg at bedtime. The dose may be increased to a maximum of 150 mg daily for refractory symptoms.
  - Carbamazepine may also be effective in relieving pain and other symptoms of peripheral neuropathy. **Carbamazepine is a strong inducer of CYP3A4 and should not be used with bedaquiline or delamanid.**

Myelosuppression (anemia, thrombocytopenia, or neutropenia)
Possible anti-TB drug causes: Lzd[1]
Possible other causes: AZT, cotrimoxazole, HIV Infection, chemotherapy

	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe[2]	Grade 4 Life-threatening[2]
Absolute neutrophil count	1,000–1,300/mm^3	750–999/mm^3	500–749/mm^3	< 500/mm^3
Haemoglobin	8.5–10.0 g/dl	7.5–8.4 g/dl	6.5–7.4 g/dl	< 6.5 g/dl
Platelets, decreased	100,000–124,999 /mm^3	50,000–99,999 mm^3	25,000–49,999/ mm^3	< 25,000/mm^3
WBC, decreased	2,000–2,500/ mm^3	1,500–1,999/mm^3	1,000–1,499 /mm^3	< 1000/mm^3

Action	Monitor carefully, and consider reduction of dose of Lzd to 300 mg daily.	Monitor carefully, and consider reduction of dose of Lzd to 300 mg daily; in case of Grade 2 neutropenia, stop Lzd immediately. Restart at reduced dose (300 mg) once toxicity has decreased to Grade 1.	Stop Lzd immediately. If Hb ⩽ 7 g/dl, transfuse. Restart at reduced dose (300 mg) once toxicity has decreased to Grade 1.	Stop Lzd immediately. Give transfusion and erythropoietin if available. Restart at reduced dose (300 mg) once toxicity has decreased to Grade 1.

Suggested management strategy

1. All patients taking linezolid should also be receiving at least 100 mg of pyridoxine daily. This is largely to prevent myelosuppression, but may also prevent peripheral neuropathy.
2. Stop the causative drug immediately.
3. Monitor full blood counts regularly.

Hospitalize the patient and consider transfusion if the myelosuppression is severe (e.g. Hb ⩽ 7 g/dl).

Optic neuritis
Possible anti-TB drug causes: Lzd, E
Possible other causes: Multiple sclerosis, quinine, herpes, syphilis, sarcoidosis, cytomegalovirus (HIV)

The first sign of optic neuritis is usually the loss of red-green color distinction. This is best tested using the Ishihara test. Other symptoms include central scotoma (loss of central vision or blind spot).

	Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Optic neuritis is inflammation of the optic nerve resulting in permanent vision loss.	Visual changes causing minimal or no interference with usual social and functional activities.	Visual changes causing greater than minimal interference with usual social and functional activities.	Visual or changes causing inability to perform usual social and functional activities.	Disabling visual loss.
Action	Stop Lzd or E immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd or E immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd or E immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd or E immediately if there are any suspicions of optic neuritis. Do not restart it.

Suggested management strategy

- Do not restart the suspected causative drug (linezolid or ethambutol).
- Refer patient to an ophthalmologist for further evaluation and management.
- Optic neuritis generally improves following cessation of offending drug, if it can be stopped early enough.
- Patients with diabetes are at increased risk for optic neuritis. They should be managed with tight glucose control as a means of prevention. Patients with advanced kidney disease are also at increased risk for optic neuritis.

Lactic acidosis **Possible anti-TB drug causes: Lzd** **Possible other causes: AZT, 3TC**				
	Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Lactate and pH	< 2.0 x ULN without acidosis.	⩾ 2.0 x ULN without acidosis.	Increased lactate with pH < 7.3 without life-threatening consequences.	Increased lactate with pH < 7.3 with life-threatening consequences.
Action	Continue treatment regimen. Patients should be followed until resolution (return to baseline).	Stop Lzd immediately. Do not restart it.	Stop Lzd immediately. Do not restart it.	Stop Lzd immediately. Do not restart it.
Early signs and symptoms include **nausea, vomiting, abdominal pain, anxiety, and increased respiration rate and heart rate.** Late symptoms include lethargy, hypotension, and septic shock. Early detection of lactic acidosis is important because full-blown lactic acidosis is often fatal. Diagnosis: analysis of an arterial blood sample showing a low pH and high lactate: anion gap, metabolic acidosis, lactate > 5 mmol/L, increased lactate/pyruvate. If laboratory is not available, start treatment with clinical features. **Suggested management strategy** 1. Stop linezolid and NRTIs if lactic acidosis occurs. It may take months for the lactic acidemia to resolve completely even after the causative drug is stopped. 2. Hospitalize patient and monitor serum electrolytes, renal function, arterial blood gas, and lactate levels. 3. Check vital signs frequently and provide supportive care. Sodium bicarbonate therapy to correct a low pH has not been shown to be of benefit in lactic acidosis. After lactic acidosis resolves, do not restart the suspected offending medication.				
Pancreatitis **Possible DR-TB drug causes: Bdq, Lzd** **Other causes: gallstones, heavy and long-term alcohol use, high triglycerides**				
	Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4** **Life-threatening**
Pancreatitis	Not applicable.	Symptomatic and hospitalization not indicated.	Symptomatic and hospitalization indicated.	Life-threatening consequences (e.g. circulatory failure, haemorrhage, sepsis).
Lipase	1.1–1.5 x ULN	1.6–3.0 x ULN	3.1–5.0 x ULN	> 5.0 x ULN
Amylase	1.1–1.5 x ULN	1.6–2.0 x ULN	2.1–5.0 x ULN	> 5.1 x ULN
Action	Continue treatment regimen. Patients should be followed until resolution (return to baseline).	Stop Lzd immediately. Do not restart it.	Stop Lzd immediately. Do not restart it.	Stop Lzd immediately. Do not restart it.

The most common symptoms and signs include severe epigastric pain (upper abdominal pain) radiating to the back in 50% cases, nausea, and vomiting.

Suggested management strategy

1. Monitor liver function tests, amylase, lipase, and full blood count.
2. Provide supportive care.

Permanently discontinue linezolid (or bedaquiline if it is suspected to be the cause of the pancreatitis).

Gastrointestinal (nausea and vomiting)
Possible DR-TB drugs: Eto/Pto, PAS, Bdq (less common H, E, Z, Amx/Clv, Cfz, Dlm)

Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
1 episode in 24 hours.	2–5 episodes in 24 hours.	> 6 episodes in 24 hours or needing IV fluids.	Physiologic consequences requiring hospitalization or requiring parenteral nutrition.

Management and comments

Nausea and vomiting are universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy. Some nausea and even vomiting may need to be tolerated at least in the initial period.

Assess for danger signs including dehydration, electrolyte disturbances, and hepatitis.

Initiate rehydration therapy if indicated and correct any electrolyte disturbances.

Initiate a step-wise approach to manage nausea and vomiting.

Phase 1:

Give a light snack (biscuits, bread, rice, tea) before the medications. Give PAS with fruit juice.

Adjust medications and conditions without lowering the overall dose:

––Give Eto or PAS twice or thrice daily.

––Give PAS two hours after other anti-TB drugs.

Another strategy is to stop the responsible medicine for 2 or 3 days and then add it back, gradually increasing the dose (advise the patient that the medicine will be increased back to a therapeutic dose in a manner that will be better tolerated).

Phase 2: Start antiemetic(s):

––Metoclopramide 10 mg, 30 minutes before anti-TB medications.

––Ondansetron 8 mg, 30 minutes before the anti-TB drugs and again 8 hours after. Ondansetron can either be used on its own or with metoclopramide. **Odansetron prolongs the QT interval; avoid with bedaquiline or delamanid.**

––If ondansetron is not available, promethazine can be used. Promethazine 25 mg PO (by mouth), 30 minutes before the anti-TB drugs (may be increased to 50 mg 3 times daily).

––Omeprazole or ranitidine can also provide relief (omeprazole decreases the acid production and is also useful in the treatment of nausea).

Phase 3: Decrease dose of the suspected drug by one weight class if this can be done without compromising the regimen. It is rarely necessary to suspend the drug completely.

Note: For patients who are particularly anxious about the nausea (and with "anticipatory nausea and vomiting"), a small dose of an anti-anxiety medicine (5 mg of diazepam) can help when given 30 minutes prior to the intake of anti-TB drugs. Do not give diazepam longer than 2 weeks.

Gastritis
Possible DR-TB drug causes: Eto, Pto, PAS, Cfz, FQs, H, E, and Z

If symptoms are associated consistent with gastritis (epigastric burning or discomfort, a sour taste in mouth associated with reflux), initiate medical therapy (prolonged duration):

- Omeprazole 20 mg once daily (proton-pump inhibitors). Give 2 hours before or 3 hours after the TB medication
- Ranitidine 150 mg twice daily or 300 mg once daily (H2-blockers).
- Avoid the use of antacids as they decrease absorption of fluoroquinolones.

Stop any nonsteroidal anti-inflammatory drugs the patient may be taking.
Diagnose and treat for Helicobacter pylori infections.

Abdominal pain
Possible DR-TB drugs: Eto, Pto, Cfz, Lzd

Abdominal pain is most commonly gastritis. However, it can also be associated with serious adverse effects, such as pancreatitis, lactic acidosis (Lzd), and hepatitis. If any of these are suspected, obtain appropriate laboratory tests to confirm and suspend the suspected agent.
For severe abdominal pain stop suspected agent(s) for short periods of time (1 to 7 days).
Lower the dose of the suspected agent, if this can be done without compromising the regimen.
Discontinue the suspected agent if this can be done without compromising the regimen.
Severe abdominal distress has been reported with the use of clofazimine (deposition of Cfz crystal). Although these reports are rare, if this occurs, clofazimine should be suspended.

Diarrhea
Possible DR-TB drugs: PAS, Eto/Pto

Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Mild or transient; 3–4 loose stools/day or mild diarrhea last < 1 week.	Moderate or persistent; 5–7 loose stools/day or diarrhea lasting >1 week.	> 7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or > 2L IV fluids required.	Hypotensive shock or physiologic consequences requiring hospitalization.

Management
1. Encourage patients to tolerate some degree of loose stools and flatulence.
2. Encourage fluid intake.
3. Check other causes of diarrhea. Fever and diarrhea and/or blood in the stools indicate that diarrhea may be secondary to bacterial enteritis or pseudomembranous colitis (C. difficile) related to FQ. If HIV-positive assess CD4 and think of other possible causes (CMV, isospora, microsporidium).
4. Check serum electrolytes (especially potassium) and dehydration status if diarrhea is severe.
5. Treat uncomplicated diarrhea (no blood in stool and no fever) with loperamide 4 mg by mouth initially followed by 2 mg after each loose stool to a maximum of 10 mg per day.

Rash, allergic reaction, and anaphylaxis
Possible DR-TB drugs: any drug

Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Erythema; moderate pruritus.	Extended maculopapular eruption (with or without pruritus).	Extensive papulovesicular eruption, palpable purpura cut., moist desquamation, or ulcerations.	Exfoliative dermatitis, mucous membrane involvement or erythema multiforme or suspected Stevens-Johnson or cutaneus necrosis requiring surgery.

Management

1. For serious allergic reactions (Grade 3–4), stop all therapy pending resolution of reaction. In the case of anaphylaxis, manage with standard emergency protocols (including adrenaline). If Stevens-Johnson syndrome, treat with IV corticosteroid, IV fluids, and IV broad spectrum antibiotic. Suspend permanently any drug identified to be the cause of a serious reaction. Any drug that resulted in anaphylaxis or Stevens-Johnson syndrome should never be reintroduced.

2. Eliminate other potential causes of allergic skin reactions (like scabies or other environmental agents).

3. For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They include
- Antihistamines.
- Hydrocortisone cream for localized rash.
- Prednisone in a low dose of 10 to 20 mg per day for several weeks can be tried.
- Dry skin may cause itching (especially in diabetics); liberal use of moisturizing lotion is recommended. Dry skin is a common and significant problem with clofazimine.

4. Once the minor rash resolves, reintroduce remaining drugs, one at a time with the one most likely to cause the reaction last. Consider not reintroducing even as a challenge any drug that is highly likely to be the cause. The order or reintroduction can be: H, Z, Eto/Pto, FQ, Cs, E, PAS, Km (or Am/Cm).

Arthralgia/arthritis
Possible DR-TB drugs: Z (less frequent FQ, Bdq)

	Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Arthralgia (joint pain)	Mild pain not interfering with function.	Moderate pain, analgesics, and/or pain interfering with function but not with activities of daily living (ADL).	Severe pain; pain and/or analgesics interfering with ADL.	Disabling pain.
Arthritis (inflammation involving a joint)	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function.	Moderate pain with inflammation, erythema, or joint swelling; interfering with function, but not with activities of daily life (ADL).	Severe pain with inflammation, erythema, or joint swelling and interfering with ADL.	Permanent and/or disabling joint destruction.

Management:

a) Give nonsteroidal anti-inflammatory drugs (NSAIDs): ibuprofen 600 mg 3 times a day.

b) Rest the joint.

c) Initiate therapy with NSAIDs:

Ibuprofen 400 to 800 mg three times a day or indomethacin 50 mg twice daily.

d) Lower the dose or discontinue the suspected agent (most commonly pyrazinamide) if this can be done without compromising the regimen.

e) Uric acid levels may be elevated in patients on pyrazinamide. There is little evidence to support the addition of allopurinol for arthralgia, although if gout is present it should be used.

If acute swelling, redness, and warmth are present in a joint, consider aspiration for diagnosis of gout, infections, autoimmune diseases, etc.

Psychosis **Possible DR-TB drugs:** Cs, H, FQ, Eto/Pto			
Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Mild psychotic symptoms.	Moderate psychotic symptoms (e.g. disorganized speech; impaired reality testing).	Severe psychotic symptoms (e.g. paranoid; extreme disorganization); hospitalization not indicated.	Acute psychosis (suicidal ideation, maniac status, hallucinations). Life-threatening consequences, threats of harm to self or others; hospitalization indicated.

Management

The most likely drug is cycloserine followed by high dose isoniazid.

1. Stop the suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control.
2. Always check creatinine in patients with new onset psychosis. A decrease in renal function can result in high blood levels of cycloserine, which can cause psychosis.
3. If moderate to severe symptoms persist, initiate antipsychotic therapy (haloperidol). Atypical antipsychotics should be used for DR-TB patients on multiple QT prolonging DR-TB drugs since haloperidol significantly prolongs the QTc interval and has been associated with torsades de pointes.

4. Hospitalize in a ward with psychiatric expertise if patient is at risk to himself/herself or others.
5. Increase pyridoxine to the maximum daily dose (200 mg per day).
6. Lower the dose of the suspected agent (most commonly cycloserine to 500 mg a day).
7. Discontinue the suspected agent if this can be done without compromising the regimen.
8. Once all symptoms resolve and patient is off cycloserine, antipsychotic therapy can be tapered off. If cycloserine is continued at a lower dose, antipsychotic therapy may need to be continued and any attempts of tapering off should be done after referring to a psychiatrist.

Some patients will need to continue antipsychotic treatment throughout DR-TB treatment (and discontinued gradually upon completion of treatment).

Previous history of psychiatric disease is not a contraindication to cycloserine, but its use may increase the likelihood of psychotic symptoms developing during treatment. Avoid if there is an alternative.

Psychotic symptoms are generally reversible upon completion of DR-TB treatment or cessation of the offending agent.

Depression **Possible DR-TB drugs: Cs, FQ, H, Eto/Pto** **Other causes:** Psychological and socioeconomic circumstances, chronic disease			
Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Mild depressive symptoms; and/or PHQ-9 depression score 1–9.	Moderate depressive symptoms; limiting instrumental activities of daily living (ADL); and/or PHQ-9 depression score 10–14.	Severe depressive symptoms; limiting self-care ADL; hospitalization not indicated; and/or PHQ-9 depression score 15–19.	Life-threatening consequences, threats of harm to self or others; PHQ-9 depression score 20–27; and/or hospitalization indicated.

Management:

- Anti-TB therapy may contribute to depression. Depressive symptoms may fluctuate during the therapy.
- Assess and address underlying emotional and socioeconomic issues.
- Provide psychological support (for the patient and family).
- If depression is significant, initiate antidepressant therapy (amitriptyline, fluoxetine).
- Avoid serotonin reuptake inhibitors and tricyclic antidepressant with linezolid (risk of serotonin syndrome).
- Lower the dose of the suspected agent if this can be done without compromising the regimen (reducing the dose of cycloserine and ethionamide to 500 mg daily).

Discontinue the suspected agent if this can be done without compromising the regimen.

Seizures
Possible DR-TB drugs: Cs, H, FQ, Imp/Cln

First address other causes of seizures: infection, epilepsy, meningitis, encephalitis, alcohol withdrawal, hypoglycemia, cerebrovascular accident, malignancy, or toxoplasma in PLHIV).
Then:

1. Hold cycloserine, fluoroquinolones, and isoniazid pending resolution of seizures.
2. Initiate anticonvulsant therapy (carbamazepine, phenytoin, or valproic acid are most commonly used).
3. Increase pyridoxine to the maximum daily dose (200 mg per day).
4. Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium, and chloride (replace accordingly).
5. Check creatinine level. A decrease in renal function can result in high blood levels of cycloserine, which can cause seizures. Adjusting the dose of cycloserine in the presence of low creatinine may be all that is needed to control the seizures
6. When seizures have resolved, restart medications one at a time. Cycloserine should not be restarted unless it is absolutely essential to the regimen. If cycloserine is reinitiated, start a dose one weight band lower.

Notes:
An anticonvulsant is generally continued until DR-TB treatment is completed or suspected agent is discontinued.
History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well controlled and/ or the patient is receiving anticonvulsant therapy. (Do not include cycloserine if an alternative drug is available.)
Carbamazepine is a strong inducer of CYP3A4 and should not be used with bedaquiline or delamanid.

Hypothyroidism
Possible DR-TB drugs: Eto/Pto/PAS

Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Sub-clinical hypothyroidism (TSH 6–10 mIu/mL, T4 free normal).	Simple hypothyroidism without complications. Treatment required (TSH > 10 mIu/mL).	Severe hypothyroidism with clinical symptoms. Urgent treatment.	Myxedematous coma.

Management

Start treatment when TSH > 10 mIu/mL.
Dose of levothyroxine:
Adults: 1.2–1.4 ucg/kg/day (50–200 ucg/dia).
Children: 4–5 ucg/kg/day (max 200 ucg/dia). Children need higher dose due to hormone metabolism.

1. Most adults will require 100–150 mcg of levothyroxine daily. Start levothyroxine in the following manner:
   - Young healthy adults can be started on 75–100 mcg daily.
   - Older patients should begin treatment with 50 mcg daily.
   - Patients with significant cardiovascular disease should start at 25 mcg daily.
2. Monitor TSH every month and increase the dose by 12.5–25 mcg until TSH normalizes. Adjust the dose more slowly in the elderly and in patients with cardiac conditions.

Note: It could be considered to start treatment with TSH > 6 mIu/mL to 10 mIu/mL with low dose of levothyroxine (25 to 50 mcg).
Thyroid dysfunction resolves upon discontinuation of the cause agent. Hormone replacement must continue at least 2 to 3 months after completed DR-TB treatment.

CHAPTER 10.
MANAGEMENT OF CLOSE CONTACTS OF DR-TB PATIENTS

10.1 Contact investigation

1. Close contacts of DR-TB patients are defined as people living in the same household or spending many hours a day with the patient in an indoor living space. All close contacts of known DR-TB patients should receive careful TB screening and clinical follow-up for a period of at least 2 years: every 3 months during the first year, and every 6 months during the second year.
2. Attention should be paid to those contacts who are below the age of 5 years; those who have HIV infection; and high-risk groups such as pregnant women, prisoners, health workers, cancer patients, and diabetic patients.
3. Contact management is crucial and should be guided by the clinical status of the contact and whether they are symptomatic or asymptomatic.
4. All asymptomatic close contacts of DR-TB patients need to undergo screening with a careful history and physical examination. If there is concern for active DR-TB, a chest X-ray should be taken and sputum sent for Xpert MTB/RIF. An HIV test should be offered, and in the case of a positive result, antiretroviral treatment and cotrimoxazole prophylaxis should be started. For children, a tuberculin skin test (TST) should be performed.
5. Contacts that are symptomatic should undergo further investigation including SL LPA, culture, and DST.
6. Bacteriological confirmation may not always be possible in young children and HIV-positive patients. Negative bacteriologic tests in a symptomatic child or HIV-positive patient does not exclude active DR-TB disease. If active DR-TB is strongly suspected or confirmed, an empiric regimen based on the resistance pattern of the index patient is warranted, particularly for small children and immune compromised adults. Each individual case should be discussed with the CEC prior to commencing treatment.

10.2 Definitions

Index patient: the initially identified patient of new or recurrent TB, in a person of any age, in a specific household or other comparable setting in which others may have been exposed. An index patient is the one around which a contact investigation is centred.

Household contact: a person who shared the same enclosed living space as the index patient for 1 or more nights or for frequent or extended daytime periods during the 3 months before the start of the current treatment episode.

Close contact: a person who is not in the household but who shared an enclosed space, such as a social gathering place, workplace, or facility, with the index patient for extended daytime periods during the 3 months before the start of the current treatment episode.

10.3 Prophylaxis in children and adults exposed to DR-TB

Prophylaxis in children or adults exposed to DR-TB who are asymptomatic is not recommended, since there is no consensus or recommendations on the optimal regimen for prophylaxis (randomized controlled trials using fluoroquinolone or delamanid based regimens are ongoing). A reasonable approach is to monitor the child or adult exposed closely for 2 years in order to identify and treat developing TB promptly.

CHAPTER 11.
ACTIVE TB DRUG SAFETY MONITORING AND MANAGEMENT (aDSM)

Active TB drug safety monitoring and management (aDSM) refers to the active and systematic clinical and laboratory assessment of patients while on DR-TB treatment. aDSM is an integral component of the programmatic management of drug-resistant TB (PMDT). Its rationale is based on recent developments in DR-TB treatment, particularly the approval for use of new medicines ahead of the completion of Phase III trials, increased use of repurposed drugs for XDR-TB treatment, and the development of novel second-line regimens. Such approaches need careful monitoring for drug-related harms, some of which may not have been described as yet.

11.1 aDSM objectives

The overall objectives of aDSM are 1) to reduce the risk of drug-related harm in patients on second-line treatment for drug-resistant TB; and 2) to generate standardized aDSM data, enable causality assessment for serious adverse events (SAE), determine the frequency of SAEs (rates), and detect signals. This will contribute to future policy updates on the use of such medicines.

11.2 Common definitions used in aDSM

Active tuberculosis drug safety monitoring and management: The term "active TB drug safety monitoring and management" (aDSM) defines active and systematic clinical and laboratory assessment of patients while on DR-TB treatment. aDSM applies to patients on treatment with: (i) new DR-TB drugs; (ii) novel DR-TB regimens, including the shorter regimen; or (iii) extensively drug-resistant TB (XDR-TB) regimens, in order to detect, manage, and report suspected or confirmed drug toxicities.

Pharmacovigilance: is one of the components of aDSM, and is defined by WHO as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem".

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

Adverse event (AE): is 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 an AE that leads to death or a life-threatening experience; hospitalization or prolongation of hospitalization; persistent or significant disability; or a congenital anomaly. SAEs that do not immediately result in one of these outcomes but that require an intervention to prevent it from happening are included. SAEs may require a drastic intervention, such as termination of the drug suspected of having caused the event. All SAEs require completion of the SAEs Reporting Form and should be reported to Zambia Medicines Regulatory Authority (ZAMRA) within 24 hours as part of the core package of aDSM.

	SERIOUS ADVERSE EVENTS (SAEs)
	Fatal
	Immediately life-threatening
	Leading to hospitalization or prolongation of hospitalization
	Leading to a persistent or significant disability
	Congenital anomaly
	Otherwise medically important, necessitating an intervention to prevent one of the above listed outcomes

Adverse event of special interest: is an AE documented to have occurred during clinical trials and for which the monitoring programme is specifically sensitized to report regardless of its seriousness, severity, or causal relationship to the TB treatment. Only provincial hospitals chosen to provide an intermediate or advanced package of active TB drug safety monitoring and management (aDSM) (e.g. a selected sentinel site) will include all AEs of special interest in their reporting. Some examples of adverse events of special interest as suggested by WHO are peripheral neuropathy (paresthesia); psychiatric disorders and central nervous system toxicity; optic nerve disorder; ototoxicity; myelosuppression; prolonged QTcF interval; lactic acidosis; hepatitis; hypothyroidism; hypokalemia; pancreatitis; phospolipidosis; and acute renal failure.

Adverse event leading to treatment discontinuation or change in drug dosage: is one 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.

Adverse event of clinical significance: is an AE which is either (i) serious, (ii) of special interest, (iii) leads to a discontinuation or change in the treatment, or (iv) judged as otherwise clinically significant by the clinician. Only provincial hospitals providing the advanced package of aDSM (e.g. a selected sentinel site) will include all AEs of clinical significance in their reporting.

Causality assessment: is the evaluation of the likelihood that a DR-TB drug was the causative agent of an observed adverse reaction. The formal causality assessment is performed by experts at the Pharmacovigilance Unit of ZAMRA, along with inputs from the Chief TB Officer/ Supply Chain and the National CEC.

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.

Signal: is reported information on a possible causal relationship between an adverse event and a DR-TB drug, the relationship being unknown or incompletely documented previously or representing a new aspect of a known association. The information may arise from one or multiple sources that are judged to be of sufficient likelihood to justify verification.

11.3 Levels of monitoring in aDSM

In addition to drug safety monitoring, aDSM also incorporates a component that promotes the clinical management of all ADRs and AEs regardless of their seriousness. In terms of monitoring, the minimum requirement for aDSM is that all AEs be registered and reported, regardless of their severity or whether they have been attributed to any of the medicines to which the patient is exposed. All detected adverse events (AEs) need to be managed clinically in a timely manner, and systematic clinical and laboratory assessments should be performed for early detection of drug toxicity and AEs. Chapter 8 and Chapter 9 outline the principles of monitoring and management of adverse events. Annexure 6 provides printable monitoring forms for documenting clinical and laboratory monitoring in the files/patient treatment card of patients on the shorter and individualized regimens.

aDSM packages according to the adverse event reported:

1. Core package: requiring monitoring for and reporting of all SAEs at each site initiating and managing patients on DR-TB treatment.
2. Intermediate package: includes SAEs as well as AEs of special interest.
3. Advanced package: includes all AEs of clinical significance.

The NTLP in Zambia will implement the core package of aDSM that requires the reporting of **only serious AEs** (SAEs). Treatment centres with additional resources may also monitor other AEs that are of clinical significance or of special interest to the programme, as part of comprehensive aDSM. These are referred as sentinel sites, which will be designated and supported by the NTLP.

11.4 Key steps to implementing aDSM

There are eight key steps recommended by WHO for the programmatic implementation of aDSM:

1.	Create a national coordinating mechanism for aDSM
2.	Develop a plan for aDSM
3.	Define management and supervision roles and responsibilities
4.	Create standard data collection materials
5.	Train staff for collection of data
6.	Define schedules and routes for data collection and reporting
7.	Consolidate aDSM data electronically
8.	Develop (or use existing) capacity for signal detection and causality assessment detection

Ideally, all eight steps should be in place before patients are enrolled on treatment with new drugs, new DR-TB regimens, or XDR-TB regimens. As this may not always be feasible, steps 1, 4, and 5 are essential ahead of any patient enrolment and implementation of the "core package" of aDSM. In Zambia, the roles and responsibilities for implementing aDSM focus on NTLP, the Zambia Medicine Regulatory Authority (ZAMRA), and key stakeholders involved in PMDT (Challenge TB [CTB]/FHI 360; Eradicate TB/PATH; Centre for Infectious Disease Research in Zambia [CIDRZ]; and the Zambia AIDS Related Tuberculosis [ZAMBART] Project).

11.4.1 Create a national coordinating mechanism for aDSM

The aDSM committee has the responsibility of oversight and coordination of aDSM activities at the national level. It is composed by members of NTLP, ZAMRA, and partners (CTB/FHI 360; Eradicate TB/PATH; CIDRZ; and ZAMBART). The aDSM committee members should be composed of programme managers, clinicians, pharmacists, and clinical experts on DR-TB care. They are also responsible for causality assessment of SAEs arising from DR-TB care.

11.4.2 Develop a plan for aDSM

An assessment of the country situation regarding aDSM was done, and the plan will be concluding with the participation of NTLP, ZAMRA, and relevant stakeholders.

11.4.3 Define management and supervision roles and responsibilities

The aDSM committee exercises national oversight and coordination of aDSM activities through regular coordination meetings among its members. The aDSM committee is led by aDSM focal persons from ZAMRA and NTLP. These two aDSM focal persons will work together to oversee all aDSM related activities including monitoring and supervision. DR-TB clinical experts (members of the CEC) and other designated members will provide clinical advice for management of adverse drug reactions (ADR) as well as advice for causality assessment.

11.4.4 Create standard data collection materials

A form to report SAEs has been created with a standard operating procedure (SOP) for instruction on how the form should be filled. The form can be sent by fax or email to ZAMRA.

11.4.5 Train staff for collection of data

The PMDT training includes one module on aDSM. This module includes clinical monitoring and management of ADR, data collection and reporting flow, aDSM principles, causality assessment, and signal detection. The methodology is based on adult education principles to facilitate skill development (practical exercises on how to fill in the form and patient scenarios).

11.4.6 Define schedules and routes for data collection and reporting: how often, where, and how to report adverse events (AEs)

All serious adverse events (SAEs) should be reported **within 24 hours**, regardless of their severity or whether they have been attributed to any of the DR-TB drugs to which the patient has been exposed. Reporting of SAEs **is mandatory** for all clinicians and treatment facilities managing DR-TB patients. The clinician should complete the SAE form (Annexure 7) and submit it directly to ZAMRA. The ZAMRA focal point will contact the reporter to verify receipt of the

report, provide the designated tracking number, and possibly request additional information. The ZAMRA focal point then forwards the SAE form to the NTLP focal point who sends the report within 48 hours to the Global Drug Facility (GDF) if the patient is on Bdq and/or Dlm. Any SAEs should also be reported to WHO Global aDSM database, which can be found at http://www.who.int/tdr/research/tb_hiv/adsm/en/. The causality assessment (CA) is done on monthly basis by the aDSM committee. The data of follow-up information and causality assessment is entered in the aDSM database. The feedback with final CA report is sent to the Provincial Health Office (PHO), District Health Office (DHO), and treating clinician at the Health facility (by aDSM focal point). The CA report is also send to GDF, WHO Global aDSM Database (by NTLP), and to WHO-UPSALA Monitoring Centre (by ZAMRA). A summary of the flow of information for SAE reporting is shown in Table 13 below.

Table 13: Steps and timelines for the reporting of SAE for patients on treatment with shorter regimen or individualized regimens containing new drugs

STEP	Event description	Action taken	Responsible party	Forms/Report sent to	Time frame
STEP 1	SAE event detected	SAE aDSM form filled out and submitted to ZAMRA	Treating physician (DR-TB facility)	ZAMRA aDSM Focal Point pharmacy@zamra.co.zm & npvu@zamra.co.zm Phone +260211220429 Fax: +260211238458	Within 24 hours or 1 working day of SAE detection
STEP 2	SAE report received at the national level at ZAMRA, shared with NTLP, and entered in National aDSM database	SAE form completed with all details, upon verification with the hospital/ DR-TB facility reporter; ZAMRA assigns tracking number and shares with NTLP	ZAMRA and NTLP aDSM Focal Point	ZAMRA will shared the SAE report with NTLP aDSM Focal Point The SAEs report will be entered in the national aDSM database and will be given a tracking serial number	Within 48 hours of SAE detection for initial reporting; then follow up
STEP 3	Bdq/Dlm SAE report sent to GDF All SAEs reported to WHO Global aDSM database	Send SAE form specific to patients treated with Bdq or Dlm to GDF; Send all SAEs to WHO Global aDSM database	NTLP Focal Point	Bdq/Dlm GDF form should be sent to: Global Drug Facility: DLMAE@stoptb.org Fax: +41225522801 All SAEs to be reported to WHO Global aDSM database: aDSM-database@who.int	Within 48 hours of SAE detection for initial reporting; then follow up

STEP 4	SAE Follow-up form (if applicable)	SAE aDSM form filled out and submitted	Treating physician (DR-TB facility)	ZAMRA aDSM Focal Point pharmacy@zamra.co.zm & npvu@zamra.co.zm Phone +260211220429 Fax: +260211238458 ZAMRA will send to NTLP aDSM focal point	Within **30 days** of SAE detection
STEP 5	Causality assessment by aDSM Committee	Meeting conducted and causality assessment done	aDSM Committee (CEC+ZAMRA and Partners) with assistance of technical advisors	NTLP/ZAMRA	Within **30 days** of SAE detection during monthly meeting
STEP 6	Feedback to treating facility, GDF, WHO Global aDSM database, and UMC	The causality assessment report will be sent back to the DR-TB facility/ PHO/DHO/ Provincial CEC; GDF; WHO aDSM database, and WHO-Uppsala Monitoring Centre	NTLP and ZAMRA aDSM Focal Point	PHO/DHO/treating facility Bdq/Dlm: Global Drug Facility: DLMAE@stoptb.org Fax: +41225522801 WHO Global aDSM database aDSM-database@who.int WHO-Uppsala Monitoring Centre (ZAMRA)	Within **30-40 days** of SAE

11.4.7 Consolidate aDSM data electronically

Each report will be given a tracking number by ZAMRA and included in the initial report during the verification call between the ZAMRA focal point and the reporter at the DR-TB facility and should be included in follow-up reports and the causality assessment. The SAEs are recorded in a database at NTLP.

The electronic data will be used to report the aDSM essential indicator: number of SAEs reported, relative to the total number of the DR-TB patients on treatment with the shorter or individualized regimen containing new drugs. The report will be generated by the aDSM focal persons (ZAMRA: numerator and NTLP: denominator).

11.4.8 Causality assessment and signal detection

Evaluating the causal association between an exposure to a TB medicine and the occurrence of an adverse reaction is an integral part of the clinical management. While the details of the systematic method of conducting CA may not be familiar to the practitioner, the overall approach is not too different from the clinical practice followed when evaluating any patient on treatment.

Steps for causality assessment
Take complete medical and drug history
Document adverse events including clinical description, lab results, date of onset/end
Determine evolution of events, severity/seriousness, outcome
Adopt the ANRS/recommended PV – TB scale for grading AEs and SAEs (Chapter 9)
Prevent or manage AE/SAE based on recommended actions (Chapter 9)
Establish association between concomitant medicines (herbal medicines and supplements), food, and comorbid conditions
Establish potential drug toxicities and overlapping adverse events in the treatment of HIV and DR-TB
Document data/findings on the SAE/ADR forms and in the aDSM database
Determine and detect signals and causal relationship

The reporter of the SAEs when filling out the form, should determine an initial presumptive causal relationship with each suspected drug using the categories defined as follows: 1) Certain; 2) Probable; 3) Possible; 4) Unlikely; and 5) Unassessable. Later, the formal causality assessment will be done on a monthly basis by the aDSM committee including experts from ZAMRA and NTLP as well as partners. Other technical advisors (national or international) may be consulted if needed. The formal causality assessment will utilize the WHO-Uppsala Monitoring Centre (UMC) classification system (Table 14).

Table 14: The WHO-UMC classification system for causality assessment

Causality term	Definition	Assessment criteria
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) • Rechallenge satisfactory, if necessary
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 • Rechallenge not required

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
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 ad- ministration 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
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
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

CHAPTER 12.
RECORDING AND REPORTING OF DR-TB

12.1 Patient registration

Any patient with DR-TB must be classified in terms of anatomical site, history of previous treatment, bacteriological status including drug resistance, and HIV status. Patient demographics (age, gender, etc.) must be recorded in the Presumptive TB Register. Once a diagnosis of DR-TB is bacteriologically confirmed, or if a decision to commence DR-TB treatment on a clinical diagnosis is made, this and other relevant information is then recorded in the following tools:

1. Drug-resistant TB Register
2. Drug-resistant TB Patient Booklet (DR-TB Treatment Card)
3. Patient ID Card
4. Electronic DR-TB database, if available

12.2 Definitions and classification

12.2.1 Classification based on bacteriological status and drug resistance

- Patients with TB can either be bacteriologically confirmed or clinically diagnosed. Bacteriological confirmation can either be through molecular methods, culture, or smear microscopy.
- Clinically diagnosed patients subsequently found to be bacteriologically positive should be reclassified as bacteriologically confirmed.
- Bacteriologically confirmed patients are further classified based on resistance to the main DR-TB drugs, based on laboratory diagnosis by genotypic and/or phenotypic drug-susceptibility tests (DST) as follows:

Drug resistance (DR) refers to mycobacterium tuberculosis that is resistant to one or more anti-tuberculosis drugs. That includes the following categories (not mutually exclusive):

- Mono-resistance: resistance to one first-line anti-tuberculosis drug only.
- Poly-resistance (PDR): resistance to more than one anti-tuberculosis drug, other than both isoniazid and rifampicin.
- Multidrug resistance (MDR-TB): resistance to at least both isoniazid and rifampicin.
- Pre-extensively-drug resistance (pre-XDR-TB): resistant to isoniazid and rifampin and either a fluoroquinolone or second-line injectable agent but not both.
- Extensive drug resistance (XDR-TB): resistance to any fluoroquinolone and at least one of three second-line injectable drugs (kanamycin, amikacin, and capreomycin) in addition to multidrug resistance.
- Rifampicin resistance (RR): resistance to rifampicin detected using phenotypic or genotypic methods, with or without other anti-TB drugs. It includes any resistance to rifampicin, whether mono-resistance, multidrug resistance, poly-drug resistance, or extensive drug resistance.

12.2.2 Classification based on previous anti-tuberculosis treatment

12.2.2.1 New TB patients

Drug resistance in a patient who has never been treated for any form of tuberculosis or received less than 1 month of anti-TB therapy (first-line and/or second-line drugs).

12.2.2.2 Previously treated TB patients

Drug resistance in a patient who has received at least 1 month of anti-TB therapy.
According to the type of anti-TB treatment previously received, which can be either:

- Previously treated with first-line drugs.
- Previously treated with second-line drugs.

Previously treated patients may be categorised as follows:

- Relapse: Patients who have previously been treated for TB (first- or second-line drugs), and whose most recent treatment outcome was cured or treatment completed, and who is subsequently diagnosed with a recurrent episode of TB.
- Treatment after failure: Patients who have previously been treated for TB (first or second-line drugs) and whose most recent outcome was treatment failure.
- Treatment after loss to follow-up: Patients who have previously been treated for TB (first- or second-line drugs) and whose most recent treatment outcome was loss to follow-up.
- Other previously treated patients: Patients who have previously been treated for TB (first- or second-line drugs) and whose most recent treatment outcome is unknown or undocumented.

12.2.2.3 Transfer in patients

A patient who has transferred from another register for treatment of drug-resistant TB to continue treatment. Their outcomes should be reported to the transferring unit so that they can report their outcomes in the cohort in which they originally started treatment. This group is excluded from the quarterly reports of the receiving unit on registration and treatment outcome.

12.2.3 Classification based on anatomical site

- Pulmonary tuberculosis (PTB): TB involving the lung parenchyma or the tracheobronchial tree.
- Extra-pulmonary tuberculosis (EPTB**):** TB involving organs other than the lungs, e.g. lymph nodes, pleura, bones and joints, abdomen, pericardium, meninges, skin, or genitourinary tract. EPTB cases can be either bacteriologically confirmed or clinically diagnosed.

Notes:

- A patient with both PTB and EPTB should be classified as a case of **PTB**.
- Miliary TB is classified as **PTB** because there are also lesions in the lungs.
- Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of **EPTB**.

12.2.4 Classification based on HIV status

HIV status must also be recorded at registration as positive/negative/unknown (if unknown, point of care counseling and testing is required). In addition, for those who are positive, the antiretroviral treatment status should be recorded, bearing in mind that all HIV-positive TB patients are expected to be on antiretroviral therapy. The ART regimen, start date, cotrimoxazole preventive therapy, CD4, and viral load must also be recorded.

12.2.5 Bacteriological classification and sputum conversion

- **Bacteriological monitoring:**

Time	Sputum smear	Culture	SL LPA and phenotypic DST
Beginning of treatment	√	√	√
Monthly until cure or treatment completion	√	√	If smear or culture positive after 4 months of treatment or any suspicion of treatment failure

- **Initial bacteriological classification**

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

  - At least one pre-treatment specimen was positive on smear microscopy, Xpert MTB/RIF, or culture.
  - The collection date of the sample on which the laboratory examination was performed was less than 30 days before or 7 days a er the initiation of second-line treatment.

- **Sputum conversion (culture):** Both smear and culture should be used to monitor patients throughout therapy. When assessing bacteriologic progress, the date the sputum was collected is used (and not the date the results were obtained).
- **Conversion (to negative):** Culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.
- **Reversion (to positive):** Culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining treatment failure, reversion is considered only when it occurs in the continuation phase.

12.3 Treatment outcome definitions

Cured: Treatment completed as recommended by national guidelines without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.

Treatment completed: A patient who has completed treatment according to national guidelines without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.

Treatment success: The sum of cured and treatment completed.

Treatment failure: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of:

- Lack of conversion by the end of the intensive phase, or
- Bacteriological reversion in the continuation phase after conversion to negative, or
- Evidence of additional acquired resistance to Fluoroquinolones or second-line injectable drugs, or
- Adverse drug reactions (ADRs).

Died: A patient who died for any reason during the course of the 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).

Patients who have transferred in should have their outcome reported back to the treatment unit at which they were originally registered.

12.4 Cohort analysis

Treatment cohort analysis focuses on treatment outcomes among patients who actually started on treatment during a defined time period.

The diagnostic cohort includes patients diagnosed with DR-TB (identified in the culture register by date of DST result/or Xpert MTB/RIF database) during a specific period of time. It is used to assess the number of patients with DR-TB in subgroups and over time. It allows the programme to evaluate delays in starting treatment and proportion of patients who started treatment. The recommended time frame for treatment cohort analysis reflects the long duration of regimens. Cohort analyses should be carried out at 24 months and repeated at 36 months after the last patient starts treatment.

The analysis is done at 24 months because most of the patients will have finished treatment, allowing preliminary assessment of cure rates. Since a few patients may be on treatment longer than 24 months, the cohort analysis is repeated at 36 months, after the last patient starts treatment. The 36-month evaluation is considered the final treatment cohort analysis result.

All patients' initial treatment outcome will be recorded and reported. Record subsequent treatment outcomes among patients followed systematically. (For example, a patient lost to follow-up on the first treatment and then returns 14 months later to be re-registered and is cured with a second treatment. This patient should receive a final outcome of "loss to follow-up" in the cohort in which he or she was first registered and "cured" in the second cohort.)

Patients who remain on treatment at the end of a designated cohort treatment period must be identified as "still on treatment".

Interim cohort analysis:
For each cohort, an interim status should be assessed at 6 months after the start of treatment to monitor programme progress. Interim outcomes are monitored to assess conversion whether still on treatment, and adverse outcomes (death, failure, and loss to follow-up). The conversion rate at 6 months may be used as a proxy for successful progression of treatment.

CHAPTER 13.
DR-TB INFECTION CONTROL

13.1 Introduction

Infection control and prevention in TB care is a combination of measures aimed at minimizing the risk of TB transmission within health facilities, communities, households, and other congregate settings. The core of TB infection control is early diagnosis and proper management of TB patients. Detailed information and guidance on TB infection control is provided in separate national TB infection control guidelines.

13.2 High-risk areas

Areas which expose people to tuberculous bacilli are high-risk environments for TB transmission. For DR-TB, high-risk areas include the outpatient department (OPD), emergency rooms/casualty, medical wards, drug-susceptible TB wards, drug-resistant TB wards, X-ray rooms, operating rooms, dentist rooms, and households with DR-TB patients.

13.3 High-risk procedures

Some procedures form aerosols and are high risk for the transmission of TB. These include intubation, bronchoscopy, culture and DST procedures, microscopy, molecular testing, sputum collection (sputum collection in both health facilities and communities), and sputum induction.

13.4 Infection control measures

TB infection control (TB IC) is implemented through a combination of recommended measures for particular settings. The measures are managerial, administrative, environmental, and personal protective equipment.

13.4.1 Managerial measures

Every TB facility should:

- Set up or strengthen a committee to coordinate TB IC and develop a comprehensive budgeted plan.
- Rethink the use of available spaces and consider renovation of existing facilities or construction of new ones to optimize implementation of controls.
- Conduct on-site surveillance of TB disease among health care workers.
- Conduct regular TB IC assessments the facility.
- Address advocacy, communication, and social mobilization (ACSM) for health workers, patients and visitors.
- Monitor and evaluate the set of TB IC measures.
- Participate in research efforts.

13.4.2 Administrative control measures

When implementing administrative controls, health care workers should aim to reduce diagnostic delays, use rapid diagnostic tests, reduce turnaround time for sputum testing and culture, and promptly initiate patients on treatment. Additionally, health care workers must:

- Promptly identify people with TB symptoms (triage).
- Separate infectious patients.
- Control the spread of pathogens (cough etiquette and respiratory hygiene) including provision of surgical masks for coughing patients.
- Minimize time spent in health care facilities.
- Provide a package of prevention and care interventions for staff, including HIV prevention and ART and isoniazid preventive therapy (IPT) for HIV-positive staff.

13.4.3 Environmental controls

Health care workers should aim to reduce the concentration of infectious particles in the air in the following ways:

1. Ventilation

Natural: It is the use of external airflows generated by natural forces including wind and differences in temperature (stack). Health care workers must ensure:

- All windows are kept open on all opposite walls to allow for cross ventilation.
- All openings are kept unrestricted by keeping ward furniture away from openings.
- High-level windows are provided for stack ventilation.

Mechanical: Is created by using inlet and outlet fans to force air exchange and to drive air flow. It works by generating negative pressure in the room to drive airflow inward. Health care workers must ensure:

- All doors and windows be kept closed.
- A minimum of 12 air changes per hour be maintained.
- The ventilation system is maintained regularly.

Mixed model: Combines the use of mechanical and natural ventilation. Is done through the installation of fans to increase the rate of air changes in the room. Health care workers must ensure:

- Ventilation design briefs are followed (opening designated doors and windows).
- Fans are maintained regularly.

2. Upper room or shielded ultraviolet germicidal irradiation (UVGI) fixtures

The UV lamps are mounted high on the wall or suspended from the ceiling. Radiation is directed into the upper portion of the room where air is disinfected. The ventilation system mixes this disinfected air with the air in the lower part of the room resulting in dilution of potentially contaminated air. This intervention cannot be used in isolation as it is usually used in conjunction with mechanical or mixed mode ventilation systems.
Health care workers should ensure:

- Fixtures are cleaned and maintained regularly as per manufacturer's recommendations (and records kept safely).
- A radiation meter be used daily to confirm that a minimum reading of 10,000 µj/cm^2.

3. Personal protective equipment (PPE)

Personal protective equipment for TB includes use of respirators to protect the health care worker from inhaling droplet nuclei and filter out infectious aerosols. Health care workers using respirators should ensure:

- Respirators fit closely to the face to prevent leakage around the edge by being fit tested yearly and when needed.
- Respirators are worn every time they are entering high-risk areas and conducting high-risk procedures.
- Proper donning and doffing procedure are followed.
- Respirators are be stored in a clean and dry place.
- Respirators should not be decontaminated or cleaned and should be inspected before each use.

13.5 Specific considerations

a) **In-patients**

Health care workers working in DR-TB wards should ensure the following:

a) Cough etiquette and respiratory hygiene (including use of surgical masks) is practiced.

b) Family members living with or who have a high likelihood of HIV infection should not provide care for patients with culture positive DR-TB; for example, the spouse of the patient with HIV and DR-TB. If there is no alternative, HIV-positive family members should wear N95 respirator or equivalent.

b) **Ambulatory care**

Patients in ambulatory care should observe the following at the household level and any congregate setting:

- Houses should be adequately ventilated, particularly the rooms where the patient will spend considerable time.
- Anyone who coughs should be educated on cough etiquette and respiratory hygiene, and should follow such practices at all times.
- Spend as much time as possible outdoors.
- Sleep alone in a separate, adequately ventilated room if possible.
- Spend as little time as possible in congregate settings or in public transport.
- If possible, potential renovation of the patient's home should be considered, to improve ventilation (e.g. building of a separate bedroom or installation of a window or wind catcher, or both).
- Children below 5 years of age should be prioritized, and spend as little time as possible in the same living spaces as culture positive DR-TB patients.
- All the DR-TB contact should be followed up with regularly for early detection of TB disease (every 3 months during the first year, and every 6 months during the second year).

CHAPTER 14:
ADHERENCE SUPPORT FOR DR-TB PATIENTS

- All patients on DR-TB treatment should have a psychosocial and economic assessment to identify those who need to be provided with psychological and social support such as transport and food to prevent treatment interruption and to reduce treatment associated costs.
- Patients with DR-TB should be treated using decentralized, ambulatory care rather than models of care based on hospitalization [5].
- A treatment supporter should be identified by the patient in consultation with the health facility.
- Every effort should be made to make sure that the patient receives treatment from home and longer duration supplies after the intensive phase; this should be adapted to the local context.
- All DR-TB patients should receive adequate counseling on adherence to treatment, including patients receiving the shorter DR-TB regimen or a new drug. Any educational materials provided to patients to explain DR-TB treatment should be in local languages.
- Patients returning to care after interrupting treatment with the shorter regimen for more than 2 months should be switched to an individualized regimen.
- Patients should be encouraged to notify their clinician of any upcoming travel to plan an adequate supply of DR-TB medications while they are away; clinic staff should be flexible to accommodate necessary travel while on DR-TB treatment.

REFERENCES

1. World Health Organization (WHO). Global Tuberculosis Report 2016. Geneva: WHO; 2016.
2. World Health Organization (WHO). Automated Real-time Nucleic Acid Amplification Technology for Rapid and Simultaneous Detection of Tuberculosis and Rifampicin Resistance: Xpert MTB/RIF System 2011. Geneva: WHO; 2011.
3. World Health Organization (WHO). The Use of Bedaquiline in the Treatment of MDR TB: Interim Policy Guidance 2013. Geneva: WHO; 2013.
4. World Health Organization (WHO). The Use of Delamanid in the Treatment of Multidrug-Resistant Tuberculosis: Interim Policy Guidance 2014. Geneva: WHO; 2014.
5. World Health Organization (WHO). Treatment Guidelines for Drug-Resistant Tuberculosis: 2016 Update. Geneva: WHO; 2016.
6. World Health Organization (WHO) Regional Office for Europe. Algorithm for Laboratory Diagnosis and Treatment Monitoring of Pulmonary Tuberculosis and Drug-Resistant Tuberculosis Using State-of-the-Art Rapid Molecular Diagnostic Technologies 2017. UN City, Copenhagen: WHO; 2017.
7. World Health Organization (WHO). Guidelines for Treatment of Drug-Susceptible Tuberculosis and Patient Care 2017 Update. Geneva: WHO; 2017.
8. Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med. 2010 Sep 9; 363(11):1005–1015.
9. DR-TB STAT. Treatment of Drug-Resistant TB with New and Re-Purposed Medications: A Field Guide. Cleveland, USA: DR-TB STAT; July 2017.
10. World Health Organization (WHO). Best Practice Statement on the Off-Label Use of Bedaquiline and Delamanid for the Treatment of Multidrug-Resistant Tuberculosis 2017. Geneva: WHO; 2017.
11. World Health Organization (WHO). Report of the Guideline Development Group Meeting on the Use of Bedaquiline in the Treatment of Multidrug-Resistant Tuberculosis. A Review of Available Evidence (2016). Geneva: WHO; 2017.
12. World Health Organization (WHO) Regional Office for Europe. Algorithm for Laboratory Diagnosis and Treatment Monitoring of Pulmonary Tuberculosis and Drug-Resistant Tuberculosis Using State-of-the-Art Rapid Molecular Diagnostic Technologies 2017. UN City, Copenhagen: WHO; 2017.
13. National Agency for Research in AIDS and Hepatitis/France/ Division of Microbiology and Infectious Diseases (DMID) grading system/ NCI's Common Terminology Criteria for Adverse Events (CTCAE) scale. ntblcp.org.ng/file/152/download?token=tajVYbWn
14. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Bethesda, USA: US Department of Health and Human Services, National Institutes of Health, NCI; 2017.
15. Kidney Disease Improving Global Outcomes (KDIGO). Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. KDIGO; 2012.
16. World Health Organization (WHO). Active Tuberculosis Drug Safety Monitoring and Management (aDSM). Framework for Implemention. Geneva: WHO; 2015.

ANNEXURES

Annexure 1: Terms of reference for a clinical expert committee (CEC)

Clinical Expert Committee
Zambia National Tuberculosis and Leprosy Programme
Terms of Reference

The 2017 national PMDT guidelines introduce the shorter DR-TB treatment regimen and individualized regimens using new and repurposed drugs (bedaquiline, delamanid, linezolid, and clofazimine). The use of the shorter regimen and new drugs will be implemented in phases, starting at four sites then expanding to every provincial DR-TB treatment facility. The national tuberculosis programme has the responsibility to form committees to oversee the clinical management of DR-TB patients; these committees, called clinical expert committees (CECs), will be strengthened or created at national and provincial level. The overall goal of each committee is to support clinicians to provide optimal management of DR-TB patients in Zambia. The specific responsibilities of the National CEC and provincial CECs are as follows:

National Clinical Expert Committee

- Meet in person on a quarterly basis; respond to clinical cases via email between meetings.
- Composition includes DR-TB physicians from across the country, at least one pediatrician, at least one obstetrician, and a pharmacist/clinical pharmacologist.
- Seek advice of other outside consultants (surgeon, cardiologist, pulmonologist, nephrologist, laboratory expert, others) as needed on an individual case basis.
- Members will serve for a minimum of 1 year, with annual review of National CEC members for any necessary changes.
- Provide feedback on complex DR-TB patient management: clinical feedback on complex patients referred from the provincial CECs should be provided via the Chair of the National CEC to the Chair of the requesting provincial CEC.
- Approve the use of bedaquiline (Bdq) or delamanid (Dlm) for longer than 6 months (Bdq or Dlm treatment extension) in patients where the regimen is insufficient (less than at least three effective drugs) without Bdq or Dlm, and the drug is well tolerated.
- Approve the use of Bdq and Dlm in combination for patients with severe resistance patterns and no other options to construct an effective treatment regimen.
- Approve the use of Bdq or Dlm in pregnant patients diagnosed with DR-TB where the regimen will be insufficient without Bdq or Dlm.
- Provide input and approval for DR-TB treatment regimen design for all children less than 18 years of age to provincial CECs, whether a shorter regimen or an individualized regimen with new drugs is used.
- Consult international experts on pediatric DR-TB management involving delamanid in children less than 6 years of age or bedaquiline in children less than 18 years of age (European Respiratory Society–hosted TB Consilium [www.tbconsilium.org] or the Sentinel Project on Pediatric Drug-Resistant Tuberculosis [tbsentinelproject@gmail.com or sentinel_project@hms.harvard.edu]).

- Provide advice on medico-legal and ethical issues from provincial CECs or requesting DR-TB clinicians, including termination of DR-TB treatment, palliative care, and patients refusing treatment.
- Provide feedback to provincial CECs in the case of discordant DR-TB genotypic and phenotypic laboratory results.
- All responses to National CECs queries should be provided to the requestor within 5 working days.
- The Chair of the National CEC will ensure a quorum of responses from CEC members is obtained, as well as summarize and achieve consensus in the case of differing opinions on optimal management.
- Ensure members of the National and provincial CECs attend PMDT trainings as needed.
- Chair or appointed CEC member should attend DR-TB subgroup meetings and report on the successes and challenges of the National and provincial CECs.
- National CEC member provides input to ZAMRA/NTLP evaluation of aDSM reports (causality assessments, data analysis, and reporting).
- National CEC team member visits provincial sites quarterly in Phase 2 of new PMDT guideline implementation (each member given provincial assignments by National CEC Chair) and conducts clinical care review exercises with the DR-TB team.
- Work in consultation with the NTLP to develop and update DR-TB guidelines.
- Support and provide input on the data and recording/reporting requirements for the DR-TB treatment programme.

Provincial Clinical Expert Committee (one per province)

- Evaluate each patient diagnosed with RR-TB on Xpert MTB/RIF in the committee's locality (including mining industry and correctional services) for shorter regimen versus individualized regimen eligibility and provide feedback on regimen choice to treating clinician within 3 days of receiving patient case details.
- Confirm the clinical diagnosis of DR-TB in patients where bacteriological confirmation is difficult, such as children, HIV-positive patients, or those with extra-pulmonary TB, and who are also close contacts of known DR-TB patients.
- Confirm any potential regimen adjustments and the final treatment regimen for patients who were initially started on an individualized regimen (RR-TB on Xpert MTB/RIF patients who did not meet eligibility for the shorter regimen) but LPA and/or culture/DST results do not show any resistance to fluoroquinolones or second-line injectable agents.
- Patients being considered for empiric DR-TB treatment based on clinical history, risk factors, and positive smear microscopy (in situations where Xpert MTB/RIF, LPA, and/or culture/DST results cannot be obtained or are significantly delayed) should be discussed with the CEC to ensure proper regimen selection.
- Evaluate patient progress; ensure adequate patient follow-up and management of adverse events; provide multidisciplinary support for patients refusing DR-TB treatment or chronically defaulting from DR-TB treatment; and advise on the management of treatment failures through quarterly patient review meetings.

- Meet in person at least on a quarterly basis; assess clinical cases via email or phone call between meetings.
- Composition includes provincial and district DR-TB physicians (member may also belong to National CEC), pharmacist, senior DR-TB nursing staff, social worker, and occupational therapist.
- Seek advice of National CEC as needed on an individual case basis (complex patients, individualized regimens containing new drugs, medico-legal/ethical issues, patients with discordant DR-TB genotypic and phenotypic lab results, and DR-TB treatment regimen design in all children less than 18 years of age); provincial CEC Chair provides feedback from National CEC to treating clinician.
- Seek advice of outside consultants (surgeon, cardiologist, pulmonologist, nephrologist, laboratory expert, others) as needed on an individual case basis.
- Members will serve for a minimum of 1 year, with annual review of provincial CEC members for any necessary changes.
- Provincial CEC Chair ensures CEC members attend PMDT trainings as needed.
- Member of provincial CEC attends each provincial PMDT committee meeting and provides input on successes and challenges of DR-TB clinical patient management to provincial management/committee members.
- Support and provide input on the data and recording/reporting requirements for the DR-TB treatment programme.

Figure 6: Roles and responsibilities of the clinical care team implementing PMDT at facility level

DR-TB Specialist	Identify presumed DR-TB patients Diagnose DR-TB patients Put patients on treatment, monitor treatment, and manage adverse events Promote DR-TB infection prevention at the health facility Supervise and train the DR-TB team at the health facility Give on-the-job support to colleagues for complicated patients DR-TB recording and data analysis
Nurse	Identify presumed DR-TB patients Management of DR TB patients DOT Patient and family education and counseling Psychosocial support Defaulter prevention and tracing Supervise and train treatment supporters DR-TB recording and data analysis
Laboratory expert	DR-TB diagnose by smear microscopy, rapid molecular test (Xpert, Hain) (LPA) culture, and phenotypic DST IQA, EQA, and quality and laboratory improvements DR-TB monitoring of AEs: full blood count and biochemistry DR-TB laboratory recording and reporting Laboratory commodity and supplies management Training and supervision on PMDT laboratory issues

Pharmacist	Order FLDs, SLDs, and ancillary drugs Quality storage of DR-TB drugs Inform DR-TB team about DR-TB drugs (regimens and adverse event) Counseling of patients Training and supervision in DR-TB logistic and medicines
Social worker	Identify presumed DR-TB patient Management of MDR-TB patients Patient and family education and counseling Psychosocial support Socioeconomic support Defaulter prevention and tracing Supervise and train treatment supporters
Nutritionist	Advise on nutritional requirement of DR-TB patients
Infection control officer	Ensure TB IC measures are adhered to Design TB IC strategies for the facility Advise on nutritional requirement of DR-TB

Annexure 2: Descriptions of new and repurposed drugs for DR-TB treatment

Table 15: New and repurposed drugs for DR-TB treatment

Drug	Dosage	Adverse drug reactions and monitoring	Contraindications	Remarks/ precautions	Drug Interactions
Bedaquiline (Bdq)	100 mg tablets **Week 1 and 2:** 400 mg daily (4 tablets of 100 mg 7 days per week) **Week 2 onwards:** 200 mg three times per week (2 tablets of 100 mg three times/ week) Better absorption with food (light meal)	**More common:** Gastrointestinal (nausea, vomiting, abdominal pain) Arthralgia Headache **Less common:** QTcF prolongation Hepatotoxicity **Monitoring:** ECG at baseline, week 2, then monthly (if abnormality, check ECG more frequently and monitor TSH and electrolytes) LFT monthly	Baseline ECG QTcF > 500 ms (repeated) History of syncopal episode, ventricular arrhythmia or severe coronary artery disease Severe hepatic failure Children < 18 years of age (consult CEC)	Use with caution if QTcF is > 450 ms in males or > 470 ms in females: perform weekly ECG and electrolytes Caution when used with other QTcF prolonging drugs (Mfx, Dlm, Cfz) Caution in hypothyroidism or low electrolytes Caution in patients with hepatic impairment Bdq has been used in adolescents (data on PK and dosage in children <12 years is not available) Pregnancy (consult CEC)	Interaction with ART: EFV not recommended with Bdq (reduces Bdq levels) LPV/r: give with caution (increases Bdq level): close ECG monitoring No interactions with NVP, NRTIs, and integrase inhibitors
Delamanid (Dlm)	50 mg tablets **Adults:** ⩾ 34 Kg: 100 mg twice daily (2 tablets /12 hours) **Children** (> 20 kg): 20–34 kg: 50 mg twice daily (1 tab/12 hours) Take with food	**More common:** Gastrointestinal (nausea, vomiting, abdominal pain) Dizziness **Less common:** QTcF prolongation **Monitoring:** ECG at baseline, week 2, then monthly (if abnormality, check ECG more frequently and monitor TSH and electrolytes) Serum albumin at baseline; if low (< 3.4 g/dL) monitor albumin and ECG more frequently	Baseline ECG QTcF > 500 ms (repeated) History of syncopal episode, ventricular arrhythmia or severe coronary artery disease Serum albumin < 2.8 g/dL Children < 6 years (and < 20 kg): consult CEC	Use with caution if QTcF is > 450 ms in males or > 470 ms in females: perform weekly ECG and electrolytes Caution when used with other QTcF prolonging drugs (Mfx, Bdq, Cfz) Caution in hypothyroidism or low electrolytes Caution in patients with hepatic impairment Pregnancy: consult CEC	Safe to administer with ART: no drug-drug interactions

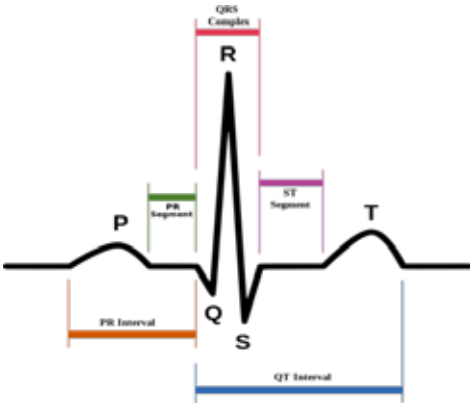
Drug	Dosage	Adverse drug reactions and monitoring	Contraindications	Remarks/ precautions	Drug Interactions
Linezolid (Lzd)	600 mg tablets Oral powder for suspension: 100 mg/5 mL, 240 mL bottle **Adults:** 600 mg once daily (add pyridoxine 50 mg) **Children:** 10 mg/kg dose If < 10 yr: twice daily If >10 yr: once daily (max 600 mg)	Myelosuppression (decreased level of platelets, white blood cells, and/or anemia) Peripheral neuropathy Optic neuritis Abdominal pain Pancreatitis Lactic acidosis **Monitoring:** Symptoms of peripheral neuropathy: monthly Vision test monthly (or when symptoms) FBC: weekly the first month, then monthly Amylase and lipase at baseline and when required	Intolerance to Lzd Symptoms of peripheral neuropathy Not recommended in pregnancy due to limited data (consult CEC)	Myelosuppression: reduction of the dose to 300 mg can be considered Peripheral neuropathy and optic neuritis are irreversible: Lzd should be stopped and not re-challenged. Lactic acidosis: patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level should receive immediate medical evaluation, including a lactic acid blood test. If Lzd is the causative agent, it should be stopped and not re-challenged	Avoid use with patients taking serotonergic agents, such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (e.g. fluoxetine, paroxetine), lithium, tricyclic antidepressants; it may cause serious serotonin syndrome Avoid concomitant use with AZT, d4T and ddI
Clofazimine (Cfz)	50, 100, or 200 mg capsules **Adults:** 100 mg once daily **Children:** 2–3 mg/kg once daily (due to formulation, can be given every second day) Take with food	**More common:** skin hyperpigmentation Dry skin, pruritus, rash Photosensitivity **Less common:** QTcF prolongation Severe abdominal symptoms Retinopathy **Monitoring:** symptomatic monitoring	Allergy to Cfz Not recommended in pregnancy due to limited data (consult CEC)	Caution when using with other QTcF prolonging drugs Avoid in breastfeeding due to hyperpigmentation of the infant	Using with drugs that prolong the QT interval may cause additive QT prolongation (e.g. bedaquiline, delamanid, fluoroquinolones, azole anti-fungal drugs, and others)

Drug	Dosage	Adverse drug reactions and monitoring	Contraindications	Remarks/ precautions	Drug Interactions
Imipenem/ Cilastatin (Imp/Cln)	Vials of 250 mg, 0 mg, 750 mg and 1,000 mg (contain equal quantities of each drug) 1,000 mg IV twice daily Must be given with Clv, available as Amx/ Clv 625 mg 1 tab 30 min before the infusion	**More common:** Diarrhea, nausea, or vomiting **Less common:** Seizure (noted with CNS infection), palpitations, pseudomembranous colitis **Monitoring:** Symptomatic monitoring	Carbapenem intolerance; meningitis (use meropenem rather than imipenem) Patients with CNS disorders	Little information is known regarding use in pregnancy; unknown safety during breastfeeding	Safe to administer with ART: no drug-drug interactions
Meropenem (Mpm)	**Adults:** 1,000 mg IV every 8 hours Must be given with Clv, available as Amx/Clv 625 mg 1 tab 30 min before the infusion **Children:** 20– 40 mg/kg/dose Given IV every 8 hours up to 2 g per dose	**More common:** Diarrhea, nausea, or vomiting **Less common:** Seizure (noted with CNS infection), but rare compared to imipenem Rarely elevated LFTs, hematologic toxicity, hypersensitivity **Monitoring:** Symptomatic monitoring	Carbapenem intolerance	Little information regarding use during pregnancy; unknown safety during breastfeeding	Safe to administer with ART: no drug-drug interactions

Annexure 3: QT interval and ECG monitoring

Bedaquiline, delamanid, moxifloxacin, and clofazimine can all cause prolongation of the QT interval. A lengthened QT interval is a marker for the potential of ventricular arrhythmias like torsades de pointes and a risk factor for sudden death. An electrocardiogram (ECG) should be performed at baseline, at 2 weeks, and then monthly with a standard 12-lead ECG machine.

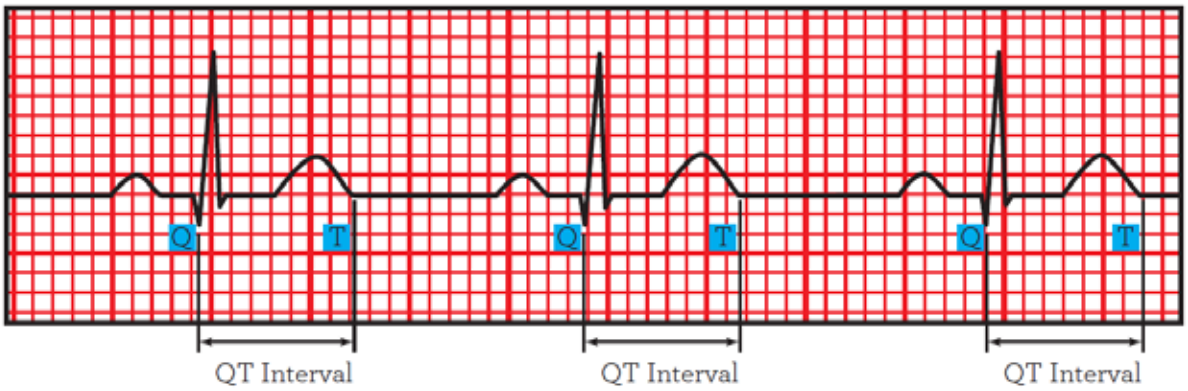
The QT interval is influenced by heart rate: it shortens at faster heart rates, and it lengthens at slower heart rates. It needs to be corrected by a formula (QTc) which estimates the QT interval at a heart rate of 60 bpm, which allows comparison of QT values over time at different heart rates. Calculation of the corrected QT interval is best done using the Fridericia formula, as it optimally adjusts for heart rate. The QTcF correction method may be automated and reported by some ECG machines or it can be manually read; where possible, even with automated reading, supplementation with manual reading is recommended.

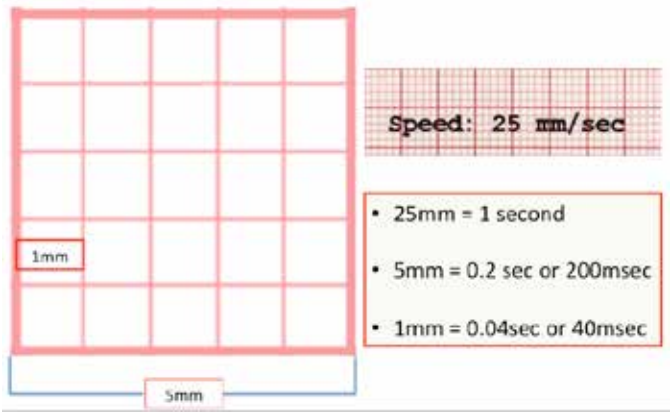


- QT interval = the time between the start of the QRS complex and the end of the T wave
- QTc = the corrected QT interval
- **QTcF = Q T/ $^{3}\sqrt{}$ RR**
- Auto-reporting from the machine may not be programmed with Fridericia formula
- Several online QTc calculators and apps are available: http://www.qxmd.com/apps/calculate-by-qxmd

  https://www.thecalculator.co/health/QTc-Calculator-385.html

A manual reading can be performed as follows:





1) From the 12-lead ECG printout, choose **Lead II, V5, or V6** as they usually best show the end of the T wave.

2) Measure the QT interval from the beginning of the QRS complex to the end of the T wave. This is the uncorrected QT. Measure at 3 to 5 successive beats and take the maximum interval.

- Make an imaginary line on Q and on T on one heartbeat on the selected lead
- Count the number of small squares between Q and T: for example, 8 small squares in the example above
- Multiply the number of squares by the unit time per square (0.04 sec): 8 small squares X 0.04 sec = 0.32 seconds
- Multiply the result by 1,000 to change seconds to milliseconds: QT = 320 ms

3) Measure the RR interval

- Make an imaginary line on two consecutive R waves
- Count the number of small squares between the two Rs: 20 small squares in the above example
- Multiply the number of small squares by the unit time per square (0.04): 20 small squares 0.04 sec = 0.80 seconds. The RR interval is 0.80 sec.

3) Calculate the QTcF using a medical calculator (online or from a smartphone application, Excel table with formula, or QTcF normogram table).

QTcF formula: (QT in msec, RR in sec)

$$\mathrm{QTcF} = \frac{\mathrm{QT(msec)}}{\sqrt[3]{\mathrm{RR(sec)}}}$$

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.
3. Find the corresponding calculated QTcF in the cell below the HR (or RR) and to the right of the QT interval. Record the calculated QTcF in the endTB ECG form.

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	510	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	638	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

Annexure 4: Dose adjustment of commonly used TB drugs in patients with renal impairment

*constant: 1.23 for males and 1.04 for females

If creatinine is reported in conventional units (mg/dl), it can be converted to an SI unit (µmol/L) by multiplying by 88.4 (for example, a creatinine = 1.2 mg/dl is equivalent to: 1.2 x 88.4 = 106.1 µmol/L).

Normal values are 97–137 mL/min for males and 88–128 mL/min for females.
If the creatinine clearance is below 30, all the drugs in the regimen should be adjusted according to Table 16.

Table 16: Dose adjustment of commonly used TB drugs in patients with renal impairment

Drug	**Recommended dose and frequency for patients with creatinine clearance < 30 mL/min or for patients on hemodialysis (unless otherwise indicated, give dose after dialysis)**
Isoniazid (H)	No adjustment necessary
Isoniazid High dose (H^{HD})	Recommendations not available
Rifampicin (R)	No adjustment necessary
Pyrazinamide (Z)	25–35 mg/kg per dose three times per week (not daily)
Ethambutol (E)	12–25 m/kg per dose three times per week (not daily)
Capreomycin[a] (Cm)	Avoid
Kanamycin[a] (Km)	Avoid
Amikacyn[a] (Am)	Avoid
Levofloxacin (Lfx)	750–1,000 mg per dose three times per week (not daily)
Moxifloxacin (Mfx)	No adjustment necessary
Cycloserine[b] (Cs)	250 mg once daily, or 500 mg/dose three times per week
Terizidone	Recommendations not available
Ethionamide (Eto)	No adjustment necessary
Para-aminosaliclic acid[c] (PAS)	4g/dose, twice daily maximum dose
Bedaquiline (Bdq)	No dosage adjustment is required in patient with mild to moderate renal impairment. Not enough evidence—Use with caution.
Delamanid (Dlm)	Not enough evidence—Use with caution
Linezolid (Lzd)	No adjustment necessary
Clofazimine (Cfz)	No adjustment necessary
Amoxicillin/clavulanate	For creatinine clearance 10–30 mL/min dose 1,000 mg amoxicillin component twice daily; for creatinine clearance < 10 mL/min dose 1,000 mg amoxicillin component once daily
Imipenem/cilastatin (Imp/Cln)	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 (Mpm)	For creatinine clearance 20–40 mL/min dose 750 mg every 12 hours; for creatinine clearance < 20mL/min dose 500 mg every 12 hours

[a]Avoid the injectable in patients with impaired renal function with clearance < 30 mL/min because of increased risk of ototoxicity and nephrotoxicity

[b]The use of cycloserine 250 mg daily doses in renal impairment has not been established; careful monitoring for evidence of neurotoxicity is essential

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

Annexure 5: Dosing recommendations for second-line DR-TB treatment, including new and repurposed drugs, in children

Table 17: Weight based dosing chart for DR-TB treatment in children (courtesy the Sentinel Project, sentinel-project.org)

Target Dose	Ethambutol (15-25 mg/kg)		Pyrazinamide (30-40 mg/kg)		Injectable anti-TB drugs (injectable agents or parental agents)	Levofloxacin (15-20 mg/kg)		Moxifloxacin (7.5-10 mg/kg)		Ofloxacin (15-20 mg/kg)	Cycloserine (15-20 mg/kg)		PAS (150-200 mg/kg)		Eto (15-20 mg/kg)	Isoniazid High Dose (15-20 mg/kg)	Target Dose
Available Formulations	100 mg tablet	Suspend 400mg tab in 8 mL of water for a 50 mg/mL suspension	400 mg tablet	500 mg tablet		250 mg tablet	25 mg/mL suspension	400 mg tablet	20 mg/mL suspension	200 mg tablet	250 mg capsule	1 capsule in 10 mL water	Daily	Twice Daily	250 mg tablet	100 mg tablet	Available Formulations
Wt (kg)	Consult with a clinician experienced in pediatric MDR-TB prescribing for neonates (<28 days of age) and infants weighing <3 kg																Wt (kg)
<3																	<3
3-3.9	1 tab	2 mL	.25 tab	.25 tab	To illustrate dose calculation, take the example of a child that weighs 6.9 kg. Both the low and high doses for the child's weight are calculated. For kanamycin Low dose: 15 mg/kg x 6.9 kg = 103 mg High dose: 20 mg/kg x 6.9 kg = 138 mg A convenient dosing is then chosen between the two numbers. Select a dose between the two numbers and towards the higher number. In this case, choose: 125 mg per day, single dose. Calculate the number of mL to draw up in the syringe based on the mg/mL concentration of the preparation	.25 tab	2.5 mL	not recommended	1.5 mL	.5 tab	.25 cap	2.5 mL	500 mg	250 mg	.25 tab	.5 tab	3-3.9
4-4.9									2 mL				1000 mg	500 mg			4-4.9
5-5.9			.5 tab			.5 tab	5.0 mL		2.5 mL		.5 cap	5 mL			.5 tab	1 tab	5-5.9
6-6.9		4 mL		.5 tab									1500 mg	750 mg			6-6.9
7-7.9	2 tabs								5 mL	1 tab							7-7.9
8-8.9																	8-8.9
9-9.9			1 tab			.75 tab	7.5 mL				.75 cap	7.5 mL	2000 mg	1000 mg	.75 tab	2 tabs	9-9.9
10-10.9																	10-10.9
11-11.9				1 tab													11-11.9
12-12.9																	12-12.9
13-13.9	3 tabs	6 mL				1 tab	10 mL				1 cap	10 mL	2500 mg	1250 mg	1 tab		13-13.9
14-14.9			1.5 tabs					.5 tab	7.5 mL	1.5 tabs						3 tabs	14-14.9
15-15.9																	15-15.9
16-16.9	4 tabs	8 mL		1.5 tabs		1.5 tabs	15 mL				1.5 caps	15 mL	3000 mg	1500 mg	1.5 tabs		16-16.9
17-17.9			2 tabs						10 mL	2 tabs							17-17.9
18-18.9													4000 mg	2000 mg		4 tabs	18-18.9
19-19.9																	19-19.9
20-20.9																	20-20.9
21-21.9				2 tabs		2 tabs	20 mL		12.5 mL	2.5 tabs	2 caps	20 mL	5000 mg	2500 mg	2 tabs	5 tabs	21-21.9
22-22.9			2.5 tabs														22-22.9
23-23.9	5 tabs	10 mL											6000 mg	3000 mg			23-23.9
24-24.9																	24-24.9
25-25.9																	25-25.9
26-26.9																	26-26.9
27-27.9																	27-27.9
28-28.9																	28-28.9
29-29.9																	29-29.9

Table 18: Dosing recommendations of new and repurposed drugs for the treatment of DR-TB in children

Drug	Dosing schedule	Remarks
Bedaquiline	Adolescents ≥ 12 years of age who weigh 33 kg or more: 400 mg daily for 14 days followed by 200 mg given three times weekly for an additional 22 weeks, with expert clinician consultation Children < 12 years of age or who weigh < 33 kg: expert clinician consultation	Current WHO recommendations for bedaquiline use are for adults ≥ 18 years of age. Resources for consultation: European Respiratory Society–hosted TB Consilium (www.tbconsilium.org) or the Sentinel Project on Pediatric Drug-Resistant Tuberculosis (tbsentinelproject@gmail.com)
Delamanid	Children between 20–34 kg: 50 mg orally twice daily for 24 weeks Children < 20 kg and < 6 years of age: expert clinician consultation	Resources for consultation: European Respiratory Society–hosted TB Consilium (www.tbconsilium.org) or the Sentinel Project on Pediatric Drug-Resistant Tuberculosis (tbsentinelproject@gmail.com)
Linezolid	Children ≥ 12 years of age: 10 mg/kg once daily for treatment duration (if tolerated) Children < 12 years of age: 10 mg/kg twice daily for treatment duration (if tolerated)	Monthly screening for peripheral neuropathy and monthly complete blood counts should be assessed while the child is receiving linezolid Always give vitamin B6 (1–2 mg/kg/day)
Clofazimine	2–3 mg/kg given daily for a maximum daily dose of 100 mg or every other day in smaller children (gel caps cannot be split) Children < 12.5 kg: 1 capsule 50 mg every other day Children 12.6–25 kg: 1 capsule 50 mg every day (or 1 capsule 100 mg every other day) Children > 25 kg: 1 capsule 100 mg every day. Duration: entire course of treatment if tolerated	Clofazimine ad-hoc formulation: • Pierce one soft gel capsule of Clofazimine 100 mg on one side. • Empty the red oily content into a sputum collection container, squeeze the capsule with the fingers in order to remove as much as possible. • Clofazimine stains; it is recommended to change gloves after emptying the capsule. Draw up 10 mL of sunflower oil with the 10-mL syringe. • Add slowly the 10mL of sunflower oil, stirring with a spoon in order to get a homogenous-looking smooth solution. Stir for at least 1 min. • Administer the medicine immediately to the patient using a syringe. • Discard the remaining solution. • Storage conditions and shelf life: for immediate use. • Remark: If the child needs 1 capsule but has problems swallowing it, the content can be suspended in a small amount of soft vehicle following the above described protocol. In that case instead of using a sputum collecting pot the liquids can be mixed in a soup spoon and directly administered to the child.

	Clofazimine (CFZ)	Amoxicillin-clavulanate (AMX-CLV)	Linezolid (LZD)
Daily Dose	2-3 mg/kg once daily; if the child is <25kg give 100mg every second day		

	Steptomycin	Amikacin	Kanamycin	Capreomycin
Daily Dose	20-40 mg/kg once daily			

The use of lignocaine to decrease pain related to second-line injectable (SLI) agents for children is recommended. The volume of lignocaine can be added to the pre-mixed solution of the SLI or included in the volume to reconstitute a powdered solution.

Body weight (Kg)	2% lignocaine
10–19.9	0.2 mL = 4 mg = 0.2–0.4 mg/kg
20–20.9	0.3 mL = 6 mg = 0.2–0.3 mg/kg
30–30.9	0.4 mL = 8mg = 0.2–0.27 mg/kg
40–40.9	0.5 mL = 10 mg = 0.2–0.25 mg/kg
⩾ 50	0.5 mL = 10 mg = ⩽0.2 mg/kg

Source: Antony Garcia-Pratts, Desmond Tutu TB Centre, South Africa

Annexure 6: Monitoring schedules for shorter and individualized regimen for documentation in clinical file/patient treatment card

DR-TB treatment monitoring schedule for the shorter DR-TB regimen
*Prompt action on abnormal clinical or laboratory findings is essential
**Write results or check completed monitoring in shaded box

Patient name: **DR-TB registration number:**

Age: **Sex:** **Height:**

Month/Year												
Examination	**Baseline**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Clinical exam												
Adverse events												
Psychosocial, functional status												
Weight/body mass index (wt/ht^2) (monthly in children)												
Xpert MTB/RIF												
SL LPA		**Repeat if smear or culture positive or suspect failure**										
Smear												
Culture												
Phenotypic DST		**Repeat if smear or culture positive or suspect failure**										
X-ray												
Full blood count[1]												
Creatinine, potassium[2]												
Liver function tests (ALT/AST)												
TSH												
Fasting blood sugar												
Vision test charts[3]												
Audiometry												
HIV test[4]												
Hepatitis B (HBsAg)												
Pregnancy test[5]												
CD4 count (HIV-positive patients)												
Viral load (HIV-positive patients)												

1. Repeat FBC as necessary if HIV-infected (especial care in patient with AZT)
2. Creatinine, potassium, and audiometry should be done monthly while on injectable
3. Repeat vision testing if any change/complaint in acuity or color vision
4. If HIV-negative at baseline, HIV testing should be repeated at month 3 and then every 6 months
5. Pregnancy test: at baseline, then offer use of effective contraceptives (Depo-Provera or intrauterine device [IUD])

DR-TB treatment monitoring schedule for individualized DR-TB regimens
*Prompt action on abnormal clinical or laboratory findings is essential
**Write results or check completed monitoring in shaded box

Patient Name: **DR-TB registration number:**

Age: **Sex:** **Height:**

Month/Year																					
Examination	**Baseline**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Clinical exam																					
Adverse events																					
Psychosocial, functional status																					
Weight/BMI (wt/ht^2) (monthly in children)																					
Xpert MTB/RIF																					
SL LPA		**Repeat if smear or culture positive presumption of failure**																			
Smear																					
Culture[9]																					
Phenotypic DST		**Repeat if smear or culture positive presumption of failure**																			
X-ray																					
FBC (monthly if on Lzd)																					
Creatinine, potassium[1]																					
LFTs (ALT/AST)																					
TSH[2]																					
Fasting blood sugar																					
Serum albumin[3]																					
Amylase/Lypase[4]																					
ECG[5]									**Continue monthly ECGs if Bdq/Dlm given > 6 months**												
Vision test charts[6] (Monthly if on Lzd)																					

Audiometry[1]																					
HIV test[7]																					
Hepatitis B, C																					
Pregnancy test[8]																					
CD4 count (if HIV+)																					
Viral load (if HIV+)																					

1. Creatinine, potassium, and audiometry should be done monthly while on injectable. Continue monthly creatinine monitoring for patients at risk of renal failure (HIV-positive patients, diabetics, patients receiving other nephrotoxic drugs). If any ECG abnormality check potassium (and magnesium, calcium if available).
2. TSH: only if on Eto/ Pto or PAS.
3. Serum albumin: If patient is on Dlm at baseline. If low (< 3,4 g/dL), provide high protein diet, repeat albumin at month 3, and follow ECG. If albumin < 2.8g/dL, Dlm is contraindicated.
4. Amylase/lipase: at baseline if patient on Bdq and Lzd. Then assess when clinically indicated.
5. **ECG** is mandatory for patients on Bdq and or Dlm at baseline, week 2, and monthly while on either drug. ECG may be done more frequently in patients with low albumin (< 3.4 g/dl), low electrolytes, hypothyroidism, or heart conditions.
6. Visual test: If patient on linezolid, perform monthly visual acuity test (Snellen charts) and color vision test (Ishiara).
7. If HIV-negative at baseline, HIV testing should be repeated at month 3 and then every 6 months.
8. Pregnancy test: at baseline, then offer use of effective contraceptives (Depo-Provera or intrauterine device [IUD]).
9. Patient is not declared cured until culture tests negative at the end of treatment period.

Annexure 7: Adverse Drug Reaction Reporting Form, Zambia Medicines Regulatory Authority

ADVERSE DRUG REACTION, MEDICATION ERROR AND PRODUCT QUALITY PROBLEM REPORTING FORM

(Identities of reporter and patient will remain strictly confidential)

NATIONAL PHARMACOVIGILANCE UNIT (NPVU)

The Director General
The Zambia Medicines Regulatory Authority
Plot No. 6903, Tuleteka Rd, Off Makishi Rd,
P.O. Box 31890, Lusaka, Zambia.

Telephone: +260211220429
Telefax: +260211238458
Email: pharmacy@zamra.co.zm

PATIENT INFORMATION

Patient initials: ..... File No. ..... Age: ..... Weight (kg): .....

Sex: Male ☐ Female ☐ Date of birth: ..../..../..... Height (cm): .....

DETAILS OF ADVERSE DRUG REACTION OR PRODUCT QUALITY PROBLEM

I am reporting on: 1) an Adverse Drug Reaction ☐ Date of onset of reaction: ...../...../.....

2) a Product Quality Problem ☐ Category: medicine ☐ medical device ☐

Description of Adverse Drug Reaction or Product Quality Problem: .....

.....

.....

1. MEDICINES/ VACCINES/ MEDICAL DEVICES: *(✓) Tick against the **suspected** medicine/ vaccine*
Indicate all medicines the patient is taking

(✓)	Trade/ Generic Name & Batch Number	Dosage & dosing frequency	Route of administration	Start date (dd/mm/yy)	Stop date (dd/mm/yy)	Reasons for use

ADVERSE DRUG REACTION OUTCOME: *(Tick all that apply)*

Outcome: ☐ Death ☐ Life threatening ☐ Disability ☐ Hospitalization ☐ Congenital abnormality

☐ Other *(specify)*: .....

Recovered: ☐ Yes ☐ No If YES, date of recovery: ...../...../.....

Additional information *(e.g. Relevant medical history, medicines taken in the last 28 days, allergies, previous exposure, baseline test results/ lab data)*.....

.....

2. PRODUCT QUALITY PROBLEM

Trade Name	Batch Number	Registration Number	Dosage Form & Strength	Expiry Date (mm/yyyy)	Size/ Type of container

Product sample(s) have been submitted for evaluation: ☐ Yes ☐ No Number of submitted samples: ☐

DETAILS OF REPORTER

Name: ..... Profession: ..... Signature: ..... Date (dd/mm/yyyy):.....

Contact address: ..... Phone: ..... Email: .....

Disclaimer

This document is made possible by the support of the American People through the United States Agency for International Development (USAID) and the US President's Emergency Plan for AIDS Relief (PEPFAR). The contents are the sole responsibility of Ministry of Health and do not necessarily reflect the views of USAID or the United States Government

Produced for the Ministry of Health, Zambia