endTB
Clinical and Programmatic Guide for Patient Management with New TB Drugs

Version 3.3

Notice

This guide is designed to give guidance to the endTB Project site on the use of new TB drugs bedaquiline and delamanid. It is intended to be a resource for physicians and other health care professionals involved in the endTB project. Every effort possible has been made to ensure that the material presented here is accurate, reliable, and in accord with current standards. However, as new research and experience expand our knowledge, recommendations for care and treatment change. Furthermore, this guide has not been field tested and is based on limited experience in the use of the new TB drugs. It is therefore the responsibility of the individual physician or other health care professional to use his/her best medical judgment in determining appropriate patient care or treatment.

Your use of this guide is provided on an "as-is" basis without warranty of any kind, and none of the entities listed above represent or warrant that the information contained herein is complete or accurate or free from error. By choosing to use this guide, you acknowledge and agree to the terms of this disclaimer.

Updated versions of this guide will be posted at www.endTB.org. Future versions will also be available in Spanish and Russian.

If reproducing part or all of this guide, please reference with the appropriate version and date:

endTB Clinical and Programmatic Guide for Patient Management with New TB Drugs. The endTB Project Publication. Version 3.3, 23/11/2016.

Table of Contents

Table of tables

Acknowledgements

This guide and endTB are generously supported by UNITAID. UNITAID is a unique funding mechanism engaged in finding new ways to prevent, treat and diagnose HIV/AIDS, tuberculosis and malaria more quickly, more cheaply and more effectively. It takes game-changing ideas and turns them into practical solutions that can help accelerate the end of the three diseases. Website: www.unitaid.eu

Core Writing Team:

KJ Seung

Michael Rich

Francis Varaine

Contributors and Reviewers:

Cathy Hewison

Alex Telnov

Charles Ssonko

Uzma Khan

Nathalie Lachenal

Lorenzo Guglielmetti

List of abbreviations

ACTG	AIDS Clinical Trial Group
AE	Adverse Event
ADL	Activities of daily living
ALT	Alanine aminotransferase
Am	Amikacin
Amx	Amoxicillin
ART	Anti-retroviral therapy
ARV	Anti-retroviral
AST	Aspartate aminotrasnferase
AZT	Zidovudine
Bdq	Bedaquiline
BMI	Body Mass Index
BPNS	Brief Peripheral Neuropathy Screen
Cfx	Clofazimine
Clv	Clavulanate
Cm	Capreomycin
Cln	Cilastatin
CNS	Central Nervous System
Cs	Cycloserine
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
d4T	Stavudine
ddI	Didanosine
DIP	Distal interphalangeal
Dlm	Delamanid
DMID	Division of Microbiology and Infectious Diseases
DR-TB	Drug-resistant Tuberculosis
DST	Drug Susceptibility Testing
E	Ethambutol
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFV	Efavirenz
EMA	European Medicines Agency
endTB	Expand New Drugs for TB
EPO	Erythropoietin
Eto	Ethionamide
FDA	United States Food and Drug Administration
FQ	Fluoroquinolone
GI	Gastrointestinal
H	Isoniazid
HIV	Human Immunodeficiency Virus
Imp	Imipenem
IRD	Interactive Research and Development
Km	Kanamycin
Lfx	Levofloxacin
Lzd	Linezolid
MCV	Mean Corpuscular Volume
MDR	Multidrug-resistance
MDR-TB	Multidrug-resistant Tuberculosis
Mfx	Moxifloxacin
MSF	Médecins Sans Frontières

MTB/RIF	Mycobacterium Tuberculosis/Rifampicin
MWF	Monday-Wednesday-Friday
NCI	National Cancer Institute
NIAID	National Institute of Allergy and infectious Diseases
NTP	National Tuberculosis Program
NVP	Nevirapine
Ofx	Ofloxacin
PAS	Para-Aminosalicylic Acid
PIH	Partners In Health
Pto	Prothionamide
PO	Per os
PV	Pharmacovigilance
QTcF	QT interval Fridericia's correction
S	Streptomycin
SAE	Serious Adverse Event
SL	Second Line
SLD	Second Line Drug
SSRI	Selective Serotonin Re-uptake Inhibitor
TB	Tuberculosis
TDF	Tenofovir
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WHO	World Health Organization
XDR	Extensive Drug Resistance
XDR-TB	Extensively Drug-resistant Tuberculosis
Z	Pyrazinamide

1 Introduction

Recently, two drugs have been granted conditional medical approval by stringent regulatory authorities, bedaquiline by the FDA (2012)[1] and EMA (2013)[2] and delamanid by EMA (2013). To gain full approval, the drug manufacturers will have to perform Phase III trials in the next few years to demonstrate efficacy and safety. In the meantime, because of the serious threat posed by MDR-TB both to the individual patient and to the community, the new TB drugs can be used under defined conditions.

Under the funding mechanism of UNITAID, the endTB Project aims to increase uptake of the new TB drugs through a number of initiatives. A main activity of the project is to place a large cohort of patients across multiple countries on regimens including new TB drugs under close monitoring and pharmacovigilance.

The objective of this guide is to provide guidance to physicians who are managing the care of MDR-TB patients enrolled in endTB. This guide is not meant to replace WHO guidelines or NTP guidelines; it aims at complementing the national guidelines if they have not yet incorporated new TB drugs. Furthermore, the guide is meant to be used as a template and to be adapted by NTPs and projects, as long as the adaptations remain consistent with WHO recommendations.

This guide provides the following instructions to aid the clinician:

- Identifying who needs new TB drugs.
- How to build a MDR regimen with the new TB drugs.
- Implementing close monitoring of patients for response to treatment and for potential adverse events.

The endTB project employs active pharmacovigilance for adverse events, including potential reactions to a new TB drug which are yet to be described, through immediate notification of serious adverse events to central pharmacovigilance unit and quarterly reporting of non-serious adverse events. This guide includes protocols on the grading and management of adverse events. The endTB Pharmacovigilance guideline provides details on pharmacovigilance processes.

Bedaquiline and delamanid are placed in the anti-TB drug Group 5 by the WHO—"Anti-TB drugs with limited data on efficacy and/or long-term safety in the treatment of drug-resistant TB". Because the new TB drugs are the Group 5 drugs with the most evidence of efficacy, they are prioritized when choosing among this group. Other Group 5 drugs also play an important role in building an effective regimen. Therefore, this guide addresses how to use Group 5 drugs as a whole.

All project sites will have access to an endTB Central Medical Committee for advice for difficult cases. Communication is done through the endTB site coordinator.

[1] FDA website [online] Available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ Anti-InfectiveDrugsAdvisoryCommittee/ucm293600.htm

[2] EMA website [Online]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/ medicines/human/medicines/002552/human_med_001699.jsp&mid =WC0b01ac058001d124.

2 Eligibility

2.1 Eligibility criteria for Group 5 drugs

There are two groups of patients eligible for the use of Group 5 drugs under the endTB Project:

1. Patients for whom the construction of a regimen with four likely effective second-line drugs (from Groups 2 to 4) including a fluoroquinolone and an injectable[3] is not possible:
   a. XDR-TB (resistance to a fluoroquinolone and at least one injectable).
   b. Pre-XDR-TB (resistance to a fluoroquinolone or to at least one second-line injectable, but not both).
   c. Patients with two or more Group 4 drugs (Eto/Pto, Cs, PAS) compromised.
   d. Contact with a patient with a strain with resistance pattern of a, b, or c.
   e. Patients unable to tolerate MDR-TB drugs necessary for construction of the regimen (for example, ototoxicity due to an injectable agent).
   f. Patients who are a "failure" of an MDR-TB regimen by WHO 2013 definitions.
2. Other patients who have high risk of unfavorable outcome but do not fit one of the above categories:
   a. Patients with extensive or advanced disease (X-ray demonstrating multiple cavities, bilateral lesions, or extensive parenchymal damage or multiple system involvement).
   b. Patients with increased likelihood of acquisition of additional resistance, treatment failure, or death due to co-morbidities or other conditions (drug contraindication, patients with low body mass index (BMI), HIV, diabetes).
   c. Patients coming from catchment areas that have poor MDR-TB treatment outcomes despite good programmatic conditions (e.g. sites with extensive second-line drug resistance background).

Patients should have a sputum sample collected for second-line DST at the time of starting treatment with new TB drugs. Second-line DST is important because the second-line resistance pattern can affect the design of the treatment regimen.

Of note, based on the above criteria, second-line DST is not a requirement for the use of new drugs. Some patients may be treated with new drugs without second-line DST, based on a clinical history that a regimen with four likely effective drugs including a fluoroquinolone and an injectable is not possible; intolerance to a key second-line anti-TB drug; or have a high risk of unfavorable outcome.

2.2 Group 5 drugs to be used in the endTB project

New drugs:

- Bedaquiline (Bdq)
- Delamanid (Dlm)

Repurposed drugs:

- Linezolid (Lzd)
- Clofazimine (Cfz)

[3] "Injectable" is defined as a second-line injectable drug: kanamycin, amikacin, or capreomycin.

- Imipenem/cilastatin (Imp/Cln) plus amoxicillin/clavulanate (Amx/Clv) (it is recommended to combine a carbapenem (imipenem/cilastatin or meropenem), an antibiotic in the beta-lactam class, with clavulanic acid, a beta-lactamase inhibitor.)
- Some countries will use other Group 5 drugs such as (Amx/Clv, meropenem, high-dose isoniazid or others).

2.3 Cautions and warnings for Group 5 drugs

Table 1 Contraindications for Group 5 drugs

Drug	**Contraindications***	**Remarks/Precautions**
All drugs	Known hypersensitivity to the drug	
Bdq & Dlm	• Baseline ECG demonstrating a QTcF > 500 ms (repeated); or • History of syncopal episodes, ventricular arrhythmias or severe coronary artery disease	Use with caution if QTcF > 450/470 ms in male/female patients. Weekly ECG monitoring and electrolytes testing should be performed.
	Children <18 years	Pharmacokinetics of these drugs have not been studied in children, so the optimal pediatric dose is not known.
	Pregnancy and lactation	No evidence exists of safety in pregnancy in humans and therefore no recommendations can be made. For Dlm, studies in animals have shown reproductive toxicity. Avoid unless absolutely necessary.
Bdq	Severe hepatic failure	Caution in patients with severe hepatic impairment.
Dlm	Serum albumin < 2.8 g/dL	Adverse events may be increased in patients with hypoalbuminemia due to increased bioavailability. Patients with serum albumin < 3.4 g/dl should have weekly ECG monitoring.
Cfz	Pregnancy and lactation	No evidence exists of safety in pregnancy or lactation in humans. Avoid unless absolutely necessary.
Imp/Cln	Patients with central nervous system disorders	Use with caution as carbapenems have been associated with seizures.

*When a contraindication is present, the possible benefits of using Group 5 drug may outweigh the potential risk. All project sites will have access to an endTB Central Medical Committee for case-by-case advice.

Table 2 Additive toxicities with concomitant therapies*

Drugs	**Potential toxicity**
Use of Dlm after Bdq	Given the long half-life of Bdq (5.5 months), a six month washout period of Bdq is recommended before using Dlm.
Use of Bdq after Dlm	Given the short half-life of Dlm (38 hours) a five day washout period of Dlm is recommended before using Bdq.
Concomitant use of Bdq and Dlm	Safety of use together is not established. Until more data is available, no recommendation for or against simultaneous use can be made. Concomitant use of Bdq and Dlm is the responsibility of individual expert clinicians and should only be considered for individual patients with no other therapeutic options, after careful risk-benefit assessments, and under close monitoring.
Drugs that prolong QT interval (Bdq, Dlm, Cfz, Mfx)	Some of the common drugs used in MDR-TB management that can prolong the QT interval include: Mfx, Lfx (to a lesser degree), Cfz and ondansetron. Avoid concomitant use of Bdq or Dlm with Mfx.
Drugs that can cause myelosuppression (Lzd, AZT, cotrimoxazole)	Avoid concomitant use with AZT, which can cause megaloblastic anemia. If AZT must be used, then screen for myelosuppression more frequently.
Drugs that can cause peripheral neuropathy (Lzd, Cs, H, d4T, ddI; less frequently: Eto/Pto, Am, Cm, Km, FQs)	Various TB drugs, especially Lzd and Cs, can cause peripheral neuropathy. Screen for peripheral neuropathy frequently if using Lzd and Cs. Avoid concomitant use of d4T and ddI when possible.
Drugs that can cause CNS toxicity/seizures (Imp, Cs, EFV)	Both Cs and Imp/Cln have been associated with seizures. It is not known if there is additive CNS toxicity when used together. Meropenem is less associated with CNS toxicity.

* All project sites will have access to the endTB Central Medical Committee for case-by-case advice when to clinicians considering using drugs with additive toxicity.

Table 3 Drug-drug interactions

Drugs	Interactions
Use of Bdq with drugs that induce the cytochrome P450	Contraindicated with concomitant administration of strong inducers (rifampicin, phenytoin, carbamazepine, etc.). Strong inducers will significantly decrease blood levels of Bdq and likely reduce the efficacy of Bdq. Avoid with weak inducers because of risk of reduced efficacy.
Use of Dlm with drugs that induce the cytochrome P450	Avoid concomitant administration of strong inducers (e.g. rifamycins, carbamazepine, phenytoin, etc.). Strong inducers will mildly decrease blood levels of Dlm. Use with weak inducers is allowed.
Use of Bdq or Dlm with drugs that inhibit the cytochrome P450 3A4	Avoid concomitant administration with any strong inhibitor (e.g. ritonavir, ketoconazole). Strong inhibitors will increase blood levels of Bdq or Dlm and there is an increased risk of toxicity.
Use of Bdq or Dlm with ARVs	Bdq: Avoid EFV (inducer), protease inhibitors (PIs) and ritonavir (inhibitors). EFV will decrease blood levels of Bdq. PIs will increase blood levels of Bdq. Dlm: Avoid PIs when possible (if a PI is absolutely necessary then Dlm is favored over Bdq). PIs will increase blood levels of Dlm.
Use of Lzd with drugs that increase serotonin levels	Lzd can rarely cause serotonin syndrome in patients taking any drug that increases serotonin levels, including selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants, serotonin 5-HT1 receptor agonists (tryptans), meperidine, bupropion, or buspirone. For most patients, stopping the antidepressant for the time period while administrating linezolid is recommended. In patients with brittle mental illness who cannot stop taking antidepressants safely, the risks and benefits of concomitant use of linezolid and the antidepressant should be weighed carefully."

2.4 Off-label use of new TB drugs

Off-label use is defined as use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labeling. The off-label use of bedaquiline and delamanid that can be presented to the endTB Medical Committee include use of more than 24 weeks, in children, pregnancy, lactation, etc. For the particular case of bedaquiline/delamanid treatment extension, refer to Sections 7.1 and 7.2 for specific guidance.

Though not strictly meeting the definition of “off-label use” it is recommended that the use of both bedaquiline and delamanid together be presented to the endTB Medical Committee. Off-label use should not be done without discussion with the central endTB Medical Committee and approval by national authorities.

3 Regimen design

3.1 Step-by-step directions for regimen design

The design or construction of a regimen with new TB drugs is done according to WHO interim guidelines for bedaquiline (2013) and delamanid (2014). While new WHO recommendations

have been produced in 2016 for drug-resistant TB, those guidelines have not changed the indications or policy for new TB drugs (*WHO treatment guidelines for drug-resistant tuberculosis, 2016 update*).A revised hierarchy of drug grouping used to treat rifampicin-resistant TB is proposed in the 2016 WHO Guidelines (Groups A to D); however, this guide will continue to use the old grouping (Groups 1 to 5) until the WHO is able to revise the interim policy guidelines on the new TB drugs. At this time there is very limited evidence that favors one of the two new TB drugs (bedaquiline and delamanid) over the other. Section 3.2 provides guidance on choosing between bedaquiline and delamanid.

Table 4 Building a MDR-TB regimen with new TB drugs

STEP 1	**Choose an injectable (Group 2)**	
	Choose an injectable based on DST and treatment history. • S is rarely used because of high rates of resistance in patients with MDR-TB. • If the history or DST suggests that resistance exists for both second-line injectable or in case of a serious adverse event (nephrotoxicity or hearing loss) consider not using an injectable. • Duration depends on the number of effective drugs in the regimen. At least 3 effective drugs after culture conversion until the end of treatment is strongly advised. Some patients with highly resistant strains may require an injectable for the entire duration of treatment.	Km, Am, Cm
STEP 2	**Choose a higher generation FQ (Group 3)**	
	Use a later-generation FQ. Avoid Mfx if possible when using Bdq or Dlm. • If only Ofx resistance is documented and there has not been a long history of Lfx use, the use of Lfx can be considered. • If Lfx resistance is likely (previous exposure or documented resistance), the use of Mfx can be considered. • If the history or DST suggests that there is resistance to both Lfx and Mfx, consider not using a FQ.	Lfx, Mfx
STEP 3	**Add Group 4 drugs**	
	Add two or more Group 4 drugs until you have at least 4 second-line anti-TB drugs likely to be effective.Eto/Pto is considered the most effective Group 4 drug. Consider treatment history and side-effect profile. DST is not considered reliable for the drugs in this group.	Eto/Pto, Cs, PAS
STEP 4	**Add Group 1 drugs that may still be effective**	
	Z is routinely added in most regimens.If H DST is unknown or pending, H at normal doses may be added to the regimen until DST results return. E is rarely used because of high rates of resistance among MDR-TB patients.	Z, H
STEP 5	**Add Group 5 drugs**	
	Add Bdq or Dlm and other Group 5 drugs as needed in order to have at least four (preferably five) likely effective second-line drugs: • Bdq or Dlm are usually the first Group 5 drugs of choice. Then add Lzd, Cfz, and Imp/Cln (in that order) so that there are at least four (preferably five) likely effective second-line drugs. • High dose H is never counted as a core drug in the regimen. • The total number of Group 5 drugs is influenced by the number of Group 4 drugs considered effective (See Table 5). **Delamanid can be added in patients with increased risk of unfavorable outcome.**	Bdq, Dlm, Lzd, Cfz, Imp/Cln (plus Amx/Clv) High dose-H, Amx/Clv

Table 5 Choosing Group 5 drugs to include in a regimen based on the number of likely effective Group 4 drugs ǂ

Patient Type	**Resistance pattern**	**Number of likely effective Group 4 drugs in the regimen**			
		All three	**Two**	**One**	**None**
Simple MDR with risk of poor outcome.	MDR where the injectable and FQ are likely effective and there is a high risk of unfavorable outcome.	Dlm	Dlm	Dlm + Lzd	Dlm, Lzd, Cfz
MDR with resistance to injectable	MDR with resistance to at least one injectable, FQ is likely effective	Dlm (or Bdq)	Dlm (or Bdq), Lzd	Dlm (or Bdq), Lzd, Cfz	Dlm (or Bdq), Lzd, Cfz, Imp/Cln
MDR with resistance to FQ	MDR with resistance to FQ, injectable is likely effective	Bdq (or Dlm)*, Lzd	Bdq (or Dlm)*, Lzd	Bdq (or Dlm)*, Lzd, Cfz	Bdq (or Dlm)*, Lzd, Cfz, Imp/Cln
XDR	XDR	Bdq (or Dlm)*, Lzd, Cfz	Bdq (or Dlm)*, Lzd, Cfz	Bdq (or Dlm)*, Lzd, Cfz, Imp/Cln	Bdq (or Dlm)*, Lzd, Cfz, Imp/Cln

ǂ Some of the Group 4 drugs may not be included in a regimen because (1) the drug(s) is likely not effective based on history or DST; and/or (2) severe intolerance to the drug(s).
* See section 3.2 below on guidance on the choice between Bdq and Dlm.

3.2 How to choose between bedaquiline and delamanid

Factors to be taken in consideration when deciding between bedaquiline and delamanid:

1. There is currently more experience with the use of bedaquiline in the treatment of XDR-TB than there is for delamanid.
2. The long half-life of bedaquiline (5 months) poses two kinds of problems:
   a. Delamanid cannot be subsequently used after bedaquiline before a wash out period of 6 months.
   b. Risk of potential monotherapy to bedaquiline when the treatment is stopped.
3. A significantly increased risk of death was observed in the bedaquiline arm of the clinical trial C208.[4]
4. Better safety profile of delamanid.

[4]Diacon AH, Pym A, Grobusch MP, et al.; TMC207-C208 Study Group. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014; 371: 723-32.

5. Delamanid presents less drug-drug interaction with ART and other drugs metabolized by the cytochrome P450 enzymes like CYP3A4.
6. There is potential cross-resistance between clofazimine and bedaquiline.
7. Bedaquiline and delamanid cannot be used in combination.

In programs where both delamanid and bedaquiline are available:

OPTION 1:

1. **Use delamanid for:**
   a. Any patient requiring Group 5 drugs and who has been previously exposed to clofazimine for more than two months.
   b. Patients whose strains are susceptible to fluoroquinolones but for whom the construction of a regimen with four likely effective drugs including an injectable is not possible:
      i. Patients with resistance to at least one injectable (and susceptible to fluoroquinolones).
      ii. Patients with two or more Group 4 drugs (Eto/Pto, Cs, PAS) compromised.
      iii. Contact with a patient meeting criteria (i) or (ii).
   c. Other patients who have high risk of unfavorable outcome:
      i. Patients with extensive lesions.
      ii. Patients with increased likelihood of acquisition of additional resistance, treatment failure, or death.
      iii. All MDR-TB patients coming from catchment areas that have poor MDR-TB treatment outcomes despite good programmatic conditions.
2. **Use bedaquiline in FQ resistance and XDR-TB:**
   a. Patients with resistance to fluoroquinolones (including XDR-TB)
   b. Contact with a patient with resistance to fluoroquinolones.
   c. Patients who are "failure" of an MDR-TB regimen by 2013 definitions.

OPTION 2: Use delamanid first (except if otherwise contraindicated) in all eligible patients for a new TB drug, given the safety profile, shorter half-life and lower drug-drug interaction. For patients that fail a regimen with delamanid, design the new regimen with bedaquiline.

Because of more experience with bedaquiline and excellent results published in FQ resistance and XDR-TB,[5] these guidelines favor Option 1.

In programs where only bedaquiline is available, use bedaquiline for:

- Patients with resistance to fluoroquinolones (including XDR-TB).
- Patients with resistance or intolerance to at least one injectable.
- Patients with two or more Group 4 drugs (Eto/Pto, Cs, PAS) compromised.

[5] Guglielmetti L, Le Dû D, Jachym M, et al.; MDR-TB Management Group of the French National Reference Center for Mycobacteria and the Physicians of the French MDR-TB Cohort. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. *Clin Infect Dis* 2015; 60(2): 188-94.

- Contact to a patient with a strain with resistance pattern of a, b, or c.
- Patients unable to tolerate MDR-TB drugs necessary for construction of the regimen.
- Patients who are a "failure" of an MDR-TB regimen by 2013 definitions.

Table 6 Examples of possible regimens

Patient type	**Typical MDR Regimen*** **plusGroup 5 drugs**	**Examples**** ǂ
Patient is very sick in severe condition or with extensive lung damage but has never been treated for MDR-TB before ("Simple MDR"; SLD resistance is unlikely).	Typical MDR Regimen + Dlm	Km-Lfx-Pto-Cs-PAS-Dlm-Z (PAS should be included even if it is not in the standard MDR regimen)
Patients coming from catchment areas that have poor MDR-TB treatment outcomes despite good programmatic conditions (e.g. sites with extensive second-line drug resistance background).	Typical MDR Regimen + Dlm	Km(or Cm)-Lfx-Pto-Cs-PAS-Dlm-Z
Patient has resistance to injectables on DST.	Typical MDR Regimen + Dlm	(Cm)-Lfx-Pto-Cs-PAS-Dlm-Z
Patient has FQ resistance on DST.	Typical MDR Regimen +/- Lfx + Bdq + Lzd	Km-(Lfx)*-Pto-Cs-PAS-Bdq-Lzd-Z
Patient does not have any SLD resistance, but cannot tolerate any injectable because of ototoxicity.	Typical MDR Regimen with no injectable + Dlm	Lfx-Pto-Cs-PAS-Dlm-Z (+/-Lzd) (for patients that are still smear or culture positive, consider adding Lzd)
Documented XDR-TB or Patient failed treatment with typical MDR regimen and likely has resistance to injectables and the fluoroquinolones ("probable XDR").	Any Group 1-4 drugs thought to still be effective plus three to four Group 5 drugs	Any Group 1-4 drugs thought to be still effective + Bdq, Lzd, Cfz; if no Group 1-4 are thought to be effective consider adding an additional Group 5 drug such as Imp/Cln

* "Typical MDR Regimen" means the 2011 WHO-recommended MDR regimen which is typically composed of at least pyrazinamide and four second-line Group 2 to 4 drugs considered to be effective (based on DST, previous use and drug resistance surveillance data): a fluoroquinolone (preferably later-generation), a second-line injectable, and two bacteriostatic drugs, preferably prothionamide or ethionamide plus cycloserine or *p*-aminosalicylic acid.

** Examples are given as illustrations. Always refer to "how to build a regimen" principles in Table 4 and Table 5.

ǂ Drugs in parentheses are added depending on "how to build a regimen" principles.

Table 7 Dosing of Group 5 drugs

Drug	**Suggested dosing***	**Remarks**
Bdq (100 mg tablets)	400 mg once daily for 2 weeks, then 200 mg 3 times per week for 22 weeks	• Minimum 48 hours between doses after the first 2 weeks. • Treatment can be extended beyond 24 weeks in case of slow culture conversion or to ensure at least 3 effective drugs in the continuation phase. Sections 7.1 and 7.2 provide guidance with regard to pre-requisites and criteria for Bdq treatment extension. It is recommended to present these cases to the endTB Medical Committee. • Safety, dosing and efficacy has not been established in patients under 18 years of age (see Section 2.4 for off-label use).
Dlm (50 mg tablets)	100 mg twice daily (200 mg total daily dose) for 24 weeks	• 7 days per week for 24 weeks. • Treatment can be extended beyond 24 weeks in case of slow culture conversion or to ensure at least 3 effective drugs in the continuation phase. Sections 7.1 and 7.2 provide guidance with regard to pre-requisites and criteria for Dlm treatment extension. It is recommended to present these cases to the endTB Medical Committee. • When indicated, the use of delamanid is permitted in children > 6 years of age and > 20 kg of weight. The recommended dosage in patients weighing >20 and <35kg is 50 mg twice daily (100 mg total daily dose). • Safety, dosing and efficacy has not been established in patients under 6 years of age or < 20 kg of weight (see Section 2.4 for off-label use).
Lzd (600 mg tablets)	600 mg once daily for duration of treatment + pyridoxine 50mg daily	• All patients taking Lzd should receive pyridoxine at least 50 mg daily for prevention of myelosuppression. • Alternative dosing regimens for patients with adverse effects: 600 mg thrice weekly (MWF), or 300 mg daily.
Cfz (50, 100 mg tablets)	200 mg once daily for 2 months, followed by 100 mg daily for duration of treatment	

Imp/Cln** (one vial has Imp 500 mg and Cln 500 mg)	1 g twice daily: two vials administered as a 40-60 minute infusion twice daily (total of four vials daily)	• 7 days per week during hospitalization, 6 days per week during the ambulatory phase • Minimum of 10 hours between infusions • The first dose always in health care setting supplied with anti-shock kit. • Meropenem can be used instead of Imp/Cln but requires 3 injections per day. • May also administer Amx/Clv if clavulanic acid is desired (see below). • Duration depends on the number of effective drugs in the regimen. At least 3 effective drugs after culture conversion until the end of treatment is strongly advised. Some patients with highly resistant strains may require Imp/Cln for the entire duration of treatment.
Amx/Clv 875/125 tablets or 1000/200 powder for injection	If dosing as adjunctive therapy with a carbapenem: • Dose based on the clavulanic acid component, 125 mg 60 minutes orally before the IV infusion of the carbapenem. • Or 200 mg IV 30 minutes before the IV infusion of the carbapenem. If dosing as a Group 5 drug in the regimen without a carbapenem, dose based on the amoxicillin component (max daily dose is 3000 mg): • **Adults and children:** 80 mg/kg/day in 2 divided doses.	• Amx/Clv is often added when a carbapenem is being used. • A carbapenem is the preferred beta-lactam antibiotic when one is indicated; however, if a carbapenem is not available, some programs may choose to use Amx/Clv instead.

* All durations are the full length of the MDR-TB treatment unless otherwise noted.

** Patients on Imp/Cln require long-term access to central veins because of twice daily IV injections. Implantable access systems such as "Port-a-cath" are the preferred option: While not required to receive imipenem, the placement of a Port-a-cath makes long-term injection of imipenem more convenient, more hygienic, and less damaging to peripheral veins than relying on repeated twice-daily injections of imipenem. Port-a-cath insertion is a minor surgical procedure that needs 30 min to 1 hour. Stitches are removed on post-operative day 7-10. Typically the delivery of fluids and medications is done through a special non-coring needle inserted through the skin and changed once per week, ideally taken out on Saturday evening and replaced on Monday morning so that the patient can have a day without the needle (to have a shower and wash hair as the site is not supposed to get wet when the needle is inserted).

4 Patient consent

4.1 Patient consent

After providing the patient education material to the patient, consent in patients starting new TB drugs must be obtained. The consent process will ensure the patient is:

- Aware of the novel nature of the new TB drug;
- Appreciates the reason why the drug is being proposed to be included in their treatment regimen;
- Recognizes the possible benefits and potential harms, including the uncertainty that surrounds outcomes.

In the case of bedaquiline, the informed consent will be documented with a signature of the patient. In the case of delamanid, the informed consent will be documented with a signature from the patient (or if allowed by local standards patient consent can be verbal).

For patients considered minor or incapacitated by national law, consent from the legal representative is additionally required.

4.2 Example of medication guide and patient consent for the clinical use of bedaquiline and delamanid

Below are examples a medication guide and consent for bedaquiline and delamanid. All patients should be informed of the risks and benefits of the new TB drugs before treatment. Patients should not be coerced into taking the new TB drugs. The information in the examples below should be provided to the patient in a one-on-one setting. If the patient is illiterate all parts of the medication guide should be read and explained to the patient. The patient should be given the opportunity to ask questions and take adequate time before making a decision on whether or not to consent to treatment with new TB drugs.

MEDICATION GUIDE AND CONSENT FOR BEDAQUILINE

What is the most important information I should know about bedaquiline?

Bedaquiline is a drug used to treat multidrug-resistant tuberculosis (MDR-TB) lungs in people with limited treatment options. MDR-TB is a serious disease that can result in death, and for which there are few treatment choices.

It is important to complete the full course of treatment of bedaquiline and your other TB medicines and not skip doses. Skipping doses may decrease the effectiveness of the treatment and increase the likelihood that your TB disease will not be treatable by bedaquiline or other medicines.

It is not known if bedaquiline is safe in:

- Children under 18 years
- In pregnancy
- In forms of TB that is not drug-resistant or not in the lungs.
- In patients with heart, kidney, liver or other health problems.

Before you take bedaquiline, tell your healthcare provider if:

- You have had an abnormal heart rhythm or other heart problems.
- Anyone in your family has or has had a heart problem called congenital long QT syndrome.
- You have liver or kidney problems or any other medical conditions, including HIV infection.
- You are pregnant or plan to become pregnant. It is not known if bedaquiline will harm your unborn baby.
- You are breastfeeding or plan to breastfeed. It is not known if bedaquiline passes into breast milk. You and your healthcare provider should decide if you will take bedaquiline or breastfeed.
- You are taking any prescription and nonprescription medicines, vitamins and herbal supplements.

How should I take bedaquiline?

- Bedaquiline must always be taken with other medicines to treat TB. Your healthcare provider will decide which other medicines you should take with bedaquiline.
- Always take bedaquiline with a light meal (not heavy in fat).
- Swallow the tablets whole with water.
- Take bedaquiline for a total of 24 weeks (6 months).
  - **Week 1 and Week 2:** Take 400 mg (4 tablets) once a day, 7 days a week.
  - **Week 3 to Week 24: T**ake 200 mg (2 tablets) thrice a week. For example, you may take bedaquiline on Monday, Wednesday and Friday of every week.
- You will need to take your other TB medicines for longer than 24 weeks, and at least for 20 months in total (the injectable drug is usually given for up to 8 months).
- Your treatment will be provided under directly observed treatment (DOT), with a patient-centred approach, which means that a healthcare provider will accompany you during the treatment.
- Do not skip bedaquiline doses. If you skip doses, or do not complete the total 24 weeks of bedaquiline your treatment may not work as well and your TB may be harder to treat.
- If for some reason you miss a dose, inform the person responsible for your treatment right away, they will tell you what to do.

What should I avoid while taking bedaquiline?

- You should not drink alcohol while taking bedaquiline.

What are the possible side effects of bedaquiline?

- Serious heart rhythm changes. Tell your health-care provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you faint. Your heart will be monitored periodically with a machine that checks that the heart rhythm is normal.
- Liver problems (hepatotoxicity). Liver toxicity can present in many ways. Tell your doctor of symptoms such as nausea or vomiting, stomach pain, fever, weakness, itching, unusual tiredness, loss of appetite, light coloured bowels, dark colored urine, yellowing of your skin or yellowing of the white of your eyes.
- Other side effects of bedaquiline include nausea, joint pain, headache, an abnormal laboratory test associated with damage to the pancreas, coughing up blood, chest pain, loss of appetite, and/or rash.

It is possible that it may also cause some problems that we are not aware of. However, you will be followed closely for any unwanted effects or any problems. Other medicines to decrease the symptoms of the side effects or reactions may also be given.

Always tell your health-care provider of any side effects or problems you are having.

Sometimes because of side effects bedaquiline or other drugs may need to be stopped.

What monitoring tests do I need while on bedaquiline?

- You will need the same monitoring test that all patients on MDR-TB treatment need. In addition, you will need heart monitoring, extra blood tests for the liver and your electrolytes. Talk to your health-care provider on the schedule of all your monitoring tests and regular doctor visits.

General information about the risks versus the benefits of taking bedaquiline

- RISK: It is possible that you will be at greater risk than you would otherwise be of certain side effects due to the drug. It is possible that a side effect could be serious and even result in death.
- BENEFIT: There is a greater chance that you will be cured of tuberculosis than if you did not take the medicine. You will possibly also become better very much sooner than if you only took the standard medicines for treatment of resistant TB. Also, it is less likely that the drugs you are taking will develop resistance if you are taking bedaquiline.

Confidentiality and sharing information

- Because bedaquiline is a new drug for which we have limited experience we are collecting information on patients taking them.
- The information that we collect from you will be kept confidential and no one but the clinical staff will be able to see your medical information.
- Any information collected to help us better use the drug in patients will be unlinked to your name (made anonymous) before we share or analyse it.

Right to refuse or withdraw

- You do not have to agree to take bedaquiline if you do not wish to do so, and refusing to accept the drug as part of your treatment schedule will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic.
- If you agree to take bedaquiline, you may also at any point after you start wish to stop without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way.

Contact person

If you have any questions, you may contact any of the following persons:

Name_____. Title_____. Phone_____

Name_____. Title_____. Phone_____

Name_____. Title_____. Phone_____

Name of responsible physician: _____

Name of clinic/hospital/institution _____

TREATMENT CONSENT

Statement from the patient:

I have read the provided Medication Guide, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent to receive bedaquiline for treating the drug-resistant tuberculosis disease that I am suffering from.

Print Name of Patient: _____

Signature of Patient: _____

Date: _____ (Day/month/year)

If illiterate, a literate witness must sign. (If possible, this person should be selected by the participant and should have no connection to the care providers). Patients who are illiterate should include their thumbprint.

Statement from the witness:

I have witnessed the accurate reading of the consent form to the potential recipient of bedaquiline, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness: _____ AND Thumbprint of patient

Signature of witness: _____

Date: _____ (Day/month/year)

Statement from the person taking consent:

I confirm that the participant was given an opportunity to ask questions about the treatment, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this informed consent form has been provided to the participant.

Print name of person taking the consent: _____

Signature of person taking the consent: _____

Date: _____ (Day/month/year)

MEDICATION GUIDE AND CONSENT FOR DELAMANID

What is the most important information I should know about delamanid?

Delamanid is a drug used to treat multidrug-resistant tuberculosis (MDR-TB) lungs in people with limited treatment options. MDR-TB is a serious disease that can result in death, and for which there are few treatment choices.

It is important to complete the full course of treatment of delamanid and your other TB medicines and not skip doses. Skipping doses may decrease the effectiveness of the treatment and increase the likelihood that your TB disease will not be treatable by delamanid or other medicines.

It is not known if delamanid is safe in:

- Children under 18 years
- In pregnancy
- In forms of TB that is not drug-resistant or not in the lungs.
- In patients with heart, kidney, liver or other health problems.

Before you take delamanid, tell your healthcare provider if:

- You have had an abnormal heart rhythm or other heart problems.
- Anyone in your family has or has had a heart problem called congenital long QT syndrome.
- You have liver or kidney problems or any other medical conditions, including HIV infection.
- You are pregnant or plan to become pregnant. It is not known if delamanid will harm your unborn baby.
- You are breastfeeding or plan to breastfeed. It is not known if delamanid passes into breast milk. You and your healthcare provider should decide if you will take delamanid or breastfeed.
- You are taking any prescription and nonprescription medicines, vitamins and herbal supplements.

How should I take delamanid?

- Delamanid must always be taken with other medicines to treat TB. Your healthcare provider will decide which other medicines you should take with delamanid.
- Always take delamanid with a light meal (not heavy in fat).
- Swallow the tablets whole with water.
- Take delamanid for a total of 24 weeks (6 months).
    - **Take 100 mg (2 tablets) early in the morning and again 100 mg (2 tablets) in the evening, every day of the week.**
- You will need to take your other TB medicines for longer than 24 weeks, and at least for 20 months in total (the injectable drug is usually given for up to 8 months).
- Your treatment will be provided under directly observed treatment (DOT), with a patient-centred approach, which means that a healthcare provider will accompany you during the treatment.
- Do not skip delamanid doses. If you skip doses, or do not complete the total 24 weeks of delamanid your treatment may not work as well and your TB may be harder to treat.
- If for some reason you miss a dose, inform the person responsible for your treatment right away, they will tell you what to do.

What should I avoid while taking delamanid?

- You should not drink alcohol while taking delamanid.

What are the possible side effects of delamanid?

- Serious heart rhythm changes. Tell your health-care provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you faint. Your heart will be monitored periodically with a machine that checks that the heart rhythm is normal.
- Other side effects of delamanid include nausea, vomiting, and dizziness. Other important adverse drug reactions are anxiety, paraesthesia, and tremor. Tell your doctor of symptoms such as nausea or vomiting, dizziness, anxiety, itching, or tremor.

It is possible that it may also cause some problems that we are not aware of. However, you will be followed closely for any unwanted effects or any problems. Other medicines to decrease the symptoms of the side effects or reactions may also be given.

Always tell your health-care provider of any side effects or problems you are having.

Sometimes because of side effects delamanid or other drugs may need to be stopped.

What monitoring tests do I need while on delamanid?

- You will need the same monitoring test that all patients on MDR-TB treatment need. In addition, you will need heart monitoring, extra blood tests for the liver and your electrolytes. Talk to your health-care provider on the schedule of all your monitoring tests and regular doctor visits.

General information about the risks versus the benefits of taking delamanid

- RISK: It is possible that you will be at greater risk than you would otherwise be of certain side effects due to the drug. It is possible that a side effect could be serious and even result in death.
- BENEFIT: There is a greater chance that you will be cured of tuberculosis than if you did not take the medicine. You will possibly also become better very much sooner than if you only took the standard medicines for treatment of resistant TB. Also, it is less likely that the drugs you are taking will develop resistance if you are taking delamanid.

Confidentiality and sharing information

- Because delamanid is a new drug for which we have limited experience we are collecting information on patients taking them.
- The information that we collect from you will be kept confidential and no one but the clinical staff will be able to see your medical information.
- Any information collected to help us better use the drug in patients will be unlinked to your name (made anonymous) before we share or analyse it.

Right to refuse or withdraw

- You do not have to agree to take delamanid if you do not wish to do so, and refusing to accept the drug as part of your treatment schedule will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic.
- If you agree to take delamanid, you may also at any point after you start wish to stop without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way.

Contact person

If you have any questions, you may contact any of the following persons:

Name_____. Title_____. Phone_____

Name_____. Title_____. Phone_____

Name_____. Title_____. Phone_____

Name of responsible physician: _____

Name of clinic/hospital/institution _____

TREATMENT CONSENT

Statement from the patient:

I have read the provided Medication Guide, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent to receive delamanid for treating the drug-resistant tuberculosis disease that I am suffering from.

Print Name of Patient: _____

Signature of Patient: _____

Date: _____ (Day/month/year)

If illiterate, a literate witness must sign. (If possible, this person should be selected by the participant and should have no connection to the care providers). Patients who are illiterate should include their thumbprint.

Statement from the witness:

I have witnessed the accurate reading of the consent form to the potential recipient of delamanid, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness: _____ AND Thumbprint of patient

Signature of witness: _____

Date: _____ (Day/month/year)

Statement from the person taking consent:

I confirm that the participant was given an opportunity to ask questions about the treatment, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this informed consent form has been provided to the participant.

Print name of person taking the consent: _____

Signature of person taking the consent: _____

Date: _____ (Day/month/year)

5 Monitoring schedule

5.1 Monitoring schedule for patient follow-up

Patient should undergo appropriate follow-up at baseline, during and after treatment, including clinical evaluation, bacteriological and laboratory testing as described in Table 8. The baseline visit refers to the beginning of the treatment with new TB drugs: this can occur at any moment during the treatment course of drug-resistant TB. The monitoring schedule should be applied to patients receiving any treatment regimen containing new TB drugs, regardless of the composition of the regimen.

Additional remarks:

- The laboratory and ECG follow-up should be continued at monthly intervals for all the duration of treatment with bedaquiline and/or delamanid (i.e. for longer than 6 months in case of treatment prolongation beyond 24 weeks)
- More frequent monitoring may be advisable in specific categories of patients, including elderly people, patients infected with HIV, affected by HBV- or HCV-related hepatitis, diabetes mellitus, with moderate to severe hepatic or renal impairment, or receiving specific drug combinations (i.e. bedaquiline and delamanid)
- In case of electrolyte disturbances, more frequent monitoring should be performed as described in the chapter on clinical management of adverse events of interest (Chapter 6.3.8)
- More frequent albumin dosing (i.e. monthly) may be indicated during treatment with delamanid in specific cases, i.e. in patients with Grade 2 or worse Hypoalbuminemia (<30 g/L) at baseline, or in patients experiencing QT interval prolongation as described in Chapter 6.3.3
- If sputum culture positive at Month 4 of treatment, baseline and Month 4 respiratory specimens should be sent to the Supranational Reference Laboratory to perform comprehensive first- and second-line DST(if possible).

Table 8 Monitoring schedule

	Baseline Visit	Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	While on injectable*	Until end of treatment	End of treatment	Post-treatment month 6
Clinical evaluation												
Vital signs	X		X	X	X	X	X	X	Monthly			
Functional status	X			X							X	
Brief peripheral neuropathy screen	X		X	X	X	X	X	X	Monthly		X	X
Audiometry	X		X	X	X	X	X	X	Monthly		X	
Visual acuity and colorblindness screen	X		X	X	X	X	X	X	Monthly		X	X
Outcome consultation											X	X
Assessment and follow-up of adverse events[6]	X	X	X	X	X	X	X	X	At each scheduled /unscheduled visit		X	X
Weight	X	X	X	X	X	X	X	X	Monthly		X	
Bacteriological testing												
Smear	X		X	X	X	X	X	X	Monthly		X	X
Culture	X		X	X	X	X	X	X	Monthly		X	X
Xpert MTB/RIF	X											
Hain GenoType MTBDRsl (some sites)	X			If smear- or culture-positive								
Culture-based first-line DST	X			If smear- or culture-positive								
Culture-based second-line DST (some sites)	X			If smear- or culture-positive								

[6]Referto section 6.

* Injectable = kanamycin, amikacin, or capreomycin.

	Baseline Visit	Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	While on injectable*	Until end of treatment	End of treatment	Post-treatment month 6
Laboratory testing												
ECG	X	X	X	X	X	X	X	X			X	X
Full Blood Count	X	X	X	X	X	X	X	X	Monthly		X	
Urea, creatinine	X		X	X	X	X	X	X	Monthly		X	
Serum electrolytes (potassium)	X		X	X	X	X	X	X	Monthly		X	
Liver function tests (AST, ALT)	X		X	X	X	X	X	X	Monthly		X	
TSH	X				X				every 3 months			
Serum albumin	X											
Hepatitis Bs Antigen	X											
Hepatitis C Antibody	X											
HbA1c (repeated every 3 months if elevated)	X											
Pregnancy test	X											
HIV serostatus	X											
CD4 (repeated every 6 months if HIV+)	X											
HIV VL (repeated every 6 months if HIV+)	X											
Chest X-Ray	X							X			X	

6 Drug safety

6.1 Scope of safety data collection and definitions

Pharmacovigilance is in place to ensure timely detection and proper transmission of information relating to drug safety, especially adverse events.

An adverse event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to this medicinal product.

All patients, irrespectively from treatment allocation, are monitored and assessed clinically for AEs (including lab abnormalities) at all visits during treatment (see also visit schedule in section 5). Systematic symptomatic screening and referral for potential AEs is a mandatory part of scheduled and unscheduled visits. In addition, the evolution and outcome of the previously recorded AEs should be systematically assessed.

Laboratory screening for hematologic and biochemical abnormalities and ECG for monitoring of the QT length are conducted at specific visits during treatment (see also visit schedule in section 5).

Safety data collection starts at time of first MDR TB treatment administration in the frame of the endTB program. Each AE is followed-up until resolution or stabilization.[7]

Safety data collection in the frame of endTB is limited to the following elements:

- **AEs of clinical significance, including:**
    - **Serious Adverse Events (SAEs)** defined as any untoward medical occurrence that, at any dose:
        - Results in death,
        - Requires hospitalization or prolongation of hospitalization,
        - Results in persistent or significant disability/incapacity,
        - Is life-threatening; life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe,
        - Is a congenital anomaly or a birth defect,
        - Is otherwise medically significant; Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Suspected transmission of an infectious agent (e.g. pathogenic or non-pathogenic) via drug is always considered an SAE.

[7]Resolution, return to pre-treatment status; stabilization, no further deterioration or improvement expected.

- **AEs of interest**, defined as all AEs regardless of their seriousness, severity or causal relationship to the MDR TB treatment, pertaining to the following medical conditions:
  - Peripheral neuropathy,
  - Myelosuppression (anemia, thrombocytopenia, or neutropenia),
  - Prolonged QT interval,
  - Optic nerve disorder (optic neuritis),
  - Hepatitis,
  - Hearing impaired,
  - Acute kidney injury,
  - Hypokalemia, and
  - Hypothyroidism.

- **Adverse events leading to treatment discontinuation or change in drug dosage**, defined as all AEs regardless of their seriousness, severity, or causal relationship to the MDR TB treatment, leading to a discontinuation of MDR TB treatment, including permanent and temporary treatment interruption, or changes in drug(s) dosage(s) or drug regimen, as decided by the clinician.
- **Adverse events judged as otherwise clinically significant**, defined as all AEs regardless of their seriousness, severity, or causal relationship to the MDR TB treatment, not pertaining to one of the above-mentioned category but considered of clinical significance by the treating physician.
- **Pregnancy** must be avoided during MDR-TB treatment and effective contraception is recommended.If despite all precautions, a patient is found to be pregnant, the pregnant patient should be referred to receive the local, standard of MDR-TB treatment for pregnant women. All pregnancies (including pregnancies of partners of male patients) should be followed-up until an outcome is known. Infants born from exposed pregnancies should be followed-up until they reach 12 months of age.
- **Medication errors** defined as unintended mistakes in the prescribing, dispensing and administration of a medicine that could cause harm to a patient (e.g. wrong drug prescribed, overdose) must be managed on a case by case basis. Hospitalization should be considered as appropriate.

The clinician is responsible for appropriately managing AEs, drug-exposed pregnancies, and potential medication errors in accordance with the local standards of care and for referring the patient to the appropriate specialist if needed. He/she should additionally assess the benefit of the continuation of the current TB treatment in the light of the whole clinical picture: weighing treatment continuation benefits vs. the risks (including AEs, pregnancy exposure, abnormal lab results, etc.). Specific clinical management suggestions are available in section 6.3 for AEs of interest.

6.2 Recording, medical assessment and notification of adverse events

Recording and notification of adverse events occurs as follows:

- **Immediate transmission** (within 24 hours of awareness) of Serious Adverse Events (as defined in section 6.1), drug-exposed pregnancies and medication errors (with or without associated AEs/SAEs) to the pharmacovigilance unit (PVunit.GVA@geneva.msf.org) as recorded using the *SAE or Pregnancy Report Form*.
- **Routine recording** of all other AEs (non-serious) using the *AE Form*.

Upon recording, all SAEs and AEs should be **graded for severity**according to the provided Severity Grading Scale (grades 1-4[8]). For those AEs not described in the Severity Grading Scale, the general definition of clinical severity should apply.

Table 9 General definition of severity

Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Transient or mild discomfort (<48 hours); no medical intervention/therapy required.	Mild to moderate limitation in activity* - some assistance may be needed; no or minimal medical intervention/ therapy required.	Marked limitation in activity*, some assistance usually required; medical intervention/therapy required, hospitalizations possible	Extreme limitation in activity*, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

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

All AEs should additionally be evaluated to determine their **causal relationship with MDR TB treatment** (including MDR TB drugs and other drugs as appropriate), using the standard terms as displayed in the table below. This evaluation should take into account all other possible causal factors (e.g. medical history, risk factors, past drug use, concomitant procedures, TB progression).

Table 10 Causality categories definition

Causality category	**Description**
Related	There is a reasonable possibility that the AE may be related to the drug(s). Elements in favour of a reasonable causal relationship include: • A favourable temporal relationship, • A positive dechallenge and/or rechallenge, • A plausible pharmacological/biological mechanism of action (whether proven or potential), • Previous knowledge of similar reaction with the drug(s), or • No other evident cause (e.g. previous disease, other drugs). There is insufficient information to evaluate the causal relationship between the AE and the exposure. Conservatively, the AE should be considered related to the drug(s) until a proper assessment is feasible (i.e. upon follow-up).
Not related	There is no reasonable possibility that the AE is related to the drug(s). This implies that there is a plausible alternative cause for the AE that better explains the occurrence of the AE or that highly confounds the causal relationship between the drug(s) and the AE.

A dedicated pharmacovigilance guideline for endTB details all processes relating to pharmacovigilance describing how SAE/Pregnancy Report Forms should be completed and providing further guidance on severity and causality assessment. A Data Management plan details the recording of clinical information (non-serious AEs, lab values) in the clinical practice database.

[8]The scale includes all terms from the National Institute of Allergy and infectious Diseases (NIAID) Division of Microbiology and Infectious Diseases (DMID) grading system and a selection of relevant terms from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) or other scales.

6.3 Clinical management of adverse events of interest

6.3.1 Peripheral neuropathy

Possible anti-TB drug causes: Lzd, Cs, H, S, Km, Cm, H, FQ, Pto/Eto, E.

Possible other causes: d4T, ddI .

- Peripheral neuropathy is a common side effect of MDR-TB treatment caused by drug toxicity to the nerves of the peripheral nervous system.
- Peripheral neuropathy is extremely common in patients taking linezolid. In one clinical trial of linezolid, 55% of the patients experienced clinically significant peripheral neuropathy.
- Skin punch biopsies, nerve conduction studies or other specialized tests are the gold standard but are not necessary for a diagnosis.
- According to the ACTG Brief Peripheral Neuropathy Screen (BPNS), a patient can be diagnosed with peripheral neuropathy if he/she reports typical symptoms (numbness, tingling, burning, pain) plus decreased vibration sense in the big toes or decreased ankle tendon reflexes.
- When assessing the patient's symptoms with the BPNS (See Step 1 of the BPNS description), assess whether his/her symptom is suggestive of neuropathic pain. Although difficult to define and variable for each individual, neuropathic pain is often described as "burning", "electric", "tingling", and "shooting" in nature. It can vary from a constant pain to intermittent sharp shooting pains. As described, the pain is most often present without associated stimulation, but can be exacerbated by stimuli.
- After a diagnosis of peripheral neuropathy, the following table should be used for grading, or the subjective sensory neuropathy score from the BPNS (See Step1 of the BPNS description).

Table 11 Clinical management of peripheral neuropathy according to severity grading

Severity grade*	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Paresthesia (Burning, Tingling, etc.)	Mild discomfort; no treatment required; and/or BPNS subjective sensory neuropathy score 1-3 on any side.	Moderate discomfort; non-narcotic analgesia required; and/or BPNS subjective sensory neuropathy score 4-6 on any side.	Severe discomfort; or narcotic analgesia required with symptomatic improvement; and/or BPNS subjective sensory neuropathy score 7-10 on any side.	Incapacitating; or not responsive to narcotic analgesia
Action	Stop Cs and Lzd. If symptoms improve, consider restarting these drugs. Consider restarting Lzd at a lower dose (300mg daily or 600 mg thrice weekly). If Cs is not essential to the regimen consider suspending the drug.	Stop Cs and Lzd. If symptoms improve, consider restarting cycloserine. Do not reintroduce Lzd. Provide symptomatic relief as described below.	Same as Grade 2.	Same as Grade 2.

*Reference: NIAID Division of Microbiology and Infectious Diseases, severity scale, Nov-2007.

Suggested management strategy:

- Many patients experience improvement when offending drugs are suspended, especially if the symptoms are mild.
- The neuropathy associated with linezolid is common after prolonged use and often extremely painful and irreversible. For this reason, linezolid should be immediately stopped and not reintroduced when symptomatic neuropathy develops (grade 2 or above). Consider additional anti-TB drugs to reinforce the regimen.
- In HIV coinfected patients, avoid use of d4T or ddI in combination with cycloserine or linezolid because of an increased risk of peripheral neuropathy.
- All patients taking linezolid should receive at least 50 mg of pyridoxine daily. This is largely to prevent myelosuppression, but may also prevent peripheral neuropathy.
- Symptomatic relief:
    - Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms.
    - Tricyclic antidepressants have also been used successfully. Start amitriptyline 25 mg at bedtime. The dose may be increased to a maximum of 150 mg daily for refractory symptoms. If possible, the co-administration of amitriptyline and Lzd should be avoided.
    - Carbamazepine may also be effective in relieving pain and other symptoms of peripheral neuropathy. Carbamazepine is a strong inducer of CYP3A4 and should not be used with bedaquiline or delamanid.

ACTG Brief Peripheral Neuropathy Screen (BPNS):

Step 1. Grade Subjective Symptoms

Ask the subject to rate the severity of each symptom on a scale from 01 (mild) to 10 (most severe) for right and left feet and legs. Enter the score for each symptom in the columns marked R (right lower limb) and L (left lower limb).

Normal	Mild ---------- Severe									
00	01	02	03	04	05	06	07	08	09	10

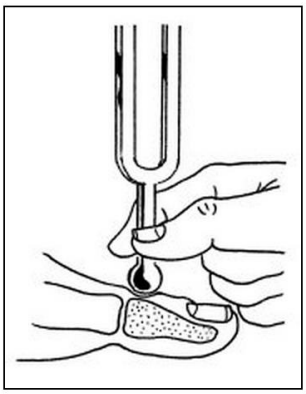
Symptoms	R	L
a. Pain, aching, or burning in feet, legs		
b. "Pins and needles" in feet, legs		
c. Numbness (lack of feeling) in feet, legs		

Use the single highest severity score above to obtain a subjective sensory neuropathy score.

Subjective Sensory Neuropathy Score	Severity grade
00	0
01 – 03	1
04 – 06	2
07 – 10	3

Step 2. Evaluate Perception of Vibration

Compress the ends of a 128-Hz tuning fork just hard enough that the sides touch. Place the vibrating tuning fork on a bony prominence on the subject's wrist or hand to be sure that he/she can recognize the vibration or "buzzing" quality of the tuning fork. Again, compress the ends of the tuning fork just hard enough that the sides touch. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint of one great toe and begin counting the seconds. Instruct the subject to tell you when the "buzzing" stops. Repeat for the other great toe. The diagram below illustrates where to place the tuning fork (adapted from International Working Group on the Diabetic Foot, Practical guidelines on the management and prevention of the diabetic, 2007).



Vibration perception	Result	Score
Felt > 10 seconds	Normal	0
Felt 6-10 seconds	Mild loss	1
Felt <5 seconds	Moderate loss	2
Not felt	Severe loss	3

Step 3. Evaluate Deep Tendon Reflexes

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

Ankle reflexes	Score
Absent	0
Hypoactive	1
Normal deep tendon reflexes	2
Hyperactive	3
Clonus	4

A diagnosis of peripheral neuropathy can be made with the combination of a subjective neuropathy grade greater than 0 and at least one bilateral objective finding (abnormal vibratory sense or abnormal deep tendon ankle reflex).

6.3.2 **Myelosuppression (anemia, thrombocytopenia, or neutropenia)**

Possible anti-TB drug causes: Lzd.

Possible other causes: AZT, cotrimoxazole.

- The mean corpuscular volume (MCV) may be helpful to assess whether anemia is normocytic versus microcytic versus macrocytic. Macrocytic anemia is more likely to be due to AZT, but AZT can also induce a normocytic anemia.
- If the patient has thrombocytopenia or neutropenia, this is more likely to be due to linezolid. AZT can do this, but it is rarer.
- Myelosuppression is very common in patients receiving linezolid. In one clinical trial of linezolid, approximately 18% of patients taking linezolid experienced clinically significant myelosuppression.
- All patients taking linezolid should also be receiving at least 50 mg of pyridoxine daily. This is largely to prevent myelosuppression, but may also prevent peripheral neuropathy.
- Acute blood loss (occult GI bleeding from a peptic ulcer) can cause anemia.
- Other causes of anemia (TB, iron-deficiency, etc.) are possible, but less likely to occur in the middle of treatment, especially if the patient is clinically improving.

Table 12 Clinical management of myelosuppression according to severity grading

Severity grade*	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Anemia	10.5 - 9.5 g/dL	9.4 - 8.0 g/dL	7.9 - 6.5 g/dL	< 6.5 g/dL
Platelets decreased	75,000 – 99,999 /mm^3	50,000 – 74,999 /mm^3	20,000 – 49,999 /mm^3	< 20,000 /mm^3
Absolute neutrophil count low	1500 - 1000/mm3	999 - 750/mm3	749 - 500/mm3	<500/mm3
Action	Monitor carefully, and consider reduction of dose of Lzd (300mg daily or 600 mg thrice weekly).	Monitor carefully, and consider reduction of dose of Lzd (300mg daily or 600 mg thrice weekly); in case of Grade 2 neutropenia, stop Lzd immediately. In case of Grade 2 anemia, consider EPO. Restart at reduced dose once toxicity has decreased to Grade 1.	Stop Lzd immediately. In case of Grade 3 anemia, consider EPO. Restart at reduced dose once toxicity has decreased to Grade 1.	Stop Lzd immediately. Consider hemotransfusion or EPO. Restart at reduced dose once toxicity has decreased to Grade 1.

Reference: NIAID Division of Microbiology and Infectious Diseases, severity scale, Nov-2007.

Suggested management strategy:

1. Stop the causative drug immediately.
2. Monitor full blood counts regularly.
3. Consider erythropoietin for anemia Grade 2 or 3.
4. Hospitalize the patient and consider transfusion or erythropoietin if the myelosuppression is severe.
5. Consider additional anti-TB drugs to reinforce the regimen.

Erythropoietin (EPO)

Treatment with erythropoietin is not intended for patients who require immediate correction of anemia (Grade 4). In this case, blood transfusions should be considered. Whole blood count should be repeated weekly to assess the response to treatment. Blood pressure should be adequately controlled before initiation and monitored during therapy. Erythropoietin treatment should in any case be discontinued at Hemoglobin levels over 12 g/dL.

Contraindications

Erythropoietin treatment should be administered with caution in the presence of:

- Untreated, inadequately treated or poorly controlled hypertension
- Epilepsy
- Thrombocytosis
- Chronic liver failure
- Hyperkalemia

Presentation

Epoetin alfa prefilled syringes of 10 000 UI or 40 000 IU/ml to be stored in cold chain (2°C to 8°C).

Dosing

Epoetin alfa: 150 IU/Kg three times a week or 450 IU/Kg once a week subcutaneously or intravenously.

6.3.3 **Prolonged QT interval**

Possible anti-TB drug causes: Cfz, Bdq, Mfx, Dlm, and Lfx (a mild QT prolonging drug)

Possible other causes: Many other drugs can cause QT prolongation (e.g. erythromycin, clarithromycin, quinidine, ketoconazole, fluconazole, antipsychotics (all have some risk including haloperidol, chlorpromazine and risperidone), many anti-nausea drugs (ondansetron/granisetron, domperidone), methadone, and some antiretrovirals); genetic causes such as long QT syndrome; hypothyroidism.

- Check an ECG if the patient has clinical symptoms (tachycardia, syncope, palpitations, or weakness or dizziness) of cardiotoxicity. Check the QT interval and rule out an arrhythmia.
- The QTc will be calculated using the Fridericia's formula which corrects for the heart rate and has been shown to be more accurate at slower or faster heart rates than other correction formulae:

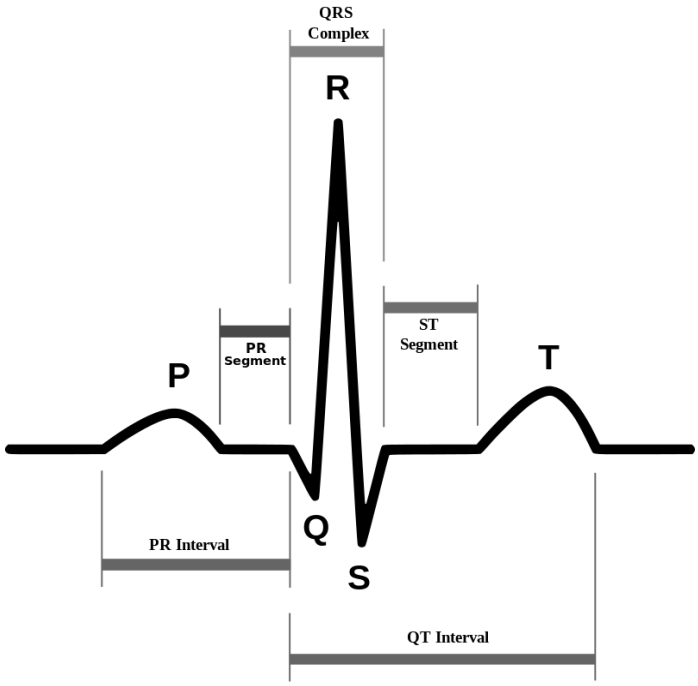
$$\text{QTcF} = \frac{QT}{\sqrt[3]{RR}}$$

Where:

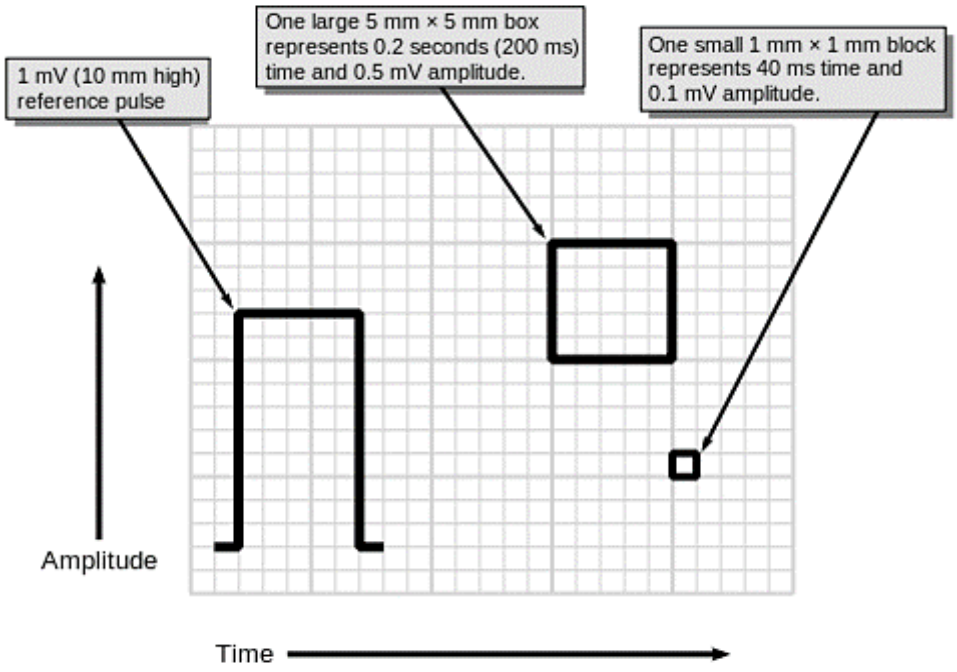
QTcF = the corrected QT interval

QT = the time between the start of the QRS complex and the end of the T wave

RR = the time between the start of one QRS complex and the start of the next QRS complex



- The ECG machine should be calibrated to ensure that the following voltage and speeds apply:

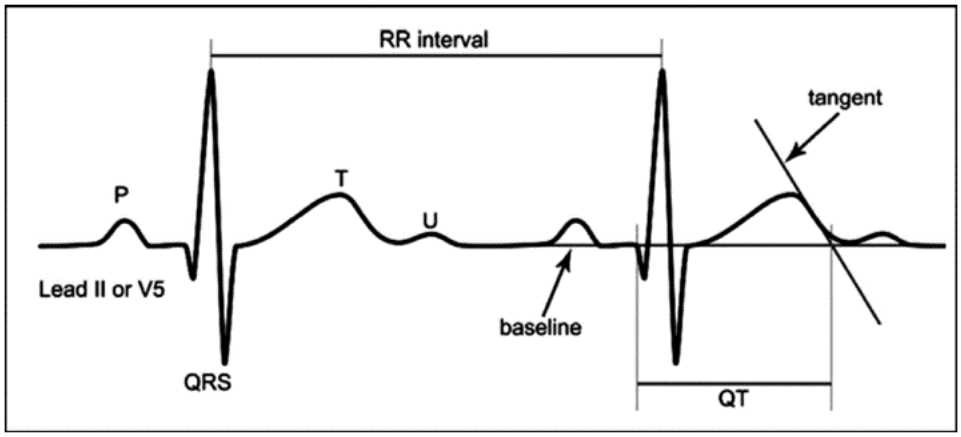


Procedure for measuring RR and QT interval

1. Obtain the 12-lead ECG:
   a) Ensure that the 12-lead ECG is performed in a relaxed patient to avoid artifacts. Use the appropriate electrodes and clean the patient's skin if necessary.
   b) Ensure the sweep speed is set to 25 mm/sec. This will allow for standard calibration and measurement of the QT interval.

2. Measure the RR and QT intervals manually (Figure 1 illustrates the intervals):
   a) The QT interval should be measured manually, preferably by using one of the limb leads that best shows the end of the T wave on a 12-lead ECG.
      i. Often, leads II or V5 may best show the end of the T wave. Try to measure the QT interval in these leads first.
      ii. If the end of the T wave is not well seen in leads II or V5, then the clinician should use their best judgment to assess which lead best shows the end of the T wave.
   b) The QT interval should be measured from the beginning of the QRS complex to the end of the T wave.
      i. If the rhythm is irregular (i.e. atrial fibrillation), the QT interval should be averaged over 3 to 5 beats. Calculate the QTcF for each of the 3 to 5 beats, and then calculate the arithmetic average QTcF of the beats.
      ii. U waves possibly corresponding to the late repolarization of cells in the mid myocardium should be included in the measurement only if they are large enough to seem to merge with the T wave. The figure below illustrates how to determine the start of the Q wave and end of the T wave by drawing a baseline and a tangent line on the back side of the T wave.

iii. Each 1 mm (small) horizontal box corresponds to **0.04** second (**40 msec**), with heavier lines forming larger boxes that include five small boxes and hence represent **0.20** sec (**200 msec**) intervals. Count the number of boxes that make up the QT interval and then multiply the number of boxes by 40 msec. if the start of the Q wave or the end of the T wave fall in the middle of the box, estimate it to the nearest ¼ of a box.



3. Correct the QT interval for the heart rate:
   a) For standardization, we will be using the Fridericia formula to correct for heart rate. The Fridericia formula performs better at lower and higher heart rates than other correction methods.
   b) The formula used by the ECG machine may not be the Fridericia formula. Thus, the QTcF should be calculated using the the nomogram below. (The QTcF can also be determined by using a calculator and using the formula in Section 6.3.3; however, it is recommended for clinicians to use the nomogram as it is less prone to error).
   c) Compare the corrected value measured manually with what the ECG machine produces (if the ECG machine has the function of automatically calculating the corrected QT interval). If there is a difference of more than 20 ms repeat the manual measurement. The manual measurement serves as the "gold standard".
4. Record RR interval, heart rate, and the QTcF interval in the patient's chart:
   a) The RR interval is measured in seconds.
   b) Record the heart rate from the ECG machine if it produces it automatically or determined it by measuring the RR interval and dividing into 60. (HR = 60/RR interval in second).
   c) Record the QTcF interval as calculated by the instructions above.

How to use the QTcF Nomogram

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

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

Table 13 Clinical management of prolonged QT interval according to severity grading

Severity grade*	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Prolongation of QTcF	QTcF 450 – 480 ms#.	QTcF interval 481 – 500 ms#.	QTcF >= 501 ms without signs/symptoms of serious arrhythmia#.	QTcF >= 501 or >60 ms change from baseline and one of the following: Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia#.
Action	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade 1. Replete electrolytes as necessary.	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade 1. Replete electrolytes as necessary.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.

*NCI Common Terminology Criteria for Adverse Event, v.4.03 14-Jun-2010.
#When multiple ECGs are recorded on a same day, average of the QTcF measures should be used to determine the grade.

Checking and repleting serum electrolytes:

- Serum potassium (K^+), ionized calcium (ionized 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 frequent repeat potassium testing (often daily or multiple times a day) to document the potassium is moving in the correct direction.
- If potassium is found low, always check magnesium and ionized calcium and compensate as needed. (If unable to check, consider oral empiric replacement doses of magnesium and calcium).
- In patients receiving delamanid, serum albumin should be obtained and repeated monthly in the event a prolonged QT interval is detected.

Suggested management strategy:

1. Stop all QT prolonging drugs immediately. ART is usually not stopped unless the patient is severely unstable.
2. Hospitalize and consider continuous electrocardiac monitoring for Grade 3. Hospitalization should occur in a facility capable in the management of Torsades de Pointes arrhythmia.
3. Check electrolytes and manage as described above.
4. Check a TSH and treat any hypothyroidism found.

5. Once stable (QT_CF interval below 450 and normal electrolytes), critical QT prolonging anti-TB drugs can be added back:
    - If the patient is on any non-TB drugs that are QT prolonging consider suspension.
    - If the patient was on moxifloxacin consider using levofloxacin instead.
    - If the patient was on clofazimine consider suspending it permanently if not critical to the regimen.
    - If the patient is on bedaquiline and it is considered critical to the regimen, consider adding the drug back to the patient's regimen while suspending all other QT prolonging drugs (with the exception of stopping ART, which should not normally be suspended in the management of QT prolongation).
    - If the patient is on delamanid and it is considered critical to the regimen, consider adding the drug back to the patient's regimen while suspending all other QT prolonging drugs (with the exception of stopping ART, which should not normally be suspended in the management of QT prolongation).

6.3.4 **Optic nerve disorder (optic neuritis)**

Possible anti-TB drug causes: Lzd, E, Eto/Pto, Cfz, rifabutin, H, S.

Possible other causes: ddI.

- Optic neuritis is inflammation of the optic nerve eventually resulting in permanent vision loss. The first sign of optic neuritis is usually the loss of red-green color distinction. This is best tested using the Ishihara test. Other symptoms include central scotomas.
- Linezolid is by far the most common cause of optic neuritis amongst all of the TB drugs. In a clinical trial of linezolid, 18% of patients eventually developed optic neuritis, mostly after four months of treatment.
- Patients with diabetes are at increased risk for optic neuritis. They should be managed with tight glucose control as a means of prevention. Patients with advanced kidney disease are also at increased risk for optic neuritis.

Table 14 Clinical management of optic nerve disorder according to severity grading

Severity grade*	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye (20/40[6/12] or better)	Limiting vision in the affected eye (worse than 20/40[6/12] but better than 20/200[6/60])	Blindness (20/200[6/60] or worse) in the affected eye
Action	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.

*NCI Common Terminology Criteria for Adverse Event, v.4.03 14-Jun-2010.

Suggested management strategy:

- Do not restart the suspected causative drug (linezolid or ethambutol).
- Refer patient to an ophthalmologist for immediate evaluation and management.
- Optic neuritis generally improves following cessation of offending drug, if it can be stopped early enough.
- Consider additional anti-TB drugs to reinforce the regimen.

6.3.5 **Hepatitis**

Possible anti-TB drug causes: Z, Lzd, Cfz, Bdq.

Possible other causes: unknown.

- Hepatitis is characterized by nausea, vomiting, jaundice, scleral icterus, tea-colored urine, pale stool, and diminished appetite in the setting of elevated liver function tests.
- Mild elevation of liver enzymes, especially at baseline, may be related to TB rather than an adverse effect of treatment.
- Generally hepatitis due to medications resolves upon discontinuation of suspected drug.
- In HIV coinfection, cotrimoxazole can be a cause of hepatotoxicity.
- NVP hepatotoxicity usually occurs shortly after exposure, accompanied by flu-like symptoms with or without rash. It can also happen late as an isolated hepatitis without constitutional symptoms. Patients who experience NVP hepatotoxicity should not be rechallenged.

Table 15 Clinical management of hepatitis according to severity grading

Severity grade*	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
ALT (SGPT)	1.1 – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
AST (SGOT)	1.1 – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Action	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Stop all drugs, including anti-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.	Stop all drugs, including anti-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.

*Reference: NIAID Division of Microbiology and Infectious Diseases, severity scale, Nov-2007.

Reintroduction of anti-TB drugs:

- Reintroduce anti-TB drugs once liver enzymes return to baseline. Anti-TB drugs should be reintroduced in serial fashion by adding a new medicine every three to four days. The least hepatotoxic drugs should be added first, while monitoring liver function tests after each new exposure.

- Consider suspending the most likely offending drug permanently if it is not essential to the regimen. This is often the case for pyrazinamide if it is less likely to be effective by clinical history. Consider additional anti-TB drugs to reinforce the regimen.

6.3.6 **Hearing impaired**

Possible anti-TB drug causes: S, Km, Am, Cm, Clr.

Possible other causes: none.

- Hearing impaired is a disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures.
- The injectables can cause damage of the hearing apparatus of the inner ear, including the cochlea, vestibule, semicircular canals, and cranial nerve VIII. Symptoms include hearing loss and tinnitus, as well as vestibular symptoms such as disequilibrium and vision problems.
- Hearing loss is commonly observed in patients receiving large cumulative doses of injectables. Capreomycin may be less ototoxic than the aminoglycosides.
- Hearing loss and vestibular dysfunction are generally not reversible upon discontinuation of therapy.
- Some degree of hearing loss occurs with most patients taking an injectable, but high-frequency loss may not significantly affect the patient's quality of life.
- Some patients may choose to tolerate significant hearing loss to achieve a higher chance of cure. This should be discussed between the patient and a physician trained in MDR-TB. Continuing the injectable in such situations almost always results in permanent hearing loss and sometimes complete deafness.
- Patients with previous exposure to aminoglycosides may have already sustained a degree of hearing loss. These patients are at the highest risk of incurring further ototoxicity. In such patients, audiometry may be helpful in guiding therapy to prevent further damage.
- Concomitant use of furosemide, particularly in the setting of renal insufficiency, may exacerbate ototoxic effects of the injectables.

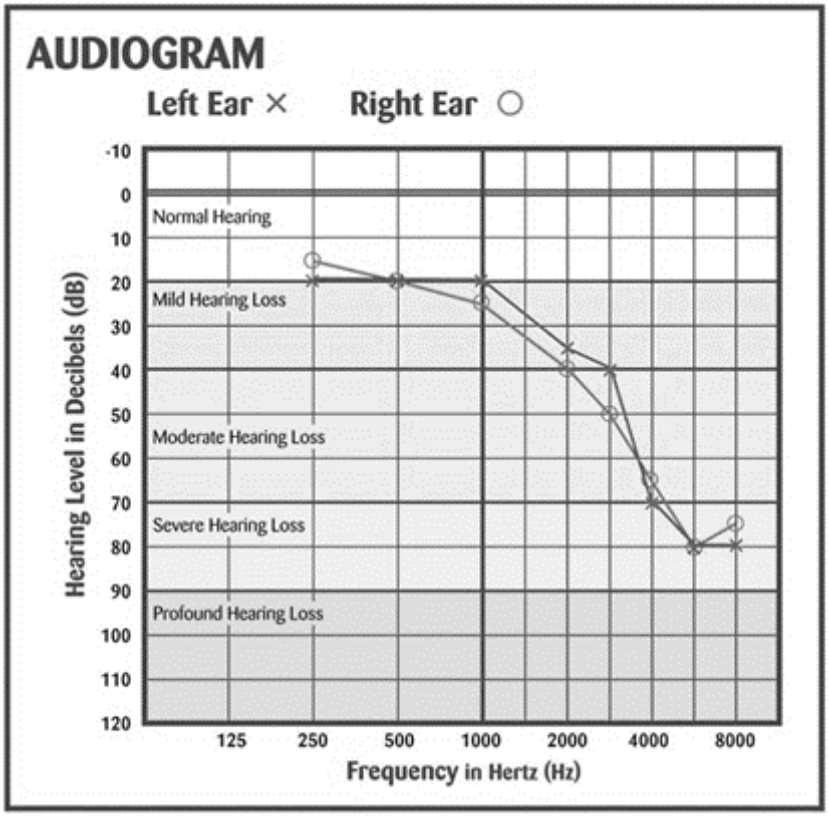
Table 16 Clinical management of hearing impairment according to severity grading

Severity grade*	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Hearing Impaired	Adults Enrolled on a Monitoring Program (on a 1, 2, 4, 3, 6 and 8 kHz audiogram): threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear or subjective change in the absence of a Grade 1 Threshold shift. Pediatric (on a 1, 2, 4, 3, 6 and 8 kHz audiogram): threshold shift >20 dB at 8 kHz in at least one ear.	Adult enrolled in monitoring program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear. Adult not enrolled in monitoring program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL. Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): threshold shift >20 dB at 4 kHz and above in at least one ear.	Adult enrolled in monitoring program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated. Adult Not enrolled in monitoring program: hearing loss with hearing aid or intervention indicated; limiting self care ADL. Pediatric (on a 1, 2, 3, 4, 6 and 8kHz audiogram): hearing loss sufficient to indicate therapeutic intervention, including hearing aids): Threshold shift >20 dB at 3 kHz and above in at least one ear ; additional speech-language related services indicated.	Adults: profound bilateral hearing loss (Threshold >80 dB HL at 2 kHz and above); nonservicable hearing Pediatric: audiologic indication for cochlear implant and additional speech-language related services indicated.
Action	Continue injectable.	Consider decreasing injectable frequency if further hearing loss is a concern. Initiate discussion with patient about risks and benefits of the injectable. Consider replacing injectable agent with a non-ototoxic TB drug. Do NOT substitute a single drug replacement if the treatment is failing, add additional TB drugs.	Consider stopping or decreasing injectable frequency (e.g. MWF). Discuss with patient the risks and benefits of further injectable use. In most cases of Grade 3 hearing loss the injectable should be stopped and replaced with a with a non-ototoxic TB drug. Do NOT substitute a single drug replacement if the treatment is failing, add additional TB drugs.	Consider continue injectable if tolerated by the patient. (In cases of complete hearing loss, some clinicians will continue the injectable agent as the damage is already done). Consider suspension of the injectable if ongoing use contributes to worsening tinnitus or vestibular disturbances (or if some hearing might be still preserved). Add additional TB drugs as needed.

*NCI Common Terminology Criteria for Adverse Event, v.4.03 14-Jun-2010.

Suggested management strategy:

- Perform a monthly assessment of hearing loss and balance. Audiometry may be helpful if the hearing loss is mild.
- If the patient is experiencing clinically significant hearing loss, decrease the dosing frequency of the injectable to two to three times a week. Consider switching to capreomycin.
- Stop the injectable if symptoms worsen despite dose adjustment, and add additional anti-TB drugs to reinforce the regimen.
- Even when additional drugs are not available, stopping the injectable can be considered based on the patient's desire to maintain hearing.
- If moderate or severe vertigo, tinnitus (ringing in the ears) or vestibular disturbances arise, with or without significant hearing loss, consider decreasing frequency or stopping the injectable agent.



Source: Auditory Neuroscience: Making sense of Sound. Accessed June 2013, http://auditoryneuroscience.com/acoustics/clinical_audiograms

Notes on audiogram:

- This audiogram represents high-frequency hearing loss, which is often the first sign of auditory toxicity due to injectables.
- The patient with this audiogram could still hear conversations. Frequencies around 2,000 Hz are the most important for understanding conversations; the patient has only moderate hearing loss in this area.
- Often patients do not notice hearing loss above 4,000 Hz.
- An audiogram that demonstrates hearing loss as illustrated above is a good example of a situation where suspending (or substituting) a different anti-TB drug is indicated; this can prevent further loss of hearing.

6.3.7 **Acute kidney injury**

Possible anti-TB drug causes: S, Km, Am, Cm.

Possible ART causes: TDF (rare).

- Acute kidney injury is characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).
- The injectables (aminoglycosides and capreomycin) are the most common cause of acute renal failure in MDR-TB patients. Capreomycin may be less nephrotoxic than the aminoglycosides.
- Injectable nephrotoxicity is often asymptomatic in the early stages and can only be diagnosed with routine laboratory monitoring. End-stage renal failure may present with oliguria/anuria or signs of volume overload including peripheral edema and shortness of breath. Mental status changes due to uremia or electrolyte abnormalities are a late symptom.
- Other common causes of acute renal failure:
    - Prerenal etiologies include hypovolemia due to dehydration from vomiting or diarrhea as a side effect of anti-TB therapy. Hypotensive shock in critically ill patients can also cause prerenal physiology.
    - Etiologies intrinsic to the kidney include acute tubular necrosis due to aminoglycosides and capreomycin or acute interstitial nephritis from other antibiotics like beta-lactams and sulfa drugs.
- TDF may cause renal injury with the characteristic features of Fanconi syndrome: Hypophosphatemia, hypouricemia, proteinuria, normoglycemic glycosuria and, in some cases, acute renal failure.
    - Even without the concurrent use of tenofovir, HIV-infected patients have an increased risk of renal toxicity secondary to aminoglycosides and capreomycin. Frequent creatinine and electrolyte monitoring is recommended.
    - Avoid TDF in patients receiving aminoglycosides or capreomycin. If TDF is absolutely necessary, serum creatinine and electrolytes should be monitored frequently (weekly at the start of treatment).

Table 17 Clinical management of acute kidney injury according to severity grading

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Acute Kidney Injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated
Action	Consider stopping injectable until creatinine has returned to baseline. Consider restarting the injectable at lower frequency (e.g. MWF).	Stop injectable until creatinine has returned to baseline. Consider restarting the injectable at lower frequency (e.g. MWF) or substitute with a non-nephrotoxic drug.	Stop injectable until creatinine has returned to baseline. Consider restarting the injectable at lower frequency (e.g. MWF) or substitute with a non-nephrotoxic drug.	Stop injectable until creatinine has returned to baseline. Consider restarting the injectable at lower frequency (e.g. MWF) or substitute with a non-nephrotoxic drug.

*NCI Common Terminology Criteria for Adverse Event, v.4.03 14-Jun-2010.

Suggested management strategy:

1. Monitor serum creatinine and electrolytes frequently in patients receiving injectables. Patients with pre-existing kidney disease, diabetes, or HIV are at high risk of injectable nephrotoxicity and may be monitored more frequently.
    a. Any increase of serum creatinine above normal limits should be considered acute renal insufficiency.
    b. A doubling of serum creatinine above baseline, even if within normal limits, should be considered worrisome for acute renal insufficiency and monitored carefully.
2. Repeat electrolytes if necessary.
    a. Injectable nephrotoxicity may be associated with injectable-induced electrolyte wasting. For example, it is possible to see elevated creatinine and severe hypokalemia/hypomagnesemia at the same time.
    b. The etiology of this phenomenon is unclear, but it may occur more often in HIV coinfected patients.
3. Discontinue the suspected drug (usually the injectable). If the acute renal failure is severe, then stop all drugs.
    a. Nephrotoxicity due to the injectable is frequently reversible after the injectable is stopped, but permanent damage can result if it is not detected early.
    b. If the acute renal insufficiency is severe or resolving slowly, the dose of other renally excreted drugs should be adjusted.
4. Consider other contributing etiologies (prerenal, intrinsic renal, and postrenal).
5. Follow serum creatinine and electrolytes closely until the creatinine has returned to baseline or has stabilized.
6. Consider reintroducing the injectable with an intermittent dosing schedule (two or three times a week) if the drug is essential to the regimen.
    a. Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen.
    b. Consider strict weight-based dosing of the injectable if the patient's weight is less than 50 kg.
    c. Suspend the injectable permanently if the nephrotoxicity recurs despite intermittent dosing, and add additional anti-TB drugs to reinforce the regimen.

6.3.8 Hypokalemia and hypomagnesemia

Possible anti-TB drug causes: Cm, Km, Am, S.

Possible ART causes: TDF (rare).

- Hypokalemia and hypomagnesemia are often asymptomatic.
    - Moderate cases may present with fatigue, myalgia, cramps, paresthesia, lower extremity weakness, behavior or mood changes, somnolence, and confusion.
    - Severe disturbances can lead to tetany, paralysis, and life-threatening cardiac arrhythmias.

- Hypokalemia and hypomagnesemia are common in patients receiving MDR-TB treatment. Common causes in MDR-TB patients are:
    - Vomiting and diarrhea.
    - Renal tubular toxicity from the injectable (probably more common in capreomycin than the aminoglycosides).
    - The injectables can cause a syndrome of electrolyte wasting, including potassium, magnesium, calcium, and bicarbonate.
    - This syndrome is more common and severe in HIV coinfected patients; hospitalization and aggressive serum electrolyte monitoring and correction may be necessary.
- Formulations of oral potassium chloride vary by manufacturer and country. Slow-release versions are common in resource-limited settings. The amount of potassium is often different than the tablet size. For example, one 200-mg tablet of Slow-K contains 8 mEq of potassium.
    - Oral potassium and magnesium should be administered either two hours before or four to six hours after fluoroquinolones as they can interfere with fluoroquinolone absorption.
    - Oral potassium can cause nausea and vomiting. Oral magnesium can cause diarrhea.
- Dietary intake of potassium should be encouraged. Bananas, oranges, tomatoes, and grapefruit juice are good sources of supplementation.
- Amiloride 5 to 10 mg PO daily or spironolactone 25 mg PO daily may decrease potassium and magnesium wasting due to the injectable and may be useful in severe cases that are refractory to replacement therapy.

Table 18 Clinical management of hypokalemia according to severity grading

Severity grade*	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Hypokalemia	3.4 - 3.0 mEq/L	2.9 - 2.5 mEq/L	2.4 - 2.0 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Action	Continue injectable. Start oral potassium replacement therapy. Check serum magnesium and replace if necessary.	Continue injectable. Start aggressive oral potassium replacement therapy. Replace magnesium as necessary.	Continue injectable. Start IV potassium replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary.	Stop injectable temporarily. Start IV potassium replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary.

*Reference: NIAID Division of Microbiology and Infectious Diseases, severity scale, Nov-2007.

Suggested management strategy:

1. Monitor serum potassium, magnesium, and calcium frequently in patients with vomiting/diarrhea and patients receiving injectables.
2. Check for signs of dehydration in patients with vomiting and diarrhea. Start oral or intravenous rehydration therapy immediately until volume status is normal.
3. Replete potassium and magnesium.
    a. Hypokalemia may be refractory if concurrent hypomagnesemia is not also corrected.
    b. If unable to check serum magnesium, give empiric oral replacement therapy in all cases of hypokalemia with magnesium gluconate 1000 mg twice daily.
4. In all cases of detected serum electrolyte disturbances (Grade 1- 4) obtain an electrocardiogram as soon as possible and then weekly until potassium and other electrolytes return to normal. Drugs that prolong the QT interval should be discontinued in patients with evidence of QT interval prolongation.
5. Electrolyte abnormalities are reversible upon discontinuation of the injectable. Even after suspending the injectable, it may take weeks or months for this syndrome to disappear, so electrolyte replacement therapy should continue for several months after completion of the injectable phase of MDR-TB treatment.

Table 19 ***Potassium replacement therapy***

Potassium level (mmol/L)	**Dosing**	**Monitoring frequency**
>3.4	None	Monthly
3.3-3.4	40 mmol PO in 2-3 divided doses daily	Monthly
2.9-3.2	60-80 mmol PO in 3 divided doses daily	Weekly
2.7-2.8	60 mmol PO every eight hours	One to two days
2.5-2.6	80 mmol PO every eight hours	Daily
< 2.5	10 mmol/hour IV and 80 mmol PO every six to eight hours	One hour after infusion, every six hours with IV replacement

Note:
Potassium chloride controlled release tablets of 600mg = 8mmol/tablet
Potassium chloride 10% (100mg/ml) ampoules= 1g per ampoule = 13.4 mmol
The normal preparation of a potassium chloride infusion is 40 mmol (3 ampoules) in 1L of NaCl 0.9% infused over 4 hours. Do not exceed an infusion rate of 10 mmol/hour (250 mL/hour).

Table 20 Clinical management of hypomagnesemia according to severity grading

Severity grade*	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Hypomagnesemia	0.60-0.70 mmol/L	0.45-0.59 mmol/L	0.30-0.44 mmol/L	<0.30 mmol/L
Action	Start oral magnesium replacement therapy.	Start aggressive oral magnesium replacement therapy.	Start intravenous magnesium replacement therapy in addition to oral. Replace other electrolytes as necessary.	Start intravenous magnesium replacement therapy in addition to oral. Replace other electrolytes as necessary.

*Reference: NIAID Division of Microbiology and Infectious Diseases, severity scale, Nov-2007.

Table21 Magnesium replacement therapy

Magnesium level (mmol/L)	**Total daily dose**	**Monitoring frequency**
>0.7.0 or more	None	Monthly
0.60-0.70	1,000 mg-1,200 mg	Monthly
0.45-0.59	2,000 mg	One to seven days
<0.45	3,000 mg-6,000 mg	Daily

Note: Quantities greater than 2,000 mg are usually given IV or IM. The normal preparation is magnesium sulfate 2 g in 100 mL or 4 g in 250 mL of normal saline. Do not exceed an infusion rate of 150 mg/min (2 g in 100 mL administered over one to two hours, 4 g in 250 mL administered over two to four hours).

6.3.9 **Hypothyroidism**

Possible anti-TB drug causes: Eto/Pto, PAS.

Possible ART causes: d4T.

- Ethionamide (or prothionamide) and PAS have a direct toxic effect on the thyroid that interferes with thyroid hormone synthesis. The exact incidence of hypothyroidism is unknown, but it is probably more common than traditionally thought.
- Patients may develop symptoms as soon as a few weeks after exposure to offending medications.
- Symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, as well as depression and inability to concentrate. Thyromegaly and delayed deep tendon reflexes may be encountered on exam.
- In primary hypothyroidism, the diagnosis is confirmed by a serum level of TSH greater than 10.0 mU/L, indicating suppression of the thyroid hormone production by the thyroid gland. No other thyroid tests (e.g., free T_4, T_3) are necessary for diagnosis or treatment monitoring.
- In HIV coinfected patients there is some evidence that subclinical hypothyroidism may be associated with some ARVs, particularly stavudine (d4T).
- Hypothyroidism can result in QT interval prolongation. Check an ECG whenever hypothyroidism is found and if QT interval prolongation or an arrhythmia is found refer for hospitalization and appropriate management.

Table 22 Clinical management of hypothyroidism according to severity grading

Severity grade*	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting iADL	Severe symptoms; limiting self care ADL hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Action	Continue anti-TB drugs.	Continue anti-TB drugs. Start thyroxine.	Continue anti-TB drugs. Start thyroxine.	Stop all anti-TB drugs. Start thyroxine.

*NCI Common Terminology Criteria for Adverse Event, v.4.03 14-Jun-2010.

Suggested management strategy:

1. In patients with hypothyroidism, most adults will require 100 to 150 mcg of levothyroxine daily.
    a. Young healthy adults can be started on 75 to 100 mcg daily.
    b. Older patients should begin treatment with 50 mcg daily.
    c. Patients with significant cardiovascular disease should start at 25 mcg daily.
2. Children clear thyroxine faster than adults, so daily replacement doses may be higher.
    a. Children (4-15 years): 4 mcg/kg/day (maximum dose is 200 mcg).
    b. Infants (1-3 years): 10-15 mcg/kg/day (maximum dose is 200 mcg).

3. Monitor TSH every one to two months and increase dose by 25 to 50 mcg until TSH is in normal range. Adjust dose more slowly in the elderly and patients with cardiac conditions.
4. Hypothyroidism is reversible upon discontinuation of ethionamide/prothionamide or PAS. As a result, thyroid hormone replacement may be stopped several months after completion of MDR-TB treatment.

6.4 Most frequent adverse events

Table 23 List of most frequent adverse events

Adverse event	Definition	Grade 1	Grade 2	Grade 3	Grade 4
Cardiovascular disorders					
Cardiac rhythm other than QT Interval Prolongation	Abnormality in cardiac rhythm.	N/A	Asymptomatic, transient signs, no treatment required	Recurrent/persistent; symptomatic treatment required	Unstable dysrythmia; hospitalization and treatment required
Chemistry					
Lactate (lactic acidosis)	Increase in blood lactate accompanied or not with blood acidification.	< 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without lifethreatening consequences	Increased lactate with pH < 7.3 with lifethreatening consequences
Ear Disorders					
Tinnitus	A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	N/A
Vestibular Disorder	A disorder characterized by dizziness, imbalance, nausea, and vision problems.	N/A	Symptomatic; limiting iADL	Severe symptoms; limiting self care ADL	N/A
Gastrointestinal Disorders					
Diarrhea	A disorder characterized by frequent and watery bowel movements.	Mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	Moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	Hypotensive shock or physiologic consequences requiring hospitalization
Dyspepsia	A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea and vomiting.	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	N/A

Adverse event	Definition	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	A disorder characterized by a queasy sensation and/or the urge to vomit.	Mild or transient; maintains reasonable intake	Moderate discomfort; intake decreased significantly; some activity limited	No significant intake; requires IV fluids	Hospitalization required
Oral Discomfort/Dysphagia	A disorder characterized by difficulty in swallowing.	Mild discomfort; no difficulty swallowing	Some limits on eating/drinking	Eating/talking very limited; unable to swallow solid foods	Unable to drink fluids; requires IV fluids
Pancreatitis	A disorder characterized by inflammation of the pancreas.	N/A	Enzyme elevation or radiologic findings only	Severe pain; vomiting; medical intervention indicated (e.g. analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated
Vomiting	A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	Physiologic consequences requiring hospitalization or requiring parenteral nutrition
Immune Disorders					
Allergic Reaction	A disorder characterized by an adverse local or general response from exposure to an allergen. Worst stage 'anaphylaxis' is characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.	Pruritus without rash	Localized urticaria	Generalized urticaria; angioedema	Anaphylaxis

Adverse event	Definition	Grade 1	Grade 2	Grade 3	Grade 4
Musculoskeletal Disorders					
Arthralgia (joint pain)	A disorder characterized by a sensation of marked discomfort in a joint.	Mild pain not interfering with function	Moderate pain, analgesics and/or pain interfering with function but not with ADL	Severe pain; pain and/or analgesics interfering with ADL	Disabling pain
Arthritis	A disorder characterized by inflammation involving a joint.	Mild pain with inflammation, erythema or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema or joint swelling; interfering with function, but not with ADL	Severe pain with inflammation, erythema or joint swelling and interfering with ADL	Permanent and/or disabling joint destruction
Myalgia	A disorder characterized by marked discomfort sensation originating from a muscle or group of muscles.	Myalgia with no limitation of activity	Muscle tenderness (at other than injection site) or with moderate impairment of activity	Severe muscle tenderness with marked impairment of activity	Frank myonecrosis
Tendinopathy	Tendon injuries from mild inflammation, partial tear to rupture.	Stretched tendon fibers (no tear). Tenderness and swelling. Joint stable.	Partial tendon tear. Moderate tenderness and swelling. Joint unstable or gives away during activity, decreased range of motion.	Complete tendon tear/rupture, Significant tenderness and swelling. Joint unstable. No joint movement on muscle contraction. Surgery required.	Life-threatening complication from surgery.
Neurological Disorders					
Dysgeusia	A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell.	Altered taste but no change in diet	Altered taste with change in diet (e.g. oral supplements); noxious or unpleasant taste; loss of taste	N/A	N/A

Adverse event	Definition	Grade 1	Grade 2	Grade 3	Grade 4
Headache	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.	Mild, no treatment required	Transient, moderate; treatment required	Severe; responds to initial narcotic therapy	Intractable; requires repeated narcotic therapy
Seizure	A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures
Psychiatric Disorders					
Anxiety	A disorder characterized by apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus.	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening; hospitalization indicated
Depression	A disorder characterized by melancholic feelings of grief or unhappiness.	Mild depressive symptoms	Moderate depressive symptoms; limiting instrumental ADL	Severe depressive symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated
Psychosis	A disorder characterized by personality change, impaired functioning, and loss of touch with reality.	Mild psychotic symptoms	Moderate psychotic symptoms (e.g., disorganized speech; impaired reality testing)	Severe psychotic symptoms (e.g., paranoid; extreme disorganization); hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated
Suicidal ideation	A disorder characterized by thoughts of taking one's own life.	Increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide without serious intent to die which may not require hospitalization	Specific plan to commit suicide with serious intent to die which requires hospitalization

Adverse event	Definition	Grade 1	Grade 2	Grade 3	Grade 4
Reproductive system and breast disorders					
Gynecomastia	A disorder characterized by excessive development of the breasts in males.	Asymptomatic breast enlargement	Symptomatic (e.g. pain or psychosocial impact)	Severe symptoms; elective operative intervention indicated	N/A
Skin Disorders					
Mucocutaneous Symptoms	General scale for skin disorders from signs and symptoms (e.g. itching) to life-threatening skin conditions (e.g. Steven Johnson syndrome).	Erythema; pruritus	Diffuse, maculo papular rash, dry desquamation	Vesiculation or moist desquamation or ulceration	Exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Pruritus	A disorder characterized by an intense itching sensation.	Slight itching at injection site	Moderate itching at injection extremity	Itching over entire body	N/A
Skin Hypo- or Hyper-Pigmentation	A disorder characterized by loss of skin pigment or a darkening of the skin due to excessive melanin deposition.	Hypo- / Hyper-pigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypo- / Hyper-pigmentation or depigmentation covering >10% BSA; associated psychosocial impact	N/A	N/A

7 APPENDIX: endTB medical Committee guidance for extension of treatment with Bdq and/or Dlm beyond 24 weeks

7.1 Pre-requisites for extension of treatment with bedaquiline (Bdq) or delamanid (Dlm) beyond 24 weeks

Pre-requisites for Bdq or Dlm extension	**Comments**
Good MDR-TB treatment adherence	Good treatment adherence during the first 24 weeks of treatment.
Good tolerability	No serious adverse events (SAE) linked to Bdq or Dlm during the first 24 weeks of treatment or SAE is resolved.
Acceptable time of MDR-TB treatment interruption	Bdq or Dlm should be prolonged without interrupting it. The acceptable time of interruption before resuming the drug should not exceed 4 weeks for Bdq and one week for Dlm. Even if a period longer than this occurs, the patient may still be eligible if approved by the endTB Medical Committee.
Informed consent	Patient should be correctly informed about the potential risks and benefits, as well as on the available evidence on prolonged Bdq and Dlm treatment. Additional informed consent for treatment extension should be requested and obtained specifically for the extension of Bdq and Dlm treatment.
Closely monitored treatment	Specific monitoring should be extended for the entire duration of Dlm or Bdq exposure.

7.2 Criteria for extension of treatment with bedaquiline (Bdq) or delamanid (Dlm) beyond 24 weeks

Criteria for Bdq or Dlm extension	**Definition**
Late treatment response	Patient still sputum culture-positive after 3 months or more of treatment with Bdq or Dlm and not meeting the criteria for treatment failure AND The bacteriological (smear and/or culture) and clinical (weight) evolution indicates positive response to the treatment
Insufficient number of effective drugs* in the treatment regimen	Less than 3 effective drugs in the regimen if Bdq or Dlm is stopped. If an injectable drug is present in the treatment regimen and it is planned to discontinue it, it should not be counted among these drugs. The paucity of effective drugs in the treatment regimen may be due to drug resistance pattern, adverse events or any other contraindications.

* Effective drug = never used before in a failing regimen, susceptible according to a reliable DST result

8 References

Relevant references to produce this guide include:

- *Companion handbook to the WHO 2011 guidelines for the programmatic management of drug-resistant tuberculosis, 2nd edition* (WHO/HTM/TB/2014.11). WHO, Geneva. 2015.
- *The use of bedaquiline in the treatment of MDR-TB: interim policy guidance*(WHO/HTMTB/2013.6). WHO, Geneva. 2013.
- *The use of delamanid in the treatment of MDR-TB: interim policy guidance* (WHO/HTM/TB2014.23). WHO, Geneva. 2014.
- *Tuberculosis: practical guide for clinicians, nurses, laboratory technicians and medical auxiliares. 2014 Edition*. Médecins Sans Frontières and Partners In Health.
- *PIH Guide to the Medical Management of MDR-TB, 2nd Edition*. Partners In Health, Boston, USA. USAID TB CARE II. 2013.
- WHO treatment guidelines for drug-resistant tuberculosis, 2016 update. (WHO/HTM/TB/2016.04). WHO, Geneva. 2016
- *The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: interim policy guidance* (WHO/HTM/TB/2016.14). WHO, Geneva. 2016.


UNITAID


Partners
In Health


MEDECINS
SANS FRONTIERES


IRD
Interactive Research & Development