CLINICAL GUIDELINES FOR THE MANAGEMENT OF DRUG RESISTANT TUBERCULOSIS

Use of new drugs and the shorter regimen

Zimbabwe National TB Control Program
December 2017

TABLE OF CONTENTS

Introduction and Purpose 1

Acknowledgements 2

Abbreviations 3

Definitions 7

Diagnosis of DR-TB 9

DR-TB treatment: choice of regimen 14

DR-TB treatment with the shorter regimen and new drugs: special populations 22

Inpatient or outpatient treatment initiation of shorter DR-TB regimen and new drugs 32

Monitoring patients on the new drugs or shorter regimen ... 33

Active DR-TB drug safety monitoring and management (aDSM) for new drugs and the shorter DR-TB regimen 42

Informed Consent to DR-TB treatment 44

Annexures 45

INTRODUCTION AND PURPOSE

After nearly five decades, two new agents, bedaquiline and delamanid, have been registered for the treatment of drug resistant tuberculosis (DR-TB) by stringent regulatory authorities, and recommended for programmatic use by the World Health Organization (WHO). More recently, the WHO has recommended the use of a nine to twelve-month regimen for uncomplicated multidrug resistant tuberculosis (MDR-TB). These guidelines provide clinical guidance on the use of the shorter regimens and new DR-TB drugs, and are meant to compliment the programmatic recommendations of the 2017 Zimbabwe Tuberculosis and Leprosy Management Guidelines. The recommendations herein are based on the most current evidence and research data; the expertise of clinicians and managers working in Zimbabwe; and international expert opinion. DR-TB management is challenging, and often requires insight from experts in the field. As new evidence becomes available through the results of ongoing studies, these guidelines will be updated to inform practice recommendations.

This resource can be used by health care workers, TB program managers, DR-TB patients, and civil society. Introduction of the shorter regimen and new drugs will be undertaken in a phased approach, which will be detailed in a comprehensive operational plan. The Government of Zimbabwe, through the Ministry of Health and Child Care (MoHCC), endorses the implementation of these guidelines.

Brigadier General (Dr.) G. Gwinji,
Secretary for Health & Child Care

ACKNOWLEDGEMENTS

The Ministry of Health and Child Care recognizes the National Tuberculosis Control Program, in-country partners, and stakeholders for their collective efforts in completion of the guidelines. The World Health Organization, The Union, and USAID/Stop TB Partnership are acknowledged for providing technical assistance. A special acknowledgment is given to the core writing team members listed below:

Dr. Charles Sandy	Deputy Director AIDS/TB Programs (National TB Control)
Dr. Vivian Cox	USAID/Stop TB Partnership MDR Clinical Consultant
Dr. Kelvin Charambira	PMDT Technical Officer, The Union
Mr. Masimba Dube	TB Medicines Control Officer, Directorate of Pharmacy Services
Dr. Patrick Hazangwe	National Professional Officer-TB, The World Health Organization
Dr. Mkhokheli Ngwenya	PMDT Officer, National Tuberculosis Program
Mr. Tawanda Mapuranga	DOTS and Training Officer, National Tuberculosis Program
Ms. Portia Antonio	Intern, National TB Programme
Dr. Wilbert Bara	District Medical Officer, City of Harare
Mr. Brooke T Chimoto	Provincial Therapist, Ministry of Health and Child Care
Ms. Yvonne Chivasa	Chief Radiographer, Parerenyatwa Hospital
Ms. Chiundo Cyvvenia	Occupational Therapist, Ministry of Health and Child Care
Dr. Efison Dhodho	Health Specialist, Programme Coordinating Unit
Dr. Marthe Frieden	Project Medical Referent, Médecins Sans Frontières
Dr. Evidence Gaka	Health Services Director, Prisons and Correctional Services
Dr. Shepherd Machekera	TB/HIV Officer, The Union
Dr. Givemore Madanzi	Medical Team Leader, Médecins Sans Frontières

Ms. Tendai Mapfumba	Data Manager, National TB Programme
Dr. Martin Mapfurira	TB/HIV Officer, National TB Programme
Dr. Simba Mashizha	PFCH/TB & HIV Officer, Manicaland Province
Mr. Gamuchirayi Matandirotya	Provincial Pharmacist, Matebeleland South
Mr. Kudzai Mtisi	Regulatory Officer, Medicines Control Authority of Zimbabwe
Mr. Hebert Mutunzi	TB Laboratories Focal Person, Directorate of Laboratory Services
Mr. Kwenziweyinkosi Ndlovu	Community TB Care Officer, National Tuberculosis Program
Dr. Ganje Ngonidzashe	Medical Officer, Epworth Polyclinic
Dr. Nehemiah Nhando	Research Director, Univ. of Zimbabwe-UCSF Research Program
Dr. Tendai Nkomo	Government Medical Officer, Filabusi District Hospital
Dr. Brian Nyagadza	Medical Team Leader, Médecins Sans Frontières
Mr. Andrew Nyambo	Advocacy, Communication and Social Mobilisation Officer, NTP
Dr. Khulamuzi Nyathi	Chief Medical Officer, City of Bulawayo
Ms. Tsitsi Sakupwanya	AACSM Officer, National Tuberculosis Program
Mr. Peter T Shiri	Assistant NTP Officer, National Tuberculosis Program
Mr. Nicolas Siziba	M & E Officer, National Tuberculosis Programme
Dr. Karembo Stewart	Medical Superintendent, Rusape General Hospital
Mr. Musoro Tendero	Provincial Therapist, Mashonaland Hospital
Ms. Nzenza Theotia	Environmental Health Officer, Ministry of Health and Child Care
Mr. Edmore Zuweni	Tutor, Mutambara Hospital

Dr. O. Mugurungi,
Director HIV, AIDS, STI & TB Programmes
Ministry of Health and Child Care

ABBREVIATIONS

ADR	Adverse drug reaction
aDSM	Active TB drug safety monitoring and management
AIDS	Acquired immune deficiency syndrome
AFB	Acid fast bacilli
ALT	Alanine aminotransferase
Am	Amikacin
ART	Antiretroviral therapy
AST	Asparate aminotransferase
ATV/r	Atazanavir/ritonavir
BDQ	Bedaquiline
BMI	Body mass index
Ca	Calcium
CFZ	Clofazamine
Cm	Capreomycin
CP	Continuation phase
Cr	Creatinine
Cs	Cycloserine
CXR	Chest x-ray
DLM	Delamanid
DOT	Directly observed therapy
DOTS	Directly observed therapy short course
DR-TB	Drug resistant tuberculosis
DST	Drug susceptibility testing
DS-TB	Drug susceptible tuberculosis
E or EMB	Ethambutol
ECG	Electrocardiogram
EFV	Efavirenz
EPTB	Extra-pulmonary tuberculosis

Eto	Ethionamide
FBC	Full blood count
FDC	Fixed dose combination
FL LPA	First-line line probe assay
FQ	Fluoroquinolone
H or INH	Isoniazid
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
H_{hd} or INH_{hd}	High dose isoniazid
HIV	Human Immunodeficiency Virus
IP	Intensive phase
IUATLD	International Union Against Tuberculosis and Lung Disease (The Union)
K	Potassium
Km	Kanamycin
LTBI	Latent tuberculosis infection
LPV/r	Lopinavir/ritonavir
Lfx	Levofloxacin
LPA	Line probe assay
LZD	Linezolid
MDR-TB	Multi-drug resistant tuberculosis
Mfx	Moxifloxacin
Mg	Magnesium
MoHCC	Ministry of Health and Child Care
MTB	Mycobacterium tuberculosis
Na	Sodium
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
PDR-TB	Poly-drug resistant tuberculosis

PHC	Primary health care
PI	Protease inhibitor
Plt	Platelets
PMDT	Programmatic management of drug resistant tuberculosis
PNP	Peripheral neuropathy
Pre-XDR-TB	Pre-extensively-drug resistant tuberculosis
PTB	Pulmonary tuberculosis
QTc	QT interval corrected
R or RIF	Rifampicin
RBC	Red blood cell count
RR-TB	Rifampicin-resistant tuberculosis
SAE	Serious adverse event
SLID	Second line injectable drugs
SL LPA	Second-line line probe assay
TB	Tuberculosis
TB-LAM	Tuberculosis lateral flow urine lipoarabinomannan assay
TSH	Thyroid stimulating hormone
Tx	Treatment
VL	Viral load
WBC	White blood cell count
WHO	World Health Organization
XDR-TB	Extensively-drug resistant tuberculosis
Xpert	GeneXpert MTB/RIF
Z or PZA	Pyrazinamide

DEFINITIONS

Note: The definitions given below apply to the terms as used in this guidance. The terms may have different meanings in other contexts.

Adolescent: refers to the 14-18-year age group.

Child: refers to the 0-14-year age group.

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 case for extended daytime periods during the 3 months before the start of the current treatment episode.

Extensively-drug resistant tuberculosis (XDR-TB): a clinical isolate confirmed to be M. tuberculosis that is resistant to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multi-drug resistance.

Extra-pulmonary tuberculosis (EPTB): refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Household contact: a person who shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods during the 3 months before the start of the current treatment episode.

Index case (index patient): the initially identified case 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 case is the case around which a contact investigation is centered.

Infection: infection with M. tuberculosis may occur following exposure to a TB case and means that the person carries the bacteria inside the body. Many people have TB infection and remain well, while others develop disease. When infection has occurred but the infected individual is showing no signs or symptoms of disease from the standpoint of clinical recognition or diagnostic detection, the term latent TB infection (LTBI) is often used.

Mono-drug resistant tuberculosis: a clinical isolate confirmed to be M. tuberculosis that is resistant to one first-line anti-TB drug only.

Multi-drug resistant tuberculosis (MDR-TB): a clinical isolate confirmed to be M. tuberculosis that is resistant to at least both isoniazid and rifampicin.

Poly-drug resistant tuberculosis (PDR-TB): a clinical isolate confirmed to be M. tuberculosis that is resistant to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).

Pre-extensively-drug resistant tuberculosis (pre-XDR-TB): a clinical isolate confirmed to be M. tuberculosis that is resistant to isoniazid and rifampin and either a fluoroquinolone or second-line injectable agent but not both.

Pulmonary tuberculosis (PTB): refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as PTB because there are 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 extra-pulmonary TB. A patient with both pulmonary and extra-pulmonary TB should be classified as a case of PTB.

Rifampicin-resistant tuberculosis (RR-TB): a clinical isolate confirmed to be M. tuberculosis that is resistant to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether mono-resistance, multi-drug resistance, poly-drug resistance or extensively-drug resistance

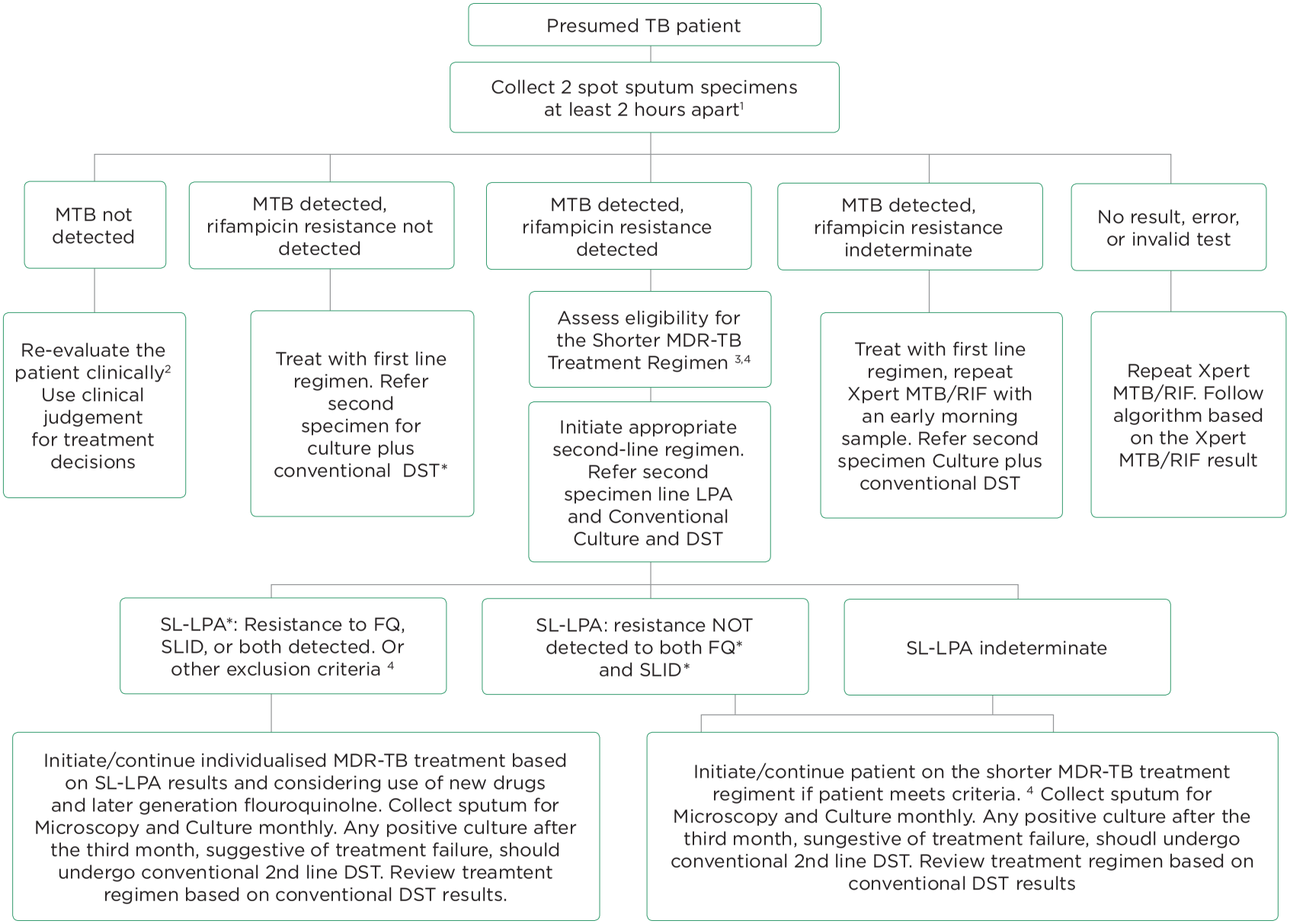
Tuberculosis (TB) disease (active TB): refers to illness that occurs in someone infected with Mycobacterium tuberculosis and is characterized by clinical signs and symptoms, with or without laboratory or radiographic evidence.

DIAGNOSIS OF DR-TB

All patients presenting to health facilities with signs and symptoms suggestive of TB should undergo Xpert MTB/RIF testing as the initial TB screening test. A chest x-ray should also be performed (especially if the patient presents with a body mass index less than 17 kg/m2), although health care workers should be aware that obtaining a CXR should not place undue time or cost burden on the patient, or create a delay in confirming a diagnosis of TB or initiating treatment.

All adult patients with a positive symptom screen and/or a low BMI and/or an abnormal chest x-ray should have TWO sputum samples collected and sent to the nearest Xpert site. The first sample is tested for TB using the Xpert MTB/RIF assay, and if MTB is detected, the second is sent to a National TB Reference Laboratory for culture and DST (Figure 1). If MTB with rifampicin resistance is detected, the sample will additionally undergo first- and second-line line probe assays. If MTB is not detected the second sample is discarded.

Figure 1: Diagnostic testing and management of presumptive cases of PTB



[1]One specimen for Xpert MTB/RIF and one for LPA and/or Culture and phenotypic DST in case of MTB detected

[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 100 cells/Ql or are seriously ill, perform TB-LAM test according to national guidelines.

[3] Patients may be initiated on the shorter MDR-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. 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.

[4] The shorter MDR-TB regimen may be used in MDR-TB patients who do not have the following conditions: 1) confirmed resistance, or suspected ineffectiveness, to a medicine (except isoniazid) in the shorter MDR-TB regimen for which there is reliable DST, 2) previous exposure for >one month to a second-line medicine included in the shorter MDR-TB regimen, 3) intolerance to one or more medicines in the shorter MDR-TB regimen or increased risk of toxicity, 4) pregnancy, or 5) extra-pulmonary disease.

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

Discordance in laboratory results may happen, usually when comparing culture-based results with molecular results. Each discordant result will need to be investigated, on a case-by-case basis. If there are discordant results between rapid diagnostic tests (e.g. rifampicin resistant on Xpert but rifampicin sensitive on LPA) or a rapid diagnostic test and culture, the focus should be on the clinical history of the patient (TB treatment history, close contacts) and the response to current treatment to make decisions about further management. The case history can also be discussed with the district DR-TB focal person or an existing TB clinical review committee. General considerations to evaluate di

1. **Rifampicin resistant on Xpert, culture negative**: treat the patient according to the Xpert result and submit another sample for culture. Reasons for negative cultures in persons with pulmonary TB:
    - Patient is being treated for TB
    - Transport or processing problems that inactivated the tubercle bacilli
    - Inadequate testing volume
    - Laboratory or clerical error
2. **Xpert negative, culture positive:** treat the patient based on the positive culture result. The rationale is:
    - The positive culture result should be considered as bacteriological confirmation of TB (culture is more sensitive)
    - Using a sputum specimen, Xpert has a pooled sensitivity of 89% for detecting MTB compared to culture
    - Xpert sensitivity is lower in HIV positive patients and children
    - False positive culture results are very rare (due to laboratory errors such as cross contamination and sample labelling problems)

3. **Rifampicin resistance on Xpert, rifampicin susceptible by phenotypic DST**: treat the patient according to the Xpert resistant result and repeat culture and phenotypic DST using solid media.

    - Certain mutations are known to generate this discordant result (i.e., a false-susceptible phenotypic result)
    - In some low DR-TB prevalence settings, silent mutations have been observed that generate a false resistant Xpert result, but this is rare

4. **Xpert positive, 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 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 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 result of rifampicin resistance not detected

5. **Xpert positive, rifampicin not detected (susceptible); FL LPA rifampicin detected (resistant)**: treat the patient based on FL LPA (Rif resistant) result. This discordance is rare.

DR-TB TREATMENT: CHOICE OF REGIMEN

1. Shorter DR-TB treatment regimen

All adult and pediatric patients with confirmed RR-TB or MDR-TB should receive a shorter regimen of 9-12 months (Figure 2) unless they have any of the following exclusion criteria:

EXCLUSION CRITERIA FOR SHORTER DR-TB TREATMENT REGIMEN*

1) Confirmed resistance or suspected ineffectiveness to a medicine in the shorter regimen (excluding isoniazid). This includes resistance to either the fluoroquinolones (FQ), the second line injectable agents (SLID), or both (either pre-XDR-TB or XDR-TB).
2) Close contact with a patient that has resistance to FQ/SLID.
3) Exposure to one or more second line medicines in the shorter regimen for a month or more.
4) Known intolerance or a high risk of toxicity to one or more medicines in the shorter regimen (including drug-drug interactions).
5) Pregnancy (refer to section on DR-TB treatment in preganacy).
6) Extrapulmonary TB**.

** Patients already on treatment with a conventional DR-TB treatment regimen cannot be switched to the shorter DR-TB treatment regimen.*

*** Inclusion of a patient with EPTB for treatment with the shorter DR-TB regimen is at the clinician's discretion after discussion with the TB clinical review committee. It is suggested that non-severe forms of EPTB such as TB pleural effusion (adults and children) and TB lymphadenitis (children) could be eligible for treatment with the shorter DR-TB regimen, with close clinical management and follow up.*

The standard shorter DR-TB treatment regimen for Zimbabwe is:

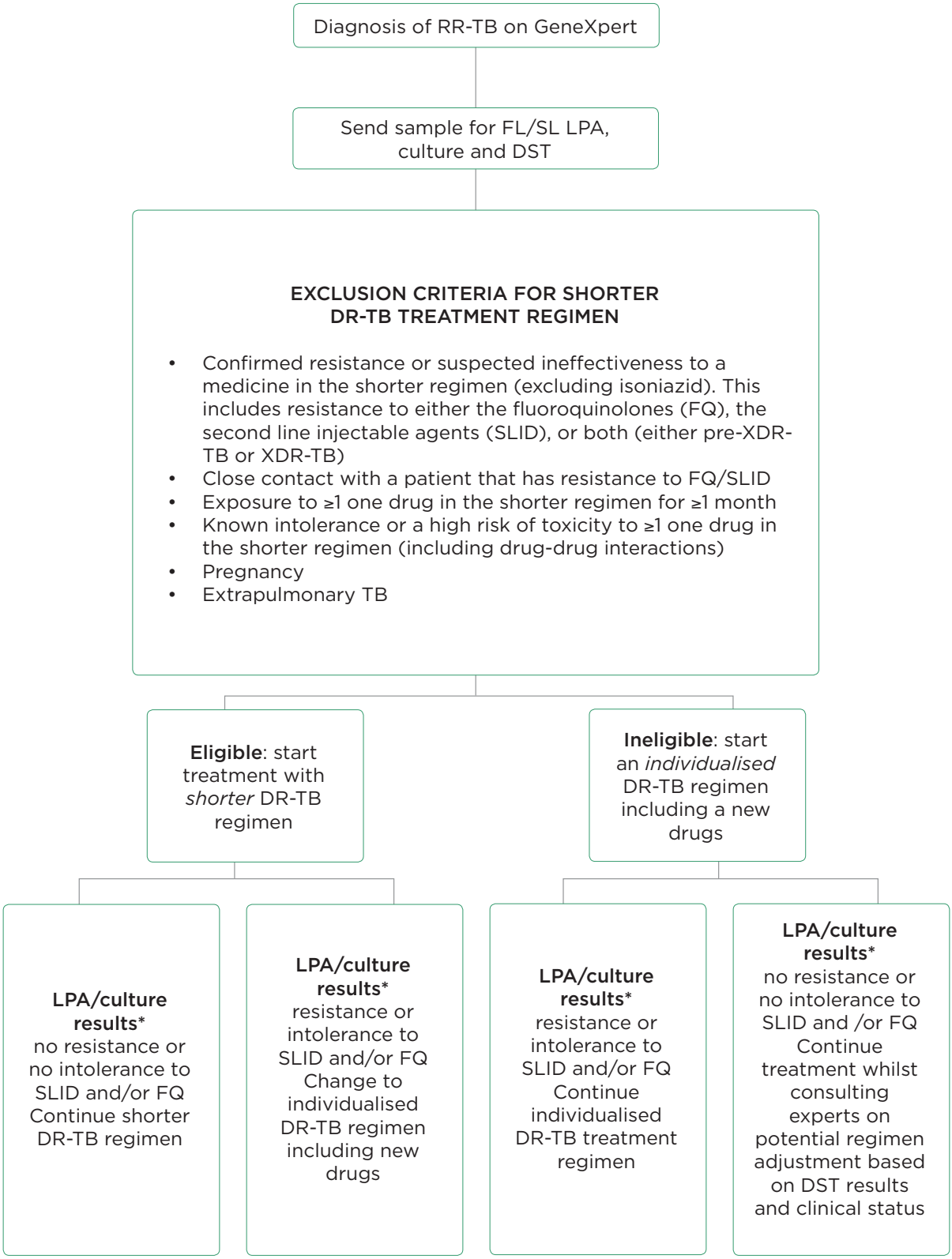
***4-6 (Km-Mfx^{600}-Eto-Cfz-H^{hd}-Z-E) / 5 (Mfx^{600}-Cfz-Z-E)**

The moxifloxacin dose for the shorter regimen is 600 mg orally daily. High dose isoniazid is considered 10-15 mg/kg/day. Numbers before parentheses are the minimum number of months the intensive phase and continuation phase should last.

Additional practice recommendations:

- All adult and pediatric patients with confirmed RR-TB should be treated with the shorter DR-TB regimen unless they meet an exclusion criteria.
- Patients may be initiated on the shorter regimen, if eligible, while awaiting LPA and culture results; all specimens sent for LPA and culture should have results confirmed and treatment changed accordingly when results are available.
- The initial treatment plan for all patients treated with the shorter DR-TB regimen will be to have a 4-month intensive phase (IP) and a 5-month continuation phase (CP).
- The decision to end intensive phase should be based on culture results, with two consecutive negative cultures one month apart. Only if there are no culture results available by month six of the intensive phase the decision to end the intensive phase be based on smear results.
- Extension of the intensive phase may be needed for 2 reasons:
  - Awaiting culture results.
  - No culture conversion by the fourth month of treatment.
- If a patient on the shorter DR-TB regimen has not achieved culture conversion by month 5, they will be declared treatment failure, and should be switched to an individualized DR-TB regimen with new drugs.
- The decision to discontinue a drug due to intolerance should not wait until the effect is severe or irreversible.
- If resistance to one or more drugs in the shorter regimen is seen on DST, the patient should be switched to an individualized regimen. If the patient is confirmed MDR with intolerance to one drug in the shorter regimen, the clinician may consider switching the offending drug for bedaquiline or delamanid.

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



**Every effort should be made to follow up on LPA and culture/DST results for all patients.*

- The duration of the CP is minimum 5 months but can be extended to a maximum of 6 months whilst awaiting culture results (total duration of treatment is at maximum 12 months).
- Patients returning to care after interrupting treatment with the shorter regimen for more than 2 months should be switched to an individualized regimen.
- Clinicians treating patients with the shorter regimen should obtain and document verbal consent, which represents an agreement between the provider and patient on the choice of DR-TB regimen.
- All women of childbearing age diagnosed with DR-TB should be counseled on pregnancy prevention during treatment and provided with appropriate contraceptives.

2. Individualized DR-TB treatment regimen

Patients who do not meet criteria for the shorter DR-TB regimen, who fail treatment with the shorter DR-TB regimen, or who are intolerant or resistant to drugs in the shorter DR-TB regimen, should have an individualized DR-TB treatment regimen containing new and repurposed drugs. The updated WHO classification of DR-TB drugs is shown in Table 1.

Table 1: medicines recommended for the individualized treatment of RR-TB and MDR-TB1

A. Fluoroquinolones[2]		Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
B. Second-line injectable agents		Amikacin Capreomycin Kanamycin	Am Cm Km
C. Other core second-line agents[2]		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	D1	Pyrazinamide Ethambutol High-dose isoniazid	Z E H_{hd}
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	*p*-aminosalicylic acid Imipenem-cilastatin[3] Meropenem[3] Amoxicillin-clavulanate[3]	PAS Ipm Mpm Amx-Clv

1 This regrouping is intended to guide the design of conventional 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 Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin.

Considerations for regimen design:

- An individualized DR-TB regimen should include at least five effective DR-TB drugs during the intensive phase, including pyrazinamide and four core second line DR-TB drugs – consideration given to one from Group D2 (bedaquiline or delamanid), one chosen from Group A, one from Group B, and at least two from Group C (Table 2).
- If the minimum number of effective DR-TB drugs cannot be composed as given above, other agents from Group C and Group D3 should be added to bring the total to five effective DR-TB drugs.
- Bedaquiline or delamanid should be used for 6 months unless discontinuation is necessary due to adverse events. The use of either drug can be extended beyond 6 months in cases where the remaining regimen is insufficient (less than 3 effective drugs) or culture conversion is delayed.
- There is more experience of extending bedaquiline beyond six months than delamanid. Extension of bedaquiline or delamanid is at the discretion of the treating clinician, and should be discussed with the TB clinical team.
- Any adult or pediatric patient with RR-TB that requires an individualized DR-TB regimen and in whom isoniazid resistance is absent or unknown should have high-dose isoniazid added to the regimen.
- If the injectable is part of the individualized regimen, it should be used for a minimum of 6 months and 4 months after culture conversion; the total duration of treatment must be at least 20 months.
- The duration of the injectable agent, and hence the intensive phase, may need to be extended according to the patient's response to treatment, culture conversion status, tolerance of the injectable, and confidence in the efficacy of other drugs in the regimen.
- The regimen should be designed based on the patient's most recent DST results and history of previous DR-TB drug use and/or exposure.

- All patients on the short treatment regimen should receive 50mg of pyridoxine in adults and 25mg of pyridoxine for paediatrics to prevent neurologic adverse events due to high dose isoniazid.
- All patients treated with Cycloserine (Cs) should receive pyridoxine (50 mg for every 250 mg of Cs) to prevent neurological adverse events.
- All women of childbearing age diagnosed with DR-TB should be counseled on pregnancy prevention during treatment and provided with appropriate contraceptives.

Table 2: Regimen design steps for RR-TB patients who are not eligible for the shorter DR-TB regimen and require an individualized regimen

Step 1: Consider use of bedaquiline or delamanid (Group D2). The choice of which drug (or potentially both drugs) is outlined in the section on 'special 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 is preferred) can still be added to the regimen, but should not be counted as one of the effective drugs. Treatment with a later generation FQ (Mfx or Lfx) significantly improves RR-TB or MDR-TB treatment outcomes; they should therefore always be included unless there is an absolute contra-indication for their use.
Step 3: Choose an injectable (Group B – Km, Cm, Am). If clinical history or DST suggests resistance to all SLID, or in case of a serious adverse event (hearing loss, nephrotoxicity), the injectable should not be used or should be promptly discontinued. 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 Group C drugs (Lzd, Cfz, Eto, Cs) thought to be effective as additional core second line drugs to BDQ/DLM, FQs, and SLID. If efficacy is uncertain, the drug can be added to the regimen, but should not be counted as an effective drug.
Step 5: Choose D1 drugs (PZA, INHhd, 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, or INH resistance is unknown. 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 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 5 drugs with confirmed or high likelihood of susceptibility from the following list: Bdq or Dlm, Lfx or Mfx, Km (Am, Cm), Eto, Lzd, Cfz, Cs, Z, H^{hd}, E.

Bedaquiline and delamanid – special considerations

- Bedaquiline, delamanid, the fluoroquinolones (Mfx more than Lfx), and clofazamine can all cause prolongation of the QT interval (Annexure 1). 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.
- Clinicians treating patients with new medicines should obtain and document verbal consent, which represents an agreement between the provider and patient on the choice of DR-TB regimen.
- Never add bedaquiline or delamanid as 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.
- Patients diagnosed with XDR-TB or who are failing an MDR-TB regimen need the addition of at least 3 new drugs to their regimen, including BDQ or DLM, LZD, CFZ, or PZA.
- If either bedaquilline or delamanid has been used in the past or there is documented drug allergy or intolerance to one, then the other drug should be chosen.
- Delamanid should be the new medicine of choice for HIV co-infected patients, due to the lack of drug-drug interactions with antiretroviral therapy.
- Delamanid should be the new drug of choice for children and adolescents between 6-18 years of age; there are no current recommendations for the use of delamanid below the age of 6 years. Individual cases of children less than 6 years old requiring delamanid due to highly resistant forms of DR-TB (often the resistance pattern of the adult index case) should be discussed with the TB clinical team and pediatric DR-TB experts.
- Delamanid has been recommended for any patient at high risk of unfavorable DR-TB treatment outcomes (HIV co-infected, diabetics, low BMI, extensive lung disease, complex DR-TB treatment history).
- When starting bedaquiline or delamanid, serum electrolytes should be checked and corrected when feasible to reduce the risk of cardiac arrhythmias. Since delamanid is metabolized by albumin, patients with low BMIs and/or a low serum albumin should be provided with high protein dietary foods.

- There is potential cross resistance between bedaquiline and clofazamine; use delamanid if there is a history of prior clofazamine use > 2 months for DR-TB.
- There has been very limited experience in using bedaquiline and delamanid in combination. In patients with highly resistant forms of DR-TB with very few treatment options remaining, the combination may be considered. The decision to use the combination should only be made after the individual case has been discussed with the district DR-TB focal person or an existing TB clinical review committee.
- Bedaquiline has a prolonged half-life of 5 months; if considering the use of delamanid after completion of bedaquiline (e.g. bedaquiline 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 reduce the dose of either bedaquiline or delamanid 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). Weight based dosing of DR-TB medications are given in Tables 3 and 4.
- 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, 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.
- Renal impairment: no dose adjustment of bedaquiline or delamanid 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, bedaquiline can be used but with caution. There are no data on the use of delamanid in patients with severe renal impairment and its use is not recommended.
- Hepatic impairment: no dose adjustment is necessary for bedaquiline or delamanid in patients with mild or moderate hepatic impairment. Bedaquiline 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. Delamanid is not recommended in patients with moderate to severe hepatic impairment.

DR-TB TREATMENT WITH THE SHORTER REGIMEN AND NEW DRUGS: SPECIAL POPULATIONS

1. Children/adolescents

- Clinicians should consult with the district DR-TB focal person or an existing TB clinical review committee for each pediatric and adolescent patient receiving the shorter regimen or new drugs.
- The WHO recommends the shorter regimen for children and adolescents that have uncomplicated MDR-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.
- If there is potential to spare the use of an injectable agent, especially in younger children, the injectable in the shorter regimen can be replaced by delamanid. Regimen duration with DLM containing shorter DR-TB regimen should ideally be 9-12 months, with the full 6-month course of DLM completed.
- 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 Tables 5 and 6.
- There should be special attention to adherence and psychosocial support for adolescents on DR-TB treatment regardless of regimen selection.
- 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.
- Monitoring of children on DR-TB treatment is the same as adults.
- Decisions on treatment duration in children, if unable to be determined from bacteriologic results, should be based on clinical improvement or standard durations

Table 3: Weight-based oral anti-TB drug daily dosing in adults ≥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	750 mg	750 mg	750 mg
p-aminosalicylic acid	8 g/day in 2 divided doses	8 g	8 g	8 g	8 g	8-12 mg
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

Table 4: Weight-based injectable anti-TB daily dosing in adults ≥30 kg

DRUGS	DAILY DOSE	30-33 kg	34-40 kg	41-45 kg	46-55 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

Table 5: weight based dosing chart for DR-TB treatment in children
(courtesy the Sentinel Project, sentinel-project.org)

<table>
<tr><th rowspan="2">Target Dose</th><th colspan="2">Ethambutol (15-25 mg/kg)</th><th colspan="2">Pyrazinamide (30-40mg/kg)</th><th rowspan="2">Injectable anti-TB drugs (injectable agents or parental agents)</th></tr>
<tr><th>100 mg tablet</th><th>Suspend 400mg tab in 8 mL of water for a 50 mg/mL suspension</th><th>400 mg tablet</th><th>500 mg tablet</th></tr>
<tr><td>Available Formulations</td><td colspan="5" rowspan="2">Consult with a clinician experienced in pediatric MDR-TB prescribing for neonates (<28 days of age) and infants weighing <3kg</td></tr>
<tr><td><3</td></tr>
<tr><td>3-3.9</td><td rowspan="4">1 tab</td><td rowspan="5">2 mL</td><td>.25 tab</td><td>.25 tab</td><td rowspan="29">To illustrate dose calculation, take the example of a child that weighs 6.9kg. Both the low and high doses for the child's weight are calculated.

For kanamycin: Low-dose: 15mg/kg x 6.9 kg = 138mg A convenient dosing is then chosen between the 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.</td></tr>
<tr><td>4-4.9</td><td rowspan="3">.5 tab</td></tr>
<tr><td>5-5.9</td><td rowspan="5">.5 tab</td></tr>
<tr><td>6-6.9</td></tr>
<tr><td>7-7.9</td><td rowspan="6">4 mL</td></tr>
<tr><td>8-8.9</td><td rowspan="5">2 tabs</td><td rowspan="5">1 tab</td></tr>
<tr><td>9-9.9</td></tr>
<tr><td>10-10.9</td></tr>
<tr><td>11-11.9</td></tr>
<tr><td>12-12.9</td><td rowspan="6">1 tab</td></tr>
<tr><td>13-13.9</td><td rowspan="3">3 tabs</td><td rowspan="3">6 mL</td></tr>
<tr><td>14-14.9</td></tr>
<tr><td>15-15.9</td><td rowspan="7">1.5 tabs</td></tr>
<tr><td>16-16.9</td><td rowspan="10">4 tabs</td><td rowspan="10">8 mL</td></tr>
<tr><td>17-17.9</td></tr>
<tr><td>18-18.9</td></tr>
<tr><td>19-19.9</td><td rowspan="6">1.5 tabs</td></tr>
<tr><td>20-20.9</td></tr>
<tr><td>21-21.9</td><td rowspan="7">2 tabs</td></tr>
<tr><td>22-22.9</td></tr>
<tr><td>23-23.9</td></tr>
<tr><td>24-24.9</td></tr>
<tr><td>25-25.9</td></tr>
<tr><td>26-26.9</td><td rowspan="4">2 tabs</td></tr>
<tr><td>27-27.9</td><td rowspan="3">5 tabs</td><td rowspan="3">10 mL</td><td rowspan="3">2.5 tabs</td></tr>
<tr><td>28-28.9</td></tr>
<tr><td>29-29.9</td></tr>
</table>

Target Dose	Levofloxacin (15-20 mg/kg)		Moxifloxacin (7.5-10mg/kg)		Ofloxacin (15-20 mg/kg)	Cycloserine (15-20 mg/kg)	
	250 mg tablet	25 mg/mL suspension	400 mg tablet	200 mg/mL suspension	200 mg tablet 25 mg/mL suspension	250 mg capsule	1 capsule in 10mL water
Available Formulations	Consult with a clinician experienced in pediatric MDR-TB prescribing for neonates (<28 days of age) and infants weighing <3kg						
<3							
3-3.9	.25 tab	2.5 mL	not recommended	1.5 mL	.5 tab	.25 cap	2.5 mL
4-4.9				2 mL			
5-5.9	.5 tab	5.0 mL		2.5mL		.5 cap	5 mL
6-6.9							
7-7.9							
8-8.9				5 mL	1 tab		
9-9.9	.75 tab	7.5 mL				.75 cap	7.5 mL
10-10.9							
11-11.9							
12-12.9	1 tab	10 mL				1 cap	10 mL
13-13.9							
14-14.9			.5 tab				
15-15.9				7.5 mL	1.5 tabs		
16-16.9							
17-17.9	1.5 tabs	15 mL				1.5 caps	15 mL
18-18.9							
19-19.9							
20-20.9				10 mL			
21-21.9					2 tabs		
22-22.9							
23-23.9							
24-24.9						2 caps	20 mL
25-25.9	2 tabs	20 mL					
26-26.9							
27-27.9				12.5 mL	2.5 tabs		
28-28.9							
29-29.9							

<table>
<tr><td rowspan="2">Target Dose</td><td colspan="2">PAS
(150-200 mg/kg)</td><td>Eto
(15-20 mg/kg)</td><td>Isoniazid High Dose (15-20 mg/kg)</td></tr>
<tr><td>Daily</td><td>Twice Daily</td><td>250 mg tablet</td><td>100 mg tablet</td></tr>
<tr><td>Available Formulations</td><td colspan="4" rowspan="2">Consult with a clinician experienced in pediatric MDR-TB prescribing for neonates
(<28 days of age) and infants weighing <3kg</td></tr>
<tr><td><3</td></tr>
<tr><td>3-3.9</td><td>500 mg</td><td>250 mg</td><td rowspan="2">.25 tab</td><td rowspan="2">.5 tab</td></tr>
<tr><td>4-4.9</td><td rowspan="2">1000 mg</td><td rowspan="2">500 mg</td></tr>
<tr><td>5-5.9</td><td rowspan="4">.5 tab</td><td rowspan="4">1 tab</td></tr>
<tr><td>6-6.9</td><td rowspan="3">1500 mg</td><td rowspan="3">750 mg</td></tr>
<tr><td>7-7.9</td></tr>
<tr><td>8-8.9</td></tr>
<tr><td>9-9.9</td><td rowspan="4">2000 mg</td><td rowspan="4">1000 mg</td><td rowspan="3">.75 tab</td><td rowspan="3">2 tabs</td></tr>
<tr><td>10-10.9</td></tr>
<tr><td>11-11.9</td></tr>
<tr><td>12-12.9</td><td rowspan="5">1 tab</td><td rowspan="4">3 tabs</td></tr>
<tr><td>13-13.9</td><td rowspan="3">2500 mg</td><td rowspan="3">1250 mg</td></tr>
<tr><td>14-14.9</td></tr>
<tr><td>15-15.9</td></tr>
<tr><td>16-16.9</td><td rowspan="5">3000 mg</td><td rowspan="5">1500 mg</td></tr>
<tr><td>17-17.9</td><td rowspan="8">1.5 tabs</td></tr>
<tr><td>18-18.9</td></tr>
<tr><td>19-19.9</td></tr>
<tr><td>20-20.9</td></tr>
<tr><td>21-21.9</td><td rowspan="4">4000 mg</td><td rowspan="4">2000 mg</td><td rowspan="4">4 tabs</td></tr>
<tr><td>22-22.9</td></tr>
<tr><td>23-23.9</td></tr>
<tr><td>24-24.9</td></tr>
<tr><td>25-25.9</td><td rowspan="4">5000 mg</td><td rowspan="4">2500 mg</td><td rowspan="5">2 tabs</td></tr>
<tr><td>26-26.9</td><td rowspan="4">5 tabs</td></tr>
<tr><td>27-27.9</td></tr>
<tr><td>28-28.9</td></tr>
<tr><td>29-29.9</td><td>8000 mg</td><td>3000 mg</td></tr>
</table>

	Steptomycin	Amikacin	Kanamycin	Capreomycin	Clofazimine (CFZ)	Amoxicillin-clavulanate (A MX-CLV)	Linezolid (LZD)
Daily Dose	20-40 mg/kh once daily	15-20 mg/kg once daily	15-20 mg/kg once daily	15-20 mg/kg once daily	2-3 mg/kg once daily; if the child is <25kg give 100mg every second day	80 mg/kg in two divided doses based on the amoxicillin component	10 mg/kg dose twice daily for children <10 years of age 300 mg daily for children >10 years of age (also give vitamin B6
Maximum Daily Dose	1000 mg	1000 mg	1000 mg	1000 mg	200 mg	4000 mg amoxicillin and 500 mg clavulanate	600 mg

Table 6: dosing recommendations of new and re-purposed drugs for the treatment of DR-TB in children.

Drug	Dosing Schedule	Remarks
Bedaquiline	Adolescents ≥ 12 year 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
Clofazimine	2–3 mg/kg given daily for a maximum daily dose of 100 mg or every other day in smaller children (gelcaps cannot be split) Duration: entire course of treatment if tolerated	Baseline and monthly ECGs to assess QTc interval

2. Pregnant women

- Bedaquiline is pregnancy category B, meaning it can be used with caution in pregnancy; many other DR-TB drugs are in a lower, or less safe, category than BDQ.
- The injectable agents are contraindicated during pregnancy, thus the use of delamanid or bedaquiline to construct a sufficient DR-TB treatment regimen should be strongly considered for the benefit of the pregnant woman.
- If pregnancy is confirmed in a patient with DR-TB, an individualized regimen should be designed based on DST.
- Clinicians should consult with the TB clinical team for each pregnant patient receiving the shorter regimen or new drugs.
- If a woman falls 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 the patient completed at least four months of intensive phase, they 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.
- Family planning is an essential component of DR-TB management and contraceptive options should be available throughout DR-TB treatment.

3. HIV co-infected patients

- Delamanid is the preferred new drug for patients co-infected with DR-TB and HIV, since there are no significant drug-drug interactions between delamanid and antiretroviral therapy (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 should not be used with any dose of efavirenz (400 mg or 600 mg), as efavirenz (EFV) reduces bedaquiline levels. Patients on a regimen containing EFV will need to be switched to either nevirapine (NVP) or a protease inhibitor (PI) based regimen.
- Patients on ART at the time of DR-TB diagnosis should have a viral load (VL) done if there are no VL results within 3 months of

DR-TB diagnosis. If the VL is undetectable, patients on EFV may be switched to NVP without the initial loading dose. If the VL is detectable (defined as VL > 1000), the patient should undergo adherence counseling and the VL should be repeated following HIV guidelines. If the VL has returned to undetectable, the patient on EFV can be switched to NVP; if the VL remains > 1000, the patient should be switched to a PI regimen containing atazanavir/ritonavir (ATV/r).

- For HIV positive DR-TB patients less than 18 years of age: if the child or adolescent is on a LPV/r based regimen, no change in ART is necessary when starting DR-TB treatment; if the child or adolescent is on EFV, the NNRTI should be switched to LPV/r if < 35 kg, or ATV/r if > 35 kg.
- 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 as soon after two weeks that a patient is tolerating DR-TB treatment.
- ART naïve patients on a bedaquiline containing regimen should start on a NVP based regimen (with a loading dose for the first 14 days); 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 PI regimen with ATV/r.
- ART naïve patients on a delamanid containing regimen may initiate ART with an EFV containing fixed dose combination.
- Currently there is no preventative 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 at the health care facility for two years.

INPATIENT OR OUTPATIENT TREATMENT INITIATION OF SHORTER DR-TB REGIMEN AND NEW DRUGS

A patient-centered community based treatment approach is the preferred method for DR-TB treatment, including DR-TB treatment initiation and follow up for patients receiving the shorter DR-TB regimen or either of the new drugs. 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. Hospitalization of patients starting treatment (or at any time on treatment) should be considered for the following indications:

- The patient is too ill (clinically or psychologically) to commence DR-TB treatment on an ambulatory basis
- DOT and adherence support are not guaranteed
- Implementation of adequate infection control measures are not feasible at home
- Patient monitoring cannot be implemented on an out-patient basis

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
- Adequate infection control measures in the home are ensured
- Adequate nutritional and social patient support is available to the patient
- Measures to ensure full implementation of DOT, adherence support and regular follow up have been put in place (including transport)
- The receiving facility has been oriented and mentored on the patient's management
- At least a three-month supply of DR-TB medications, including drugs for the shorter regimen, should be sent to the receiving facility; the complete six-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, through their drugs ordering system from NatPharm

- Recording forms for treatment adherence and reporting of adverse events, patient information and education materials should also be provided

Promoting adherence to DR-TB treatment

All patients on DR-TB treatment should have a psychosocial 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. 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 the community setting unless a facility based model is more favorable for the patient; this should be adapted to the local context. All DR-TB patients should receive adequate counselling 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 a language preferred by the patient. Patients returning to care after interrupting treatment with the shorter regimen for more than 2 months should be switched to an individualized regimen. During clinic based DOT, patients should take delamanid along with their other oral medications on the day they do not attend clinic. 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.

MONITORING PATIENTS ON THE NEW DRUGS OR SHORTER REGIMEN

The principles of monitoring patients on DR-TB treatment –whether the shorter DR-TB regimen, treatment with bedaquiline or delamanid, or the conventional DR-TB treatment regimen – are the same: all patients with DR-TB need close clinical and laboratory monitoring before and while on treatment (Tables 7 and 8). Common adverse events to the new and re-purposed drugs for DR-TB (bedaquiline, delamanid, linezolid, and clofazimine) are listed in Tables 9 and 10.

- Monitoring response to treatment is done through regular history taking, physical examination, chest radiograph and laboratory monitoring.
- For children, height and weight should be measured monthly to ensure that they are growing normally. For adults, weight should be recorded monthly (height is only recorded at the start of treatment).

- Chest radiographs should be taken at baseline and at least every six months to document progress and to use for comparison if the patient's clinical condition changes.
- The most important evidence of improvement is conversion of the sputum culture to negative.
- A set of laboratory tests should be performed according to schedule (Tables 7 and 8) to identify adverse effects not detected through history and physical exams. Moxifloxacin, clofazimine, and the new drugs bedaquiline and delamanid, may induce QT prolongation, thus monitoring of ECGs is essential and required under this guidance Annexure 1).
- Drug susceptibility testing (DST) should be repeated for patients who remain smear and culture positive or who are suspects for treatment failure.
- In the intensive phase of DR-TB treatment, all treatment should be given under direct observation and DOT providers should be trained on the signs of treatment failure. If longer duration supplies are provided after the intensive phase, treatment supporters should similarly continue to promote good adherence and support the patient to report side effects or challenges with adherence to clinic staff.

Table 7: clinical and bacteriological monitoring of patients on the shorter DR-TB treatment regimen

	BL	Wk2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
Clinical evaluation														
Clinical evaluation	X		X	X	X	X	X	X	X	X	X	X	X	X
Weightº	X		X	X	X	X	X	X	X	X	X	X	X	X
Functional status	X			X				X*			X			X
PNP	X		X	X	X	X	X	X			X			X
Audiometry	X		X			X		X		X				
Vision test**	X		X	X	X	X	X	X			X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BMI	X													
Bacteriological														
Smear/ culture	X		X	X	X	X	X	X	X	X	X	X	X	X
Xpert§	X													
LPA#	X	Repeat if smear or culture positive or presumption of failure												
DST@	X	Repeat if smear or culture positive or presumption of failure												
Laboratory tests														
FBC¶	X													
Cr/ electrolytes	X		X	X	X	X								
K	X		X	X	X	X								
Mg, Ca (if low K)	X		X	X	X	X								
ALT/AST	X		X	X	X	X	X	X						
TSH	X				X			X						
Albumin	X													
HIV rapid test	X													
VL (if on ART)	X													
Fasting glucose	X													
HbSAg	X													
CXR	X							X					X	

ºHeight should be checked at baseline in adults and monthly in children

**Check functional status at month 6 if clinical status has deteriorated*

***Vision test should be emphasized for patients on linezolid and ethambutol*

§Xpert should not be ordered for patients that have started DR-TB treatment

#First and second line LPA should only be tested for patients with RIF resistance on Xpert

¶Additional FBC for patients on linezolid should be ordered if clinically indicated

@DST should be done at baseline for first and second line anti-TB drugs. Repeat DST is indicated for patients who remain culture positive or revert after month four

^Smear and culture should be done every 6 months for two years after completing treatment with the shorter regimen, BDQ, or DLM

Table 8: clinical and bacteriological monitoring of patients on an individualized DR-TB treatment regimen

	BL	Wk2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
Clinical evaluation														
Clinical evaluation	X		X	X	X	X	X	X	X	X	X	X	X	X
Weight$^{\varphi}$	X		X	X	X	X	X	X	X	X	X	X	X	X
Functional status	X			X				X*			X			X
PNP	X		X	X	X	X	X	X			X			X
Audiometry	X		X			X		X		X				
Vision test**	X		X	X	X	X	X	X			X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BMI	X													
Bacteriological														
Smear/ culture	X		X	X	X	X	X	X	X	X	X	X	X	X
Xpert§	X													
LPA#	X	Repeat if smear or culture positive or presumption of failure												
DST@	X	Repeat if smear or culture positive or presumption of failure												
Laboratory tests														
FBC¶	X													
Cr/ electrolytes	X		X	X	X	X								
K	X		X	X	X	X								
Mg, Ca (if low K)	X		X	X	X	X								
ALT/AST	X		X	X	X	X	X	X						
TSH	X				X			X						
Albumin	X													
HIV rapid test	X													
VL (if on ART)	X							X						X
Fasting glucose	X													
HbSAg	X													
CXR	X							X						X

Table 8: clinical and bacteriological monitoring of patients on an individualized DR-TB treatment regimen- continued

	M13	M14	M15	M16	M17	M18	M19	M20
Clinical evaluation								
Clinical evaluation	X	X	X	X	X	X	X	X
Weightº	X	X	X	X	X	X	X	X
Functional status								X
PNP								
Audiometry								
Vision test**			X					
Adverse events	X	X	X	X	X	X	X	X
BMI								
Bacteriological								
Smear/ culture	X	X	X	X	X	X	X	X
Xpert§								
LPA#	Repeat if smear or culture positive or presumption of failure							
DST@	Repeat if smear or culture positive or presumption of failure							
Laboratory tests								
FBC¶								
Cr/ electrolytes								
K								
Mg, Ca (if low K)								
ALT/AST								
TSH								
Albumin								
HIV rapid test								
VL (if on ART)						X		
Fasting glucose								
HbSAg								
CXR						X		

ºHeight should be checked at baseline in adults and monthly in children

**Check functional status at month 6 if clinical status has deteriorated*

***Vision test should be emphasized for patients on linezolid and ethambutol*

§Xpert should not be ordered for patients that have started DR-TB treatment

#First and second line LPA should only be tested for patients with RIF resistance on Xpert

¶Additional FBC for patients on linezolid should be ordered if clinically indicated

@DST should be done at baseline for first and second line anti-TB drugs. Repeat DST is indicated for patients who remain culture positive or revert after month four

^Smear and culture should be done every 6 months for two years after completing treatment with the shorter regimen, BDQ, or DLM

Additional monitoring practice recommendations:

- All baseline and follow-up tests should be recorded in the DR-TB treatment card. A sample monitoring sheet to record all clinical, bacteriological, and lab results as part of the clinical record is shown in Annexure 2.
- Patients should be re-assessed for eligibility to receive new or re-purposed DR-TB drugs after a baseline abnormality (elevated QTc, lab value).
- There should be a clinical follow up for all patients on DR-TB treatment with a doctor at two weeks after treatment initiation, then monthly until treatment completion.
- All patients receiving the shorter DR-TB regimen, BDQ, or DLM should be followed with six monthly smear and culture for two years after completing treatment.
- Checking and repleting serum electrolytes
  - » Serum potassium (K), calcium (Ca), and magnesium (Mg) should be obtained in the event a prolonged QT interval is detected
  - » Abnormal electrolytes are most commonly due to the injectable and should be corrected
  - » Whenever a low potassium is detected, it should trigger urgent management with replacement and repeat K testing to document that serum K is being corrected
  - » If K is found to be low, check Ca and Mg levels if possible and compensate as needed. If unable to check, strongly consider empiric oral replacement doses of Mg and Ca
- Post DR-TB treatment care: all patients completing treatment for DR-TB should have a chest x-ray to determine if long term post-DR-TB pulmonary care is needed. Patients with any disability due to DR-TB disease or DR-TB treatment should receive close follow up and supportive services.

Table 9: adverse events associated with new and re-purposed DR-TB medications

Drug	Moderate to severe adverse events	Mild adverse events
Bedaquiline	• Cardiotoxicity (QTcF prolongation): mean increase 10 ms at 8-24 weeks, then decreases* (Annexure 1) • Hepatotoxicity (increase in ALT/AST)	Nausea, anorexia, arthralgia, headache, increased blood lipase/amylase, rash
Delamanid	• Cardiotoxicity (QTcF prolongation): 6-10 weeks after initiation, stable afterwards	Nausea, vomiting, dizziness, anxiety, paresthesia, itchiness, tremor
Linezolid	• Anemia • Thrombocytopenia • Optic neuropathy	Peripheral neuropathy **avoid linezolid in combination with other serotonergic agents*
Clofazimine	• QTcF prolongation • Skin discoloration (slowly reversible)	

**Patients with a history of severe cardiac disease such as cardiac arrhythmias should not receive bedaquiline*

Table 10: response to adverse events associated with new and re-purposed DR-TB medications based on severity (for prolonged QTcF intervals, see Annexure 1)

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Hepatotoxicity (BDQ, LZD, CFZ)				
Increased ALT/ AST	>1 to <2 times ULN*	>2 to <3 times ULN	>3 to <8 ULN	>8 times ULN
Action	Continue treatment and follow until return to baseline or stabilization of AST/ALT elevation	Continue treatment and follow until return to baseline or stabilization of AST/ALT elevation.	Stop all drugs, measure LFTs weekly; reintroduce drugs after toxicity is resolved	Stop all drugs, consider admission; measure LFTs weekly, reintroduce drugs after toxicity is resolved
Mild baseline elevation of liver enzymes may be due to TB itself *Sequentially reintroduce anti-TB drugs with potential hepatotoxicity every 3-4 days with regular checking of liver enzymes* *Consider suspending the most likely offending drug permanently if it is not essential to the regimen, e.g. PZA*				
Myelosuppression (anemia, thrombocytopenia)				
Anemia	9.5 - 10.5 g/dL	8.0 - 9.4 g/dL	6.5 - 7.9 g/dL	< 6.5 g/dL
Decreased platelets	75,000 – 99,999 /mm^3	50,000 – 74,999 /mm^3	20,000 – 49,999 /mm^3	< 20,000 /mm^3
Action	Monitor carefully, consider dose reduction of Lzd (300mg daily or 600 mg thrice weekly)	Monitor carefully, consider dose reduction of Lzd. Continue at reduced dose when subsided to Grade 1	Stop Lzd immediately, consider transfusion. Restart at reduced dose when subsided to Grade 1	Stop Lzd immediately, transfuse. Restart at reduced dose when subsided to Grade 1
Optic nerve disorder (optic neuritis): LZD, EMB (higher risk in diabetics)				
	Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye; early sign is loss of red-green color distinction, central scotomas	Limiting vision of the affected eye; early sign is loss of red-green color distinction, central scotomas	Blindness in the affected eye Action
Action	Stop Lzd immediately if suspicions of optic neuritis; only re-start if ophthalmologic exam is normal	Stop Lzd immediately if suspicions of optic neuritis; only re-start if ophthalmologic exam is normal	Stop Lzd immediately if suspicions of optic neuritis; only re-start if ophthalmologic exam is normal	Stop Lzd immediately if suspicions of optic neuritis; only re-start if ophthalmologic exam is normal

Peripheral neuropathy: LZD, FQ, Eto, Cs, INH				
	Mild discomfort, no analgesic required	Moderate discomfort; non -narcotic analgesic required and improves symptoms	Severe discomfort; narcotic analgesia required and improves symptoms	Incapacitating or not responsive to narcotic analgesia
Action	May stop Lzd and Cs: if symptoms improve, consider restart of Lzd at a lower dose (300mg daily or 600 mg thrice weekly) Consider discontinuing Cs if not essential	Stop Lzd and Cs: if symptoms improve, consider restart of Lzd at a lower dose (300mg daily or 600 mg thrice weekly) Consider discontinuing Cs if not essential	Stop Lzd and Cs; if symptoms improve, do not reintroduce Lzd but add BDQ or DLM if not in regimen Discontinue Cs if not essential	Same as Grade 3
Amitriptyliine and linezolid should not be used together; carbamazepine is strong CYP3A4 inducer and should not be used with BDQ or DLM				

**ULN = upper limits of normal*

ACTIVE DR-TB DRUG SAFETY MONITORING AND MANAGEMENT (ADSM) FOR NEW DRUGS AND THE SHORTER DR-TB REGIMEN

- Clinical and laboratory monitoring should be done to detect, manage and report suspected or confirmed drug toxicities.
- Serious adverse events (SAEs) should be monitored in a systematic and timely manner; at every encounter with the patient, health workers should ask the patient about clinical symptoms of common adverse events and record them on the patient's DR-TB treatment card.
- Consider additive or potentiating side effects with concomitant therapy, as well as potential drug-drug interactions.
- Ototoxicity (hearing loss) from the injectable agents requires baseline screening audiometry followed by monthly assessments at each scheduled visit.

- There should be clinical follow up with a doctor for all patients at 2 weeks after DR-TB treatment initiation and then monthly until treatment completion. At each visit, a clinical assessment with an evaluation of treatment efficacy and adverse events (AEs) should be conducted and recorded (Figure 9, Annexure 2).
- Management of AEs should take patient safety and treatment need into consideration. For all AEs, re-assurance to enhance adherence is needed. For any AEs that require additional evaluation and/or medical treatment, a treatment decision in consultation with the DOT provider should be made.
- The management of adverse events is based on severity grading:
  - grade 1 (mild) or grade 2 (moderate) – the drug may be continued
  - grade 3 (severe) or grade 4 (life threatening) – the patient should be closely monitored and managed by a doctor. The drug may be discontinued if, in the opinion of the doctor, the AE or lab toxicity poses a significant risk in continuing treatment.
- Additional tests and ancillary medicines for adverse events should be available and accessible, free of charge.
- If drug(s) thought to cause the AE are considered a core drug but need to be removed from the regimen, replacement is required throughout treatment. Replacement of drugs should take the clinical condition and bacteriological status of patients into account. Ensure provision of at least 4 effective second line medicines during the intensive phase and 3 effective drugs during the continuation phase.
- Patients with a serious adverse event to any drug in the shorter DR-TB regimen (aside from isoniazid) should be switched to an individualized regimen after consulting with the regional DR-TB focal person from regional treatment centers.

All Adverse Drug Events should be reported to the National Pharmacovigilance Center (MCAZ) through existing national pharmacovigilance tools

Recording and reporting of adverse events on DR-TB treatment

Adverse events should be reported using the ADR reporting forms shown in Annexure 3. Clinicians can also use the electronic reporting platform that can be found on the Medicines Control Authority of Zimbabwe (MCAZ) website (http://www.mcaz.co.zw/index.php/2016-01-08-06-40-00/e-reporting). Scanned copies of the ADR reporting form can be sent to MCAZ on the following email mcaz@mcaz.co.zw.

INFORMED CONSENT TO DR-TB TREATMENT

A patient centered approach to treatment should be developed for all MDR-TB patients to improve adherence, quality of life and relieve suffering. This approach should be based on the patients' needs and mutual respect between the patient and the provider. Patients should receive full information regarding treatment regimens and new drugs and be given opportunities to ask questions which should be addressed satisfactorily before treatment is commenced. The following guidance should be used:

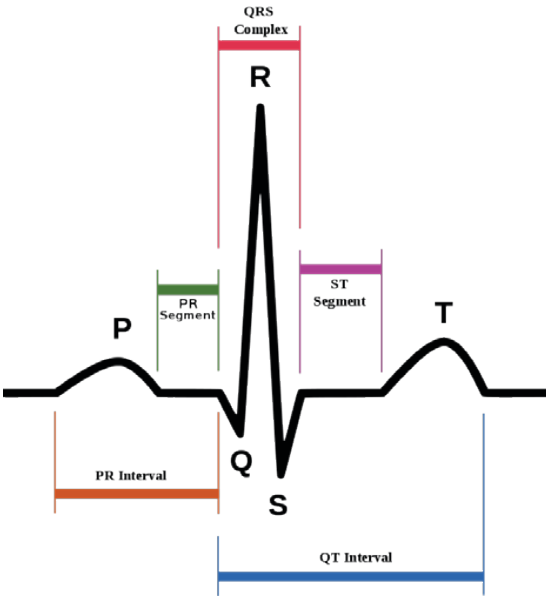
- Inform the patient about the medicines in general terms; i.e. there are at least five or more different anti-TB medicines that the patient will take, with or without an injectable agent. Try to emphasize the names of medicines and show the patient what the pills look like.
- Inform the patient about the length of treatment according to the regimen selected (at least 9 months for the shorter DR-TB regimen and at least 20 months for the individualized regimen).
- Discuss where treatment will start. If at a hospital, estimate the approximate length of (stay) time. If at home, ask about living situation and whether the patient feels that home treatment will be possible.
- Inform the patient about possible side effects (especially those with serious consequences like hearing loss, ringing in the ears, an irregular heartbeat, or suicidal ideation), the importance of reporting these to the health care provider, and the actions to take once detected.
- The impact of bedaquiline on culture conversion and mortality is large enough to outweigh the harms for most patients requiring DR-TB treatment with an individualized regimen.
- Inform the patient about monitoring requirements for smear, culture and laboratory tests for early detection of side effects.

- Inform the patient to visit the health facility at any time during their treatment if the feel they need to see a clinician.
- Inform the patient and/or caregiver on what to do in case of an emergency (like severe shortness of breath, seizure, psychosis)
- Inform the patient and family caregivers on social support and social protection programs that patient is eligible for, including palliative and end of life care as needed.
- Inform the patient about the Patients Right Charter and provide a copy were available. Ensure you emphasize the patient's rights and responsibilities related to treatment as well as the prevention and control of TB.
- Ensure that the patient understands, solicit a verbal consent to treatment from the patient, and document verbal consent clearly in the patient's file.

ANNEXURES

Annex 1: ECG monitoring for patients on bedaquiline or delamanid for DR-TB treatment.

Calculation of the corrected QT interval is best done using the Fridericia formula, as it optimally adjusts for heart rate. A lengthened QT interval is a marker for the potential of ventricular arrhythmias like torsades de pointes and a risk factor for sudden death.



- 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√ 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

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
QTcF prolongation	450 to 480 msec	> 480 to 500 msec	> 500 msec without signs/ symptoms of arrhythmia	QTcF≥ 501 msec or > 60 msec change from baseline and one of the following: torsades de pointes, polymorphic ventricular tachycardia, or signs/ symptoms of serious arrhythmia
Action	Monitor closely, weekly ECG until QTcF < grade 1 or baseline; correct electrolytes as needed	Monitor closely, weekly ECG until QTcF < grade 1 or baseline; correct electrolytes as needed.	Stop the suspected causative drug(s); hospitalize and correct electrolytes as needed	Stop the suspected causative drug(s); hospitalize and correct electrolytes as needed
Cardiac rhythm disturbance	Asymptomatic	Asymptomatic or transient rhythm abnormality, no treatment required	Recurrent, persistent, symptomatic arrhythmia requiring treatment	Unstable dysrhythmia requiring hospitalization and treatment

Annex 2: Sample monitoring sheet for recording laboratory and bacteriologic test results while on DR-TB treatment.

Blood results					Smear microscopy				Culture		
	Date:	Date:	Date:	Date:	Month	Date:	Sample #	Result	Date:	Sample #	Result
WBC					1						
Hb					2						
RBC					3						
Plts					4						
TSH					5						
ALT					6						
AST					7						
albumin					8						
Cr					9						
Na					10						
Mg					11						
Ca					12						
K					13						
Fasting glucose					14						
QTc interval					15						
Audiometry					16						
Pregnancy test					17						
HIV rapid test					18						
CD4 count					19						
Viral load					20						
HBsAg					21						
Adverse event:					22						
					23						
					24						

Annex 3: Adverse drug reaction reporting form (Medicines Control Authority of Zimbabwe).

MCAZ Medicines Control Authority of Zimbabwe

PVF 01

Spontaneous Adverse Drug Reaction (ADR) Report Form						
Identities of Reporter, Patient and Institute will remain confidential						
MCAZ Reference Number (MCAZ use only)						
Patient Details (to allow linkage with other reports)						
Clinic/hospital Name:			**Clinic/Hospital Number**			
Patient Initials:			**VCT/OI/TB Number**			
Date of Birth:			Weight (Kg)	Sex:		
Age:			Height (meters)			
Adverse Reaction						
Date of Onset:						
Duration:	Less than one hour	Hours	Days	Weeks	Months	
Description of ADR						
Serious: Yes ☐ No ☐	Reason for Seriousness	☐ Death	☐ Life-threatening			
		☐ Hospitalization prolonged	☐ Disabling			
		☐ Congenital-anomaly	☐ Other medically important condition			
Relevant Medical History						
Relevant Past Drug Therapy						
Outcome of ADR	Recovered	Not yet recovered	Fatal	Unknown		
Current Medication						
Generic Name	Brand Name	Batch Number	Dose	Indication	Date Started	Date Stopped
Concomitant (Other) drugs taken, including herbal medicines & Dates/period taken:	Name of drug:				Date started	Date stopped
Suspected drug(s), if known:						
Laboratory tests results:						
Reported by						
Forename(s) & Surname:						
Designation:						
Address:						
Signature:		Date:				
Send to: The Director-General, Medicines Control Authority of Zimbabwe, 106 Baines Avenue, P O Box 10559, Harare **Tel**: +263-4-708255 or 792165, **E-mail**: mcaz@mcaz.co.zw, **website**: www.mcaz.co.zw						

NB. This form may be completed for any ADR related to medicines or medical devices
***Please attach any other additional information, including an anonymized picture of the ADR (with patient's consent)**

Rev 6_November 2016 Page 1 of 1