CLINICAL GUIDELINES
FOR THE MANAGEMENT OF

DRUG RESISTANT TUBERCULOSIS

Use of New Drugs and the Shorter Treatment Regimen

Zimbabwe National TB and Leprosy Control Programme
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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 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 complement 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

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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	Aspartate aminotransferase
ATV/r	Atazanavir/ritonavir
BDQ	Bedaquiline
BMI	Body mass index
Ca	Calcium
CFZ	Clofazimine
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 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.

Chapter 1: 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 preferred TB diagnostic test. A chest x-ray should also be performed (especially if the patient presents with a body mass index less than 17 kg/m^2), although health care workers should be aware that obtaining a CXR should not place an 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 one sputum sample collected and sent to the nearest Xpert site. The sample is tested for TB using the Xpert MTB/RIF assay, and if MTB is detected, with rifampicin resistance, the patient is requested to produce an early morning specimen which is forwarded to the reference laboratory for first and second-line LPA testing (Figure 1).

Discordance in laboratory results may occur, 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 within the district TB clinical team. General considerations to evaluate.

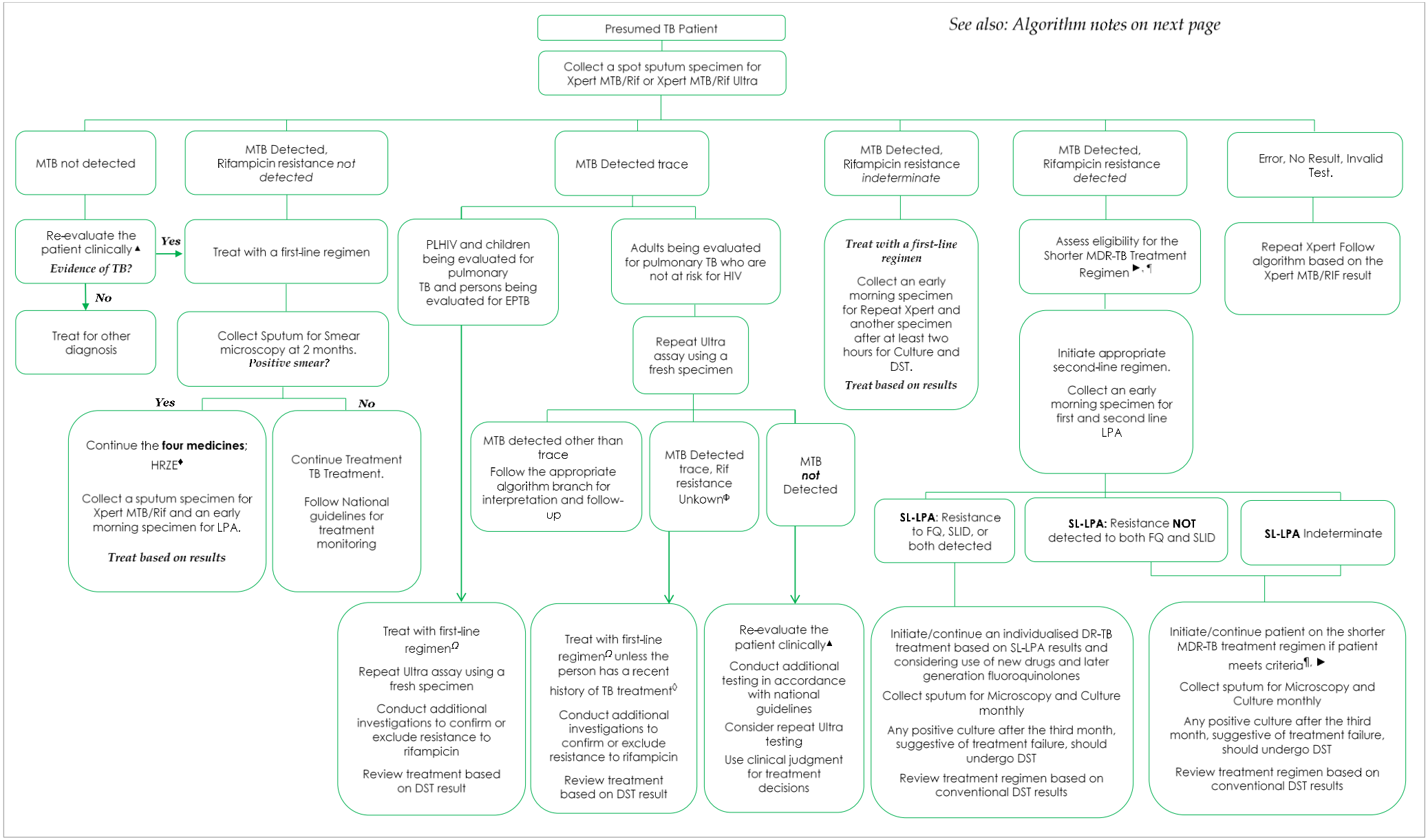
1. Rifampicin resistant on Xpert, culture negative: treat the patient according to the Xpert result and submit another sample for culture. Reasons for negative cultures in persons with pulmonary TB:
    - Patient is being treated for TB
    - Transport or processing problems that inactivated the tubercle 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. Certain mutations are known to generate this discordant result (i.e. a false-susceptible phenotypic result)
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.

Figure 1: Diagnostic and Treatment Algorithm for Presumptive TB Patients



Algorithm Notes

▲ *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/µl or are seriously ill, perform TB-LAM test according to national guidelines.*

◆ *Treatment with the four drugs (HRZE) should be continued for the full duration of treatment unless results of LPA demonstrate susceptibility to isoniazid where the patient will be switched to continuation phase. The period extended on four drugs after the intensive phase, while awaiting LPA results, is considered as part of the continuation phase*

► *Patients may be initiated on the shorter MDR-TB regimen if they are 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.*

¶ *The shorter MDR-TB regimen may be used in MDR-TB patients who do not have the following conditions:* ***i)*** *confirmed resistance, or suspected ineffectiveness, to a SLID or FQ* ***ii)*** *previous exposure for more than one month to a SLID or FQ* ***iii)*** *A contraindication to any medicines in the shorter MDR-TB regimen* ***iv)*** *Pregnancy,* ***v)*** *Close contact with a patient that has resistance to FQ/ SLID*

Φ *MTB detected trace results do not provide any information regarding rifampicin resistance or susceptibility.*

◊ *For adults who successfully completed a course of therapy within the past 2 years (i.e., recent TB treatment), the possibility of both Ultra trace results being false-positive results because of the presence of non-viable bacilli must be considered. Clinical decisions must be made on all available information and clinical judgment.*

Ω *Patients should be initiated on a first-line regimen according to national guidelines with exception of the patient at very high risk of having MDR-TB or if a second Ultra assay indicates rifampicin resistance. Such patients should be initiated on an MDR-TB regimen.*

*****DST****=Drug susceptibility testing;* ***SL-LPA****=Second-line line probe assay;*
FQ*=Fluoroquinolone;* ***SLID****=Second-line injectable drugs;* ***LAM test****=Lipoarabinomannan Test;* ***EPTB****=Extra-pulmonary Tuberculosis;*
PLHIV*=People Living with HIV;*

Chapter 2: 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*

i) Confirmed resistance, or suspected ineffectiveness, to a SLID or FQ

ii) Previous exposure for more than one month to a SLID or FQ

iii) A contraindication to any medicines in the shorter MDR-TB regimen or increased risk of toxicity

iv) Pregnancy

v) Close contact with a patient that has resistance to FQ/ SLID.

** 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 within the TB clinical team. It is suggested that non-severe forms of EPTB such as TB pleural effusion (adults and children) and TB lymphadenitis (children) may be considered 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 months (Km-Mfx^{hd}-Eto-Cfz-H^{hd}-Z-E)

plus

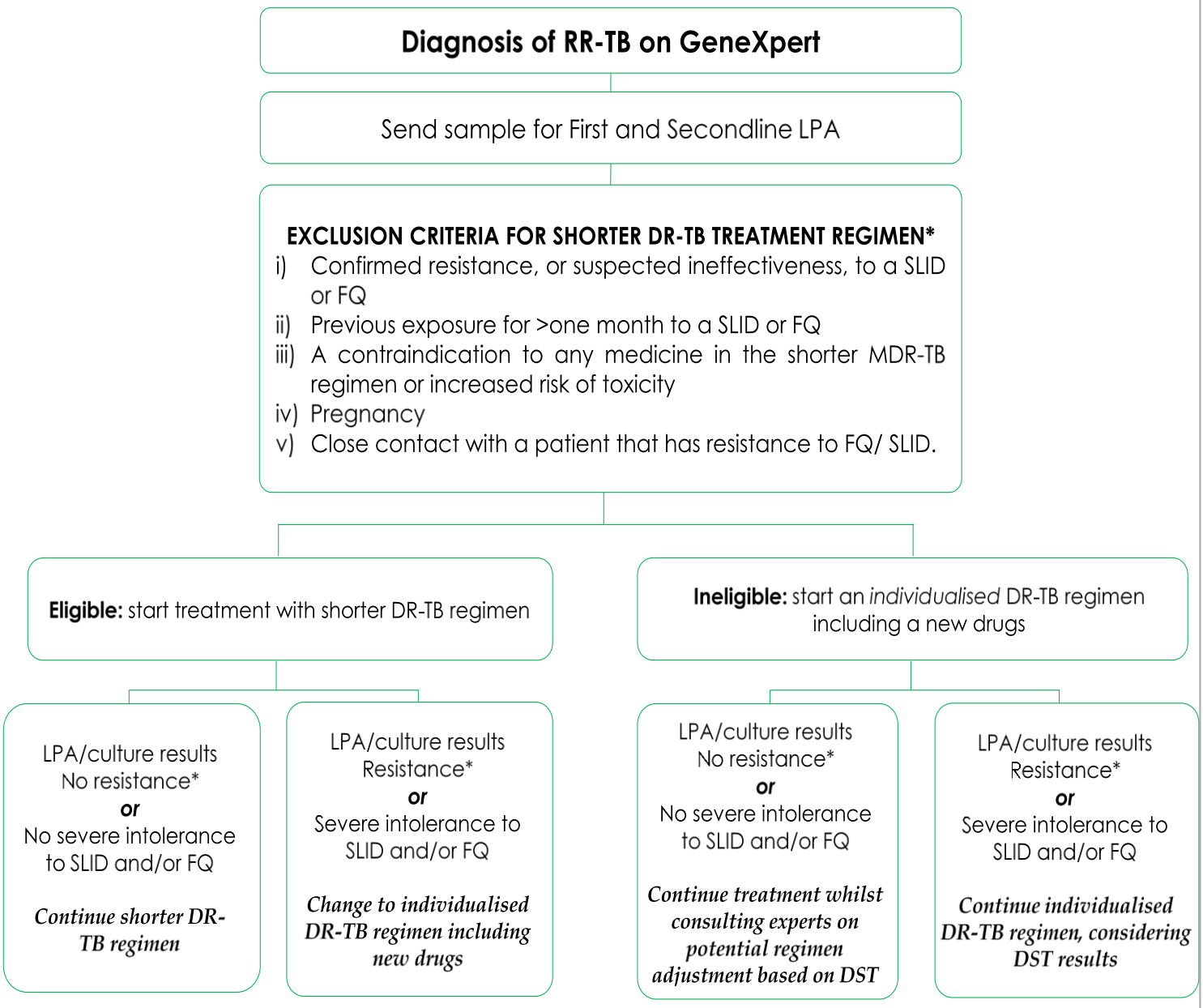
5 months (Mfx^{hd}-Cfz-Z-E)

The number of months before parentheses are the minimum number of months that the intensive 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 there are exclusion criteria.

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.*

- 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 the 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, should 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 a second-line injectable or fluoroquinolone 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.
- The duration of the continuation phase is a minimum of 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.
- All women of childbearing age diagnosed with DR-TB should be counseled on pregnancy prevention during treatment and provided with appropriate contraceptives.

2. Standard XDR-TB Treatment Regimen

- Patients who are considered to be at high risk of XDR TB and are diagnosed of TB should be treated for TB using an empiric regimen that is most closely matches the susceptibility pattern. This includes patients previously treated for MDR TB and contacts to XDR TB cases.
- The standard regimen for XDR TB for Zimbabwe is:

6 months (Cm-LZD-BDQ-Lfx-Cfz-Amx/clv- H^{hd})

plus

12 months (LZD-BDQ-Lfx-Cfz-Amx/clv-H^{hd})

3. Isoniazid (INH) Resistant TB Treatment

- Patients who are confirmed sputum positive at month 2 of TB treatment shall have an Xpert MTB/Rif assay repeated and shall also be investigated by first line LPA if there is no rifampicin resistance detected on Xpert. Should there be underlying rifampicin resistance, patients must be assessed and commenced on a suitable DR-TB treatment regimen and investigated by first and second line LPA.
- If there is no rifampicin resistance, patients continue on the four drug regimen while awaiting LPA results. Patients for whom rifampicin resistance is confirmed should be promptly be switched onto an appropriate second-line regimen.
- If LPA results indicate susceptibility to isoniazid, the patient may then be switched to the continuation phase, where the time extended on the intensive phase pending LPA results is counted as part of the continuation phase.
- Cases where isoniazid mono-resistance is confirmed, however, shall continue on four drugs until the end of treatment. Hence for pulmonary tuberculosis the treatment regimen shall be:

6 months HRZE

4. Individualized DR-TB treatment regimen

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

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 in Table 2, 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 within 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.
- The injectable should be included as part of the individualized regimen, unless there are contraindications and 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, clinical evolution 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 in paediatric patients to prevent neurologic adverse events due to high dose isoniazid.

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

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

- 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 child-bearing 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, 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, 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, INH^{hd}, E.

Bedaquiline and delamanid – special considerations

- Bedaquiline, delamanid, the fluoroquinolones (Mfx more than Lfx), and clofazimine 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.
- 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 bedaquiline 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 has been recommended for patients 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 clofazimine; use delamanid if there is a history of prior clofazimine 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 within the district TB clinical team.
- 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 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.
- 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.

Chapter 3: DR-TB Treatment with the Shorter Regimen and New Drugs: Special Populations

1. Children/adolescents

- Clinicians should consult with the district TB Clinical Team for each paediatric 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.
- 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	46-50 kg	51-55 kg	56-70 kg	>70 kg
Isoniazid*hd*	Daily dose by weight	400 mg			600 mg		
Rifampicin	8-12 mg/kg once daily	300 mg	450 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	
Rifabutin	5-10 mg/kg once daily	300 mg					
Levofloxacin	750-1000 mg once daily	750 mg		1000 mg			
Moxifloxacin*hd*	400- 800 mg daily	600 mg			800mg		
Ethionamide	500-750 mg daily	500 mg		750 mg			1000 mg
Prothionamide	500-750 mg daily	500 mg		750 mg			1000 mg
Cycloserine	500-750 mg daily	500 mg				750 mg	
p-aminosalicylic acid	8 g daily	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 mg daily (2 first months) then reduce to 100 mg daily (alternative dosing 100 mg daily)						
Linezolid	600 mg once daily	600 mg					
Amoxicilin-Clavulanate	Twice daily dosing of the listed doses	*Below 40kg, See* ***Table 5***	1 tablet Amoxicillin-Clavulanate$_{625mg}$ and 3 tablets Amoxicillin$_{500mg}$				

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	56-70 kg	>70 kg
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

The clinician may either use a fraction of a tablet, or part of a suspension made by dissolving whole tablets in water as indicated.

<table>
<tr><th>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>Available Formulations</th><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><3</td><td colspan="5">Consult with a clinician experienced in pediatric MDR-TB prescribing for neonates (<28 days of age) and infants weighing <3kg</td></tr>
<tr><td>3-3.9</td><td rowspan="4">1 tab</td><td rowspan="3">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><td rowspan="4">.5 tab</td></tr>
<tr><td>5-5.9</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></tr>
<tr><td>9-9.9</td></tr>
<tr><td>10-10.9</td><td rowspan="4">1 tab</td></tr>
<tr><td>11-11.9</td></tr>
<tr><td>12-12.9</td><td rowspan="5">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="6">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="5">1.5 tabs</td></tr>
<tr><td>20-20.9</td></tr>
<tr><td>21-21.9</td><td rowspan="6">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)	
Available Formulations	**250mg 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**
<3	Consult with a clinician experienced in pediatric MDR-TB prescribing for neonates (<28 days of age) and infants weighing <3kg						
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><th>Target Dose</th><th colspan="2">PAS
(150-200 mg/kg)</th><th>Eto
(15-20 mg/kg)</th><th>Isoniazid High Dose (15-20 mg/kg)</th></tr>
<tr><th>Available Formulations</th><th>Daily</th><th>Twice Daily</th><th>250 mg tablet</th><th>100 mg tablet</th></tr>
<tr><td><3</td><td colspan="4">Consult with a clinician experienced in pediatric MDR-TB prescribing for neonates (<28 days of age) and infants weighing <3kg</td></tr>
<tr><td>3-3.9</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></tr>
<tr><td>13-13.9</td><td rowspan="3">2500 mg</td><td rowspan="3">1250 mg</td><td rowspan="8">3 tabs</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="9">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="8">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="5">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>

(Courtesy the Sentinel Project, sentinel-project.org)

	Steptomycin	Amikacin	Kanamycin	Capreomycin	Clofazimine (CFZ)	Amoxicillin-clavulanate (A MX-CLV)	Linezolid (LZD)
Daily Dose	20-40 mg/ kg 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.
- 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 and other clinical considerations.
- Clinicians should consult within 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 she has culture converted, the number of months she has been on treatment, and whether she is receiving the injectable and Ethionamide. If culture converted and she has completed at least four months of intensive phase, she can be switched to continuation phase of the shorter regimen; if neither of these criteria are met, she 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

- 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 prior to DR-TB diagnosis. If the VL is suppressed, patients on EFV may be switched to NVP without the initial lead-in period. If the VL is not suppressed (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 second line regimen.

- Since delamanid is metabolized by albumin, patients with low BMIs and/or a low serum albumin should be provided with high protein dietary foods.
- 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, ATV/r if > 35 kg or other alternative regimen following national guidelines.
- 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 lead-in period; once daily doses 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.

Chapter 4: 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 they can be managed on an ambulatory basis
- Adequate infection control measures in the home are ensured
- Adequate nutritional and social 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 medicines 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. The treatment supporter's role is to facilitate the administration of medicines under Directly Observed Treatment, hence they should be someone respected and accepted by the patient. 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. A community health worker should be identified to support the patient for the duration of treatment.

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.

Every effort should be made for patients to get all the important information on DR-TB to prevent treatment interruption. In addition, effort must be made to retrieve back to care patients who have missed doses or clinic appointments.

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 plans so that they obtain 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.

Chapter 5: Monitoring Patients on the New Drugs or Shorter Treatment 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 examination. 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 DR-TB patients◊

	BL	Wk2	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
Clinical evaluation														
Weightº	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Peripheral Neuropathy	X	X	X	X	X	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	And when indicated												
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													
CXRΩ	X							X					X	

◊ *This constitutes the complete monitoring guide for patients on the Shorter Treatment Regimen and the initial monitoring schedule for monitoring patients on individualised regimens. Other post treatment tests to be done as guided in this text*

º *Height 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 two weekly for a month then monthly for two months then 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*

Ω *The interval of performing Chest X-rays is 6 months. However, patients on the shorter treatment regimen get a chest X-ray at 6 months and the end of treatment at 11 months*

Table 8: Monitoring schedule **beyond 12 months;** for patients on an individualized DR-TB treatment regimen

	M13	M14	M15	M16	M17	M18	M19	M20
Clinical evaluation								
Clinical evaluation	X	X	X	X	X	X	X	X
Weight°	X	X	X	X	X	X	X	X
Peripheral Neuropathy	X	X	X	X	X	X	X	X
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		

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 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-up with six monthly smear and culture for two years after completing treatment.
- Checking and replacing 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 2.5 times ULN*	>2.5 to 5 times ULN	>5 to 10 ULN	>10 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 /mm3	50,000 – 74,999 /mm3	20,000 – 49,999 /mm3	< 20,000 /mm3
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*

Chapter 6: 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 clinical assessments at each scheduled visit. Audiometry is recommended as shown in Table 7.
- 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 general 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.

Chapter 7: Patient Counselling DR-TB Treatment

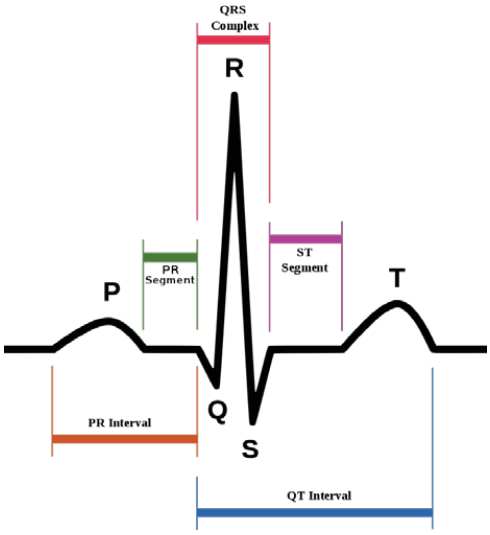
A patient centered approach to treatment should be developed for all MDR-TB patients to improve adherence, quality of life and relieve suffering. This approach should be based on the patients' needs and mutual respect between the patient and the provider. Patients should receive full information regarding 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).
- If treatment will start at a hospital, estimate the approximate length of (stay) time, and if at home, ask about living situation and whether the patient feels that home treatment will be possible.
- Patients should also be informed about the role of a treatment supporter and assisted in making the choice of a suitable treatment supporter. Inform the patient that the community health worker closest to them will support their treatment through directly observed treatment (DOT). Health facility DOT may be chosen if the patient perceives it more convenient than the earlier option. The least preferred option of family member DOT should only be chosen where there difficulties implementing the earlier two models.
- 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.
- 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 they 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.

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 / $\sqrt[3]{RR}$
- 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	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						
PIts					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)**

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