**Clinical Guide for All-Oral Shorter MDR-TB Regimens**

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**Notice**

This guide is designed to give clinical guidance on implementing all-oral shorter MDR-TB treatment under operational research conditions. It is intended to be a resource for physicians and other health care professionals. Every effort possible has been made to ensure that the material presented here is accurate, reliable, and in accord with current standards.

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The guide also uses material from a revised edition of the MSF/PIH Guide Tuberculosis: Practical Guide for Clinicians, Nurses, Laboratory Technicians and Medical Auxilliaries (publication pending in 2019).

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# List of abbreviations

**ADSM** active TB Drug-Safety Monitoring and Management

**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 aminotransferase

**AZT** Zidovudine

**Bdq** Bedaquiline

**BMI** Body Mass Index

**BPNS** Brief Peripheral Neuropathy Screen

**BSA** Body Surface Area

**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

**DAA** Direct-acting Antivirals

**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

**EFV** Efavirenz

**EMA** European Medicines Agency

**EMR** Electronic medical record

**endTB** Expand New Drugs for TB

**EPO** Erythropoietin

**Eto** Ethionamide

**FDA** United States Food and Drug Administration

**FQ** Fluoroquinolone

**GI** Gastrointestinal

**H** Isoniazid

**Hh** High-dose isoniazid

**HIV** Human Immunodeficiency Virus

**Ipm** Imipenem

**IRD** Interactive Research and Development

**Km** Kanamycin

**Lfx** Levofloxacin

**LLN**  Lower Limit of Normal

**LTR** Longer treatment regimen

**Lzd** Linezolid

**MDR** Multidrug-resistance

**MDR-TB** Multidrug-resistant tuberculosis

**Mfx** Moxifloxacin

**Mfxh** High-dose moxifloxacin

**MSF** Médecins Sans Frontières

**MTB/RIF** Mycobacterium Tuberculosis/Rifampicin

**MWF** Monday-Wednesday-Friday

**NTP** National Tuberculosis Program

**NVP** Nevirapine

**Ofx** Ofloxacin

**PAS** Para-Aminosalicylic Acid

**PIH** Partners In Health

**PLHIV**  People living with HIV

**PO** Per os

**Pto** Prothionamide

**PV** Pharmacovigilance

**QTcF** QT interval Fridericia’s correction

**RR-TB**  Rifampicin-resistant TB

**S** Streptomycin

**SAE** Serious Adverse Event

**SLD** Second Line Drug

**SSRI** Selective Serotonin Re-uptake Inhibitor

**STR** Shorter treatment regimen

**SUSAR** Suspected-Unexpected SAEE

**TB** Tuberculosis

**Trd** Terizidone

**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

# Introduction

In 2019 the WHO published new consolidated guidelines on treatment of drug-resistant tuberculosis (DR-TB).[[2]](#footnote-3) The new recommendations provide an option for the treatment of rifampicin-resistant tuberculosis (RR-TB) and multidrug-resistant tuberculosis (MDR-TB) with all-oral shorter treatment regimens (STRs) under “operational research conditions”. This clinical guide is aimed at physicians and other health care professionals that are using all-oral STRs under operational research conditions to treat patients with RR-/MDR-TB.

This guide provides the following instructions to aid the clinical care provider in:

* Identifying patients that are candidates for use of an all-oral STR.
* Designing all-oral STRs to be used in a programmatic setting.
* Adjusting all-oral STRs based on individual patient characteristics, including co-morbidities and tolerance to the medications.
* Implementing close monitoring of patients for response to treatment and for potential adverse events (AEs).
* Assuring treatment is implemented under operational research conditions.

The implementation of all-oral STRs under operational research conditions is not complicated and is very similar to implementing the standard conditions of good programmatic management of drug-resistant TB (PMDT). A toolkit for operational research of all-oral STRs will be published on the endTB website[[3]](#footnote-4) that provides templates, examples and guidance of the elements needed to safely implement as well as monitor and evaluate all-oral STRs. The toolkit will be periodically updated.

The elements of implementing all-oral STRs under operational research conditions include:

* **A study protocol**. Templates of study protocols for all-oral STRs have been developed by endTB3, the StopTB Partnership and the Global Drug-Resistant TB Initiative (GDI)[[4]](#footnote-5), USAID as the DESTRoy TB protocol[[5]](#footnote-6) and TDR, a Special Programme for Research and Training in Tropical Diseases hosted by the WHO[[6]](#footnote-7).
* **A patient consent process**. A consenting process as per local requirements is a minimum requirement. The consent process is discussed in Section 5.2.
* **A list of all the data points or variables that the program will collect to evaluate the shorter regimen.** This list of variables is known as a ” data-dictionary”. The d data-dictionary is defined ahead of the implementation of the all-oral STR. Examples of data-dictionaries are provided on the endTB website.
* **Data collection forms.** Enrolment, follow-up, treatment outcome, quarterly post-treatment follow-up and post-end-of-treatment forms are all required. Enrollment and follow-up forms can be the same forms used in the programmatic management drug-resistant TB (PMDT) or be specially designed forms to ease the collection of data or link to an electronic medical record (EMR).
* **A clinical treatment guide on all-oral STR**. This guide is designed to be used as a template that can be easily modified for the specific needs of a country. A copy in Microsoft Word format can be downloaded from the endTB website.3
* **Patient education material**. Also see Section 5.1.
* **A** **system to monitor and manage adverse events and report serious ones**. At a minimum, the core package of active TB Drug-Safety Monitoring and Management (aDSM)[[7]](#footnote-8) should be implemented. See Section 6 and 7 for more details.

For programs using a combination of all-oral STRs and injectable-containing STRs, this guide advises to use the same rigorous operational research conditions for both regimens. Additional monitoring will be required for injectable-containing STRs.

The endTB Medical Committee[[8]](#footnote-9) is available to provide advice on the design of all-oral STRs as well as advice on individual case management to the projects associated with Partners In Health (PIH), Médecins Sans Frontières (MSF), Interactive Research and Development (IRD). For projects not associated with these organizations but interested in using the endTB Medical Committee as a resource, the endTB Medical Committee may be contacted to discuss an arrangement.

# Criteria to decide if an all-oral STR can be used in a patient

All-oral STRs should only be used in patients who consent to treatment after being informed of the risks/benefits of being treated with a regimen that is novel in nature (also see Section 5 on patient consent and patient education).

All-oral STRs are not to be used if any of the following criteria is present:

* Patient is unwilling or unable to give informed consent (signed or witnessed consent from a legal custodian if patient is not competent; signed or witnessed consent from a minor’s parent or legal guardian).
* Confirmed or suspected resistance to the fluoroquinolones (FQs):
  + It is recommended to rule out FQ-resistance with a line probe assay (LPA) test prior to starting the all-oral STR.
  + If second-line drug LPA is not available and phenotypic DST is available, the regimen can be adjusted when the phenotypic DST become available (in many cases the regimen will be robust enough to have a low probability of resulting in drug resistance amplification if FQ resistance is discovered, see Section 4.1 on adjusting the regimen for FQ-resistance).
* Confirmed or suspected resistance to a drug in the regimen and the drug cannot be replaced by an oral drug of similar efficacy to maintain an adequate number of likely effective drugs in the regimen.
  + One exception to this criteria may be pyrazinamide resistance where the drug is sometimes included in the regimen despite suspected resistance (see discussion on pyrazinamide in Section 3.2).
* Intolerance to medicine(s) in the regimen or high risk of toxicity (e.g. drug–drug interactions or a baseline morbidity that could potentiate the risk for a known adverse drug reaction) and the medicine(s) and the drug cannot be replaced by another oral drug of similar efficacy.
* Disseminated, meningeal or central nervous system (CNS) TB.

For patients who do not meet the criteria for receiving the standard all-oral STR, this guide recommends that these patients receive a longer treatment regimen (LTR) that is individually designed.

Patients who fall into the following patient populations can be included for treatment with an all-oral STR but may require additional explanation on the risks and benefits of using such regimens. The STR often requires a modification in the drug composition (see Sections 4.4 to 4.11 of this guide on the use of all-oral STRs in special populations):

* Children (see Section 4.8)
* Pregnant women (see Section 4.9)
* Patients with extrapulmonary disease (see Section 4.10)
* Patients with co-morbidities (HIV, diabetes, hepatitis C: see Section 4.11)

The consent process should include an explanation of how the risks and benefits to the patient may change when using the all-oral STR in these situations and the discussion documented in patient’s medical chart.

# Characteristics of the drugs recommended for use in all-oral STRs

## Drugs commonly used to compose all-oral STRs

All-oral STRs are composed of a combination of drugs that have high efficacy, a good side-effect profile and low likelihood of resistance. Regimen design is discussed in Section 4. The drugs recommended in this guide for use in all-oral STRs include:

* Group A drugs:
  + Levofloxacin (or Moxifloxacin)
  + Bedaquiline
  + Linezolid
* Group B drugs:
  + Clofazimine
* Group C drugs:
  + Delamanid
  + Pyrazinamide

The Group B drug cycloserine is not included in the above list as a good core candidate for all-oral STRs due to its poor side-effect profile and in part to a long history of previous use in many countries and no reliable DST. The Group C drugs other than delamanid and pyrazinamide are also not considered to be good candidates for use in all-oral STRs due to either their low efficacy, poor-side effect profile, or high likelihood of being resistant.

While other TB drugs can be used in all-oral STRs, this guide focuses on using the above drugs to design all-oral STRs that contain four to five drugs. In cases when a drug substitution is necessary, cycloserine and other Group C drugs may be considered for use in the STR.

## Individual drug characteristics of the drugs used in all-oral STRs

**Group A drugs: Later generation FQs, bedaquiline, linezolid**

Group A drugs are considered as the most efficacious TB drugs based on an individual patient data meta-analysis conducted by the WHO (reference 2019 WHO consolidated guidelines). All-oral STRs often, but not always, include two or more Group A drugs. The Group A drugs consist of:

* **Later generation fluoroquinolones: levofloxacin, moxifloxacin**

Fluoroquinolones (FQs) are highly effective against TB and have an excellent safety profile. Because all-oral STRs are only used in the treatment of FQ-susceptible or highly-likely FQ-susceptible strains of MDR-TB, this class of drug is used as a core drug in all STR designs.

Levofloxacin and has fewer QT-prolonging effects than moxifloxacin and is therefore often chosen over moxifloxacin for use in regimens containing bedaquiline, which also prolongs the QT interval.

Moxifloxacin (at high-dose) may be preferred when the regimen being used does not contain bedaquiline.

* **Bedaquiline**

Bedaquiline is a diarylquinoline with bactericidal activity against TB.[[9]](#footnote-10),[[10]](#footnote-11) Bedaquiline has a very long half-life of 5.5 months.

Bedaquiline is prescribed with an initial loading dosage. For a typical adult the loading dose is 400 mg once daily for two weeks, followed by a dose reduction to 200 mg three times per week for the remaining treatment duration. See Table 6 for full dosing information for bedaquiline.

Bedaquiline is often well tolerated and as a Group A drug is used in most all-oral STRs. Bedaquiline should be used for the entirety of the treatment duration unless an intolerance develops or it meets criteria for likelihood of being ineffective. Two reports published thus far have found no safety issues with using bedaquiline for longer than the originally recommended 6-month timeframe.[[11]](#footnote-12),[[12]](#footnote-13)

Bedaquiline is metabolized by the cytochrome P450 system enzymes in the liver. Drugs that induce or inhibit this system of enzymes will result in drug-drug interactions that can affect the blood levels of bedaquiline. Cytochrome P450 inducers decrease blood levels of bedaquiline, resulting in the possibility of inadequate levels of bedaquiline in the body for elimination of TB infection. Conversely, cytochrome P450 inhibitors will increase the blood levels of bedaquiline, resulting in the possibility of an increased risk of toxicity. Table 1 provides examples of drugs to avoid with the use of bedaquiline.

### 

### Table 1 Possible drug-drug interactions with bedaquiline

|  |  |  |
| --- | --- | --- |
|  | **Drugs** | **Examples/notes** |
| **Avoid use with Bdq** | Strong/moderate inducers of cytochrome P450 may decrease blood levels of Bdq | Efavirenz (ART and Bdq interaction are also discussed in Table 2)  Rifamycins:  Rifampicin  Rifapentine  Rifabutin  Phenytoin  Carbamazepine  Phenobarbital  St. John’s Wort |
| Strong/moderate inhibitors of cytochrome P450 may increase blood levels of Bdq | Ritonavir-boosted protease inhibitors (ART and Bdq interaction are also discussed in Table 2) Oral azole antifungals (can be used up to two weeks):  Itraconazole  Fluconazole\*\*  Macrolide antibiotics other than azithromycin†:  Clarithromycin  Erythromycin |
| \*For a more comprehensive list of drugs that affect and are affected by the cytochrome P450 system, see the Drug Interactions webpage of the Department of Medicine of Indiana University (<http://medicine.iupui.edu/clinpharm/ddis/>).  \*\*All four oral azoles inhibit CYP3A4; itraconazole and posaconazole are more potent inhibitors and fluconazole or voriconazole.[[13]](#footnote-14)  † Azithromycin does not inhibit CYP isoenzymes but does prolong the QT interval so may want to be avoided for this reason. | | |

### Table 2 Possible drug-drug interactions between antiretrovirals and bedaquiline

|  |  |  |
| --- | --- | --- |
|  | **Drugs** | **Instructions** |
| **ARVs to avoid with Bdq** | Efavirenz (EFV)  (Using EFV with Bdq will result in low levels of Bdq in the blood) | * Substitute nevirapine (NVP) or an integrase inhibitor instead of EFV. Allow a five-day washout period of EFV if possible (substitute NVP on day one and then start MDR regimen five days later). If patient is critically ill with MDR-TB, no washout period is necessary. * When switching back to EFV after ending treatment with Bdq, this can be done immediately after Bdq is stopped. |
| Ritonavir containing protease inhibitors (PIs)  (Using ritonavir with Bdq will result in high levels of Bdq in the blood) | * If possible, use an ARV regimen with no PI. One possible solution is to substitute the PI with an integrase inhibitor (INSTI), e.g. dolutegravir (DTG) or raltegravir (RAL). * If a ritonavir-containing PI must be used, perform an ECG every two weeks for the first 8 weeks. |

Adverse effects that have been associated with bedaquiline are QT prolongation and hepatitis (also see Section 7 for management of adverse effects)

A relative contraindication for use of bedaquiline is a baseline ECG demonstrating a QTcF > 500 ms (demonstrated on at least a second repeated ECG), history of syncopal episodes, ventricular arrhythmias or severe coronary artery disease. These are not absolute contraindications as the risk of death for some patients infected with highly resistant strains and inadequately treated TB outweighs the increased risk of a serious adverse event.

Mild or moderate QT prolongation during treatment with bedaquiline is common, while severe QT prolongation (>500 ms) is relatively uncommon (3%% of patients of patients in the endTB cohort).12 Regular ECG monitoring is recommended in all patients taking bedaquiline (see Table 11 ).

Other TB drugs such as clofazimine, fluoroquinolones, and delamanid, as well as many non-TB drugs, can also cause QT prolongation (see Section 3.4). Caution is warranted when combining multiple QT prolonging TB drugs; however, in practice, this is often done if the benefit of a stronger regimen is determined to outweigh the risk of QT prolongation in a well monitored patient. ECG monitoring should be performed when multiple QT-prolonging drugs are used together. The monitoring schedule for ECGs is provided in Table 11.

Bedaquiline can also cause hepatotoxicity. Physicians should avoid using bedaquiline in patients with pre-existing severe hepatic impairment. This is not an absolute contraindication as the benefit of using bedaquiline in a patient with severe TB disease may outweigh the increased risk of hepatotoxicity, even with severe hepatic impairment. Hepatotoxicity is often reversible if caught early and can be monitored with regular testing for an increase in serum liver enzymes (see Table 19 ).

**Linezolid**: Linezolid is a broad-spectrum antibiotic in the oxazolidinone drug class. Linezolid has excellent activity against TB. Among the Group A drugs, linezolid has the most safety concerns. The most serious adverse effects of linezolid include peripheral neuropathy (which can be permanent if not caught early), blindness secondary to optic neuritis (which also can be permanent if not caught early) and severe myelosuppression. These adverse events are well-documented to be dose-related adverse event profile, which means the longer one uses linezolid the higher the risk of experiencing a serious adverse effect.

Appropriate monitoring for these specific adverse events is necessary, with reactive management that often result in dose adjustment or complete withdrawal of linezolid (also see Section 7.3 on managing adverse events). Given the adverse event profile of linezolid, a reasonable strategy can be to routinely reduce the dose (for example, at month 4 or month 6 of treatment, routinely decrease the dose from 600 mg daily to 300 mg daily, or 600 mg Monday-Wednesday-Friday) or remove it routinely from the regimen after a period of time. Evidence is very limited on routinely decreasing the dose or stopping linezolid at a set point in time. The more common strategy used by the authors of this guide is to reduce the dose or stop it if intolerance develops (see Section 7.3 for management of side-effects). The drug should not be used if regular monitoring for the development of peripheral neuropathy, optic neuritis and myelosuppression is not possible. See Table 11 for routine monitoring and follow-up of MDR-TB patients.

The TB drugs cycloserine and isoniazid are both associated with the adverse effect of peripheral neuropathy; avoid the use of these TB drugs with linezolid if possible. Also, be aware many non-TB drugs can cause peripheral neuropathy.[[14]](#footnote-15) Often it may not be possible to avoid the use of certain drugs that increase the risk of peripheral neuropathy concomitantly with linezolid, as is often the case with ART; however, if possible, use as few non-TB drugs that have an association with peripheral neuropathy as possible.

Linezolid can have drug-drug interactions with drugs that affect the body’s serotonin levels. Serotonergic syndrome, which can be serious and life-threatening, can result when linezolid is given concomitantly with certain drug classes (see Table 3 ).

### Table 3 Non-TB drugs that when used with linezolid may result in serotonergic syndrome

|  |  |  |
| --- | --- | --- |
|  | **Drugs** | **Examples/notes** |
| **Avoid with Lzd** | Medicines that increase serotonin levels | * Serotonin re-uptake inhibitors (SSRIs): fluoxetine, paroxetine * Tricyclic antidepressants: amitriptyline, nortriptyline * Serotonin 5-HT1 receptor agonists * MAO inhibitors: phenelzine, isocarboxazid * Other serotoninergic agents: meperidine, bupropion, or buspirone, quetiapine |

Every effort should be made to avoid the use of drugs that have drug-drug interactions or overlapping toxicity with linezolid. However, there may be circumstances in which no other option is available, and the potential benefits outweigh the risks of using linezolid. For example, a fragile mental health patient with a high risk of suicide that must have linezolid in the regimen (no other anti-TB drug options) could also require a serotoninergic medication.

**Group B: Clofazimine, Cycloserine or Terizidone**

All-oral STRs often contain the Group B drug clofazimine. Cycloserine is used less often in all-oral STRs because of the safety profile – psychosis, seizures, neuropathy, and depression. Therefore, only the characteristics of the Group B drug clofazimine is discussed in this guide.

**Clofazimine.** Clofazimine is an anti-leprosy drug that also has activity against TB. Of the Group B drugs, it has the better safety profile. Clofazimine has a long tissue half-life of around 70 days.

There is a potential cross-resistance between bedaquiline and clofazimine, although the degree of cross-resistance and clinical implications are not well understood. In patients who have previously been treated with clofazimine and resistance is likely, bedaquiline can be used but is not considered a likely effective drug.

Clofazimine prolongs the QT interval and ECG monitoring should be implemented when used with bedaquiline or if multiple QT prolonging drugs are also part of the regimen. Non-TB drugs that cause QT-prolongation (see Section 3.4) should be avoided if possible.

Patients should be well informed of the reversible skin color changes in advance, which occur in almost all patients. The orange-brown skin changes are reversible a few months after the drug is stopped and is not considered dangerous. Dry skin changes can also be common but also not considered dangerous. The skin changes can be quite concerning to patients and reassurance is required.

**Group C drugs: delamanid and pyrazinamide.**

The Group C drugs delamanid and pyrazinamide are commonly included in all-oral regimen, while the other Group C drugs have either a poor side-effect profile, low efficacy or high resistance in MDR-TB. Only the characteristics for Group C drugs of delamanid and pyrazinamide are discussed in this guide

**Delamanid.** The low side-effect profile and low background resistance make delamanid an excellent choice for a drug component in an all-oral STR. Delamanid also has advantages in patients with co-morbidities (HIV patients on certain ARVs and viral hepatitis co-infected patients) because of few drug-drug interactions (DDIs) and low hepatotoxicity.

Delamanid has shown better culture conversion at month 2 in the Phase 2 trial.[[15]](#footnote-16) The Phase 3 trial[[16]](#footnote-17) had as its primary outcome time-to-conversion and the trial did not show a statistically significant faster culture conversion. Both the Phase 2 and 3 trials demonstrated a good safety profile for delamanid. There have also been observational studies that further support the safety of delamanid; however, because delamanid was used in a multi-drug regimen the efficacy data from the observational studies does not determine the exact contribution of delamanid in MDR-TB regimens. The WHO ranks delamanid as the second highest Group C drug based on a combination of evidence of efficacy and safety.

All programs should plan on having delamanid in their armament of drugs, even if they are using standardized all-oral STRs that do not contain delamanid. This is because delamanid is a good replacement drugs for when patients cannot tolerate a drug in non-delamanid containing regimens.

The dosing of delamanid is twice daily and seven days a week (see Table 6). Some experts feel that it is reasonable to shift to once daily dosing after the first two months for convenience. Because it is not known if the once daily dosing is equally efficacious to the twice daily dosing, this guide recommends going to once-daily dosing only in cases where twice daily dosing is impossible. Options for the evening doses and Sunday doses include family treatment supporters, self-administered treatment in adherent patients or electronic DOT (of which video DOT is gaining evidence as an effective case management strategy).

Delamanid is particularly useful in the following groups:

* ***Children.*** Delamanid has been studied in children. It is recommended use is described in Section 4.8.
* ***HIV co-infected patients on ART.*** Delamanid has very few drug interactions, less impact on the therapeutic drug levels and no significant overlapping toxicities with ART.
* ***Patients with liver toxicity or viral hepatitis***. Delamanid has not been reported to be associated with liver toxicity and could be used in preference in patients with liver co-morbidities, such as viral hepatitis or alcoholic liver disease.
* ***As a drug replacement when a Group A or B drug is causing toxicity***. When drug toxicity develops early, it is often desirable to replace the culprit drug with another TB drug. Delamanid is often a good choice due to its high safety profile. Delamanid is commonly used to replace linezolid when toxicities develop, and it is preferable to maintain the number of drugs in the regimen.

Delamanid should be given with food, often a light meal. This increases the absorption of the drug quite significantly.

Delamanid is a partially metabolized by the cytochrome P450 system enzymes in the liver, but is not influenced significantly by the inducers or inhibitors of the P450 enzyme system. Delamanid can be given with all ART medicines without dose adjustment.

Delamanid has a mild QT prolonging effect. QT monitoring for all-oral STRs is described in Section 7. The non-TB drugs that cause QT-prolongation (see Section 3.4) should be avoided.

First-line anti-TB therapy with fixed dose combination of HREZ appears to decrease levels of delamanid in early studies. The mechanism is not clear. Avoid the use of delamanid with first-line anti-TB therapy.

**Pyrazinamide.** Pyrazinamide is often employed in all-oral STRs, with the acknowledgement that its role in the regimen may be non-critical as many circulating MDR-TB stains have high rates of pyrazinamide resistance.

If DST through molecular testing involving gene sequencing or reliable phenotypic DST done in a high-quality lab is available, it can help guide the composition of the STR.

If DST to pyrazinamide demonstrates resistance, the authors of this guide recommend not using the drug in the STR, or stopping the drug if it has already been started, as the benefits are likely minimal or none and the potential harms due to side-effects are significant.

In five-drug all-oral STRs, when resistance to pyrazinamide is documented the drug can be stopped without replacement if there is high confidence that the other 4 drugs are likely effective. Some programs aim to have five-effective drugs for the whole 9-months and for programs that use this strategy when resistance is documented to pyrazinamide the drug is often replaced.

Some experts would continue pyrazinamide in the regimen even if resistance is documented for possible synergy with other drugs. In fact, the endTB randomized controlled trial (RCT) will examine the role of pyrazinamide in resistant vs susceptible strains. The endTB experimental regimens use pyrazinamide whether or not resistance is present, and similar strategies can be employed programmatically for all-oral STRs. The results of the endTB clinical trial will not be available until the end of 2022, so it will be some time before it can be determined whether this is a good strategy or not.

Many programs do not have access to reliable pyrazinamide DST and the rates of pyrazinamide resistance in MDR-TB strains may help determine the program’s choice of drugs used in the all-oral STRs.

Pyrazinamide is often the cause of drug-induced liver toxicity and should be avoided in patients with elevated liver enzymes or active hepatitis. In theory, there may be additive liver toxicity when bedaquiline and pyrazinamide are used together. On the other hand, data from laboratory animals suggest bedaquiline and pyrazinamide are synergistic, even when pyrazinamide is resistant.[[17]](#footnote-18)

## Contraindications for drugs commonly used in all-oral STRs

There are very few absolute contraindications for the use of any drug in the treatment of MDR- and XDR-TB, a disease that poses serious risk of death or debilitation to the patient if treated inadequately. However, there are relative contraindications for the use of many of the drugs used in all-oral STRs. If the clinician, together with the patient’s input, judges that the potential benefits outweigh the potential risk, treatment may proceed with caution.

### ***Table*** 4 ***Contraindications for TB drugs commonly used in all-oral STRs\****

|  |  |  |
| --- | --- | --- |
| **Drug** | **Relative contraindications** | **Remarks/Precautions** |
| All drugs | Known hypersensitivity to the drug | A history of anaphylaxis or severe drug reaction like Stevens-Johnson syndrome is an absolute contraindication. |
| Bdq, Cfz, Dlm, Mfxhd | * Baseline ECG demonstrating a QTcF > 500 ms (repeated); or * History of syncopal episodes, ventricular arrhythmias or severe coronary artery disease | Use with caution if baseline QTcF > 450/470 ms in male/female patients.  Weekly ECG monitoring and serum electrolyte measurements should be performed for the first 8 to 12 weeks if a drug is being used despite a cardiac contraindication. |
| Bdq, Z | Severe hepatic failure | Caution in patients with severe hepatic impairment. |
| Bdq, Dlm, Lzd | Severe renal failure | Caution in patients with severe renal impairment. |
| \* See Table 7 for safety during pregnancy. | | |

## Non-TB drugs that cause QT prolongation or affect the heart rhythm

Every effort should be made to avoid the use of drugs with the overlapping toxicity of QT prolongation. However, there may be circumstances where no other option is available, and the potential benefits outweigh the risks.

Psychiatric drugs are commonly used in MDR-TB patients with existing psychiatric disease as well as for the treatment of cycloserine-induced psychosis or reactive depression. The anti-psychotics in particular are well-known to prolong the QT interval. It is the responsibility of the TB physician to understand the effects and adverse effects of psychiatric drugs, and to monitor MDR-TB patients taking these drugs carefully, even if the patient is referred to a psychiatrist.

Table 4 lists drugs that may affect the QT interval. Caution is warranted when non-TB drugs that can prolong the QT interval or affect the rhythm of the heart are used concomitantly with TB drugs that affect the QT interval. Avoid the combined use if possible. When the use of an additional QT prolonging drug is not avoidable, then more frequent QT interval monitoring may be needed (for example, every two weeks instead of monthly)

### Table 5 Non-TB drugs that have potential to cause QT prolongation or affect the heart rhythm

|  |
| --- |
| **Examples of non-TB QT prolonging drugs/notes** |
| * Tricyclic antidepressants * Amitriptyline * Nortriptyline * (all tricyclic antidepressants) * Oral azole antifungals (can be used up to two weeks): * Ketoconazole * Itraconazole * Fluconazole * Macrolide antibiotics: * Azithromycin * Clarithromycin * Erythromycin * Antipsychotics (all have some risk), including: * Haloperidol * Risperidone * Many anti-nausea drugs, for example: * Ondansetron * Granisetron * Domperidone * Chlorpromazine * Methadone * Cardiac drugs that may affect the heart rhythm, for example: * Amiodarone * Beta-blockers * Digoxin * Quinidine |

Cardiac drugs are used in MDR-TB patients for a number of incorrect reasons, such as to “prevent” arrhythmia, to treat cardiac symptoms, or to decrease the QT interval. In fact, there is no cardiac drug that can counteract or “protect” from QT prolongation. Cardiac rhythm-controlling and rate-controlling drugs should therefore only be used for clear indications.

Sinus tachycardia is often a physiologic response to other pathologies. It should be viewed as a symptom, not as a cardiac disorder. Importantly, beta-blockers should not be used to treat sinus tachycardia or prevent QT prolongation in TB patients.[[18]](#footnote-19) The authors of this guide strongly recommend to avoid using beta-blockers in patients with TB that are on QT prolonging TB drugs, as a non-beta-blocker substitute can be found in most cases.

# Design and implementation of an all-oral shorter regimen

## Duration of the regimen in all-oral STR

In general, all-oral STRs are standardized four- or five-drug regimens that are given for 9 to 12 months.

The Month 4 clinical assessment and bacteriological response is routinely used to determine if the patient is responding to treatment. If there is no response to treatment at 4 months (on clinical assessment or month 4 culture is positive) then consideration for stopping the all-oral STR and designing a new individualized LTR can be done. Treatment can also be stopped before 4 months if there is evidence of a poor clinical response and the treatment regimen is determined to be failing.

Some programs may choose to extend total treatment to 11 or 12 months if the smear or culture is still positive at month 4 or 5, and the patient is clinically doing well. If the culture is still positive at month 6 or beyond, then the treatment outcome should be declared failed and a new LTR should be individually designed. Salvage regimens for patients in whom an all-oral STR has failed are discussed in Appendix 2.

This guide does not address STRs for FQ-resistant MDR-TB (including XDR-TB). STRs for FQ-resistant MDR-TB have limited evidence; however, the the Nix-TB which used 6 to 9 months of pretomanid, bedaquiline, and linezolid is under evaluation and initial results are very promising. Until more evidence on STRs and FQ-resistant MDR-TB is available, programs may want to treat all FQ-resistant MDR-TB with LTRs.

If the FQ-resistance is discovered a few months after the start of the all-oral STR, the patient should be assessed, and regimen reviewed. In many cases, the patient will be doing well, and the regimen has enough drugs that are “likely effective” against the FQ-resistant strain, that either the regimen can be continued or reinforced with one or two drugs. (Be sure to never add a single drug to a regimen that may be failing). The regimen is usually extended in time, often to 18 months total. Using shorter durations, like 12 months, is possible under operational research conditions.

## Duration of the post-end-of-treatment follow-up after an all-oral STR

Shorter regimens have many advantages for patients and programs; however, the ultimate proof of their efficacy is to demonstrate that all-oral STRs have no increase in TB recurrence compared to the LTRs. Therefore, patients that have completed the STR with a successful treatment outcome need to be monitored for recurrence for a duration of at least 12 months after the end of treatment.

A patient who presents with TB after treatment completion may be sick due to a relapse with the same TB strain or due to re-infection with a new strain. Genetic fingerprinting can compare the initial infecting TB strain to the recurrent TB strain. In many settings it is not possible because genetic fingerprinting is not available. In areas with access to genetic fingerprinting, documenting relapse from re-infection can be an important sub-study imbedded in the operational research on STRs. If programs have the capacity, they are encouraged to freeze the baseline specimen so that it can be used for future comparison should the patient relapse.

In all cases it is important to detect recurrence and to design a new LTR with drug which have not been previously used and are thought to be likely effective. The principles of on how to design a salvage regimen are provided in Appendix 2; however, this appendix is not a substitute for WHO guidance on DR-TB regimen design2 and consulting with MDR-TB treatment experts. Patients that fail a STR present unique challenges and often their next regimen may be their last opportunity for cure.

This guide suggests the following post-end-of-treatment schedule, described in Table X. Monitoring cultures are sent at month 6 and month 12 regardless if the patient has symptoms of TB or not. A combined monitoring table for during treatment and post-end-of-treatment follow is provided in Table 6.

### Table 6 Post-end-of treatment schedule

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Activity** | **3 months post-end-of-treatment** | **6 months post-end-of-treatment** | **9 months post-end-of-treatment** | **12 months post-end-of-treatment** |
| In-person clinic visit\* or telephone contact\*\* | √ | √ | √ | √ |
| Monitoring smear and culture (done regardless of signs of recurrence being present. | If indicated | √ | If indicated | √ |
| Chest X-ray | If indicated | If indicated | If indicated | If indicated |
| Any positive culture in the post- treatment period | Send baseline and post-end-of treatment culture for LPA to second-line drugs and DST to FQs, Bdq, Lzd, Dlm, Cfz, Z, and injectables | | | |
| Genetic fingerprinting | Perform genotyping on baseline strain to compare with any positive post-treatment period culture (if possible) | | | |

\*The clinical visit should consist of the weight, body mass index, brief peripheral neuropathy screen and visual acuity in all patients, as well as any other clinical and laboratory examination needed based on symptoms.

\*Telephone contact is acceptable only when it is not feasible for the patient come for an in-person clinic visit. Discuss directly with the patient only, unless permission has been granted to discuss the patient’s illness with a family member or health proxy.

The patient should be well informed to contact the program should symptoms of TB reoccur or if any family members or close contacts develop symptoms of TB.

At the end of 12 months of post-end-of-treatment follow-up the patient will be given a post-end-of-treatment outcome: sustained successful treatment (no evidence of recurrence), recurrence, death or lost to follow-up.

## Number of drugs used in an all-oral STR

Similar to WHO recommended LTRs the number of drugs in the STR should contain at least 4 likely effective drugs. Many programs choose regimens that contain 5 likely effective drugs to cover for the possibility that one of the drugs may not be effective.

This guide recommends that all drugs in the regimen are used for the full treatment duration if tolerated. Routinely stopping one drug in the regimen has not been properly evaluated in terms of effectiveness.

While not the preference of the authors of this guide, it is recognized that some programs may prefer to routinely stop one of the drugs, such as linezolid or bedaquiline, after a set period of time. Because linezolid is difficult to tolerate in comparison to bedaquiline, dropping linezolid would be the logical choice for programs that desire to routinely drop one drug. Alternatively, the dose of a drug like linezolid may be routinely reduced at month 4. (Note: in the endTB clinical trial all patients receiving linezolid will have a dose reduction of linezolid at month 4 – from 600 mg daily to either 300 mg daily or 600 mg Monday-Wednesday-Friday. The analysis of this practice is expected in late 2022).

## Choosing the drug composition of the all-oral STR

As described in Section 3.1, all-oral STRs are composed of a combination of drugs that have high efficacy, a good side-effect profile and low prevalence of resistance. This clinical guide only addresses regimens that use WHO endorsed Group A drugs (levofloxacin or moxifloxacin, bedaquiline, linezolid) the Group B drug clofazimine or the Group C drugs of delamanid or pyrazinamide. Because the drug pretomanid is not yet available commercially and has not been evaluated by the WHO or a stringent regulatory authority, it is not included as an option in drug composition in this guide.

The advantage of using regimens that are currently undergoing randomized control trials (RCTs) is that the operational research done on the regimen can add to the knowledge of the results of the RCT and because eventually robust information will be available on the effectiveness of these all-oral STRs .

Examples of all-oral regimens being used in RCTs that use drugs that are available through the Global Drug Facility (GDF) are provided below:

**Regimen being used in the MDR END clinical trial:**

* **MDR END:** Dlm-Lzd-Lfx-Z (36-52 weeks)

**Regimens being used in the endTB clinical trial:**

* **endTB regimen 1:** Bdq-Lzd-Mfx-Z (39 weeks)
* **endTB regimen 2:** Bdq-Cfz-Lzd-Lfx-Z (39 weeks)
* **endTB regimen 3:** Bdq-Dlm-Lzd-Lfx-Z (39 weeks)
* **endTB regimen 4:** Dlm-Cfz-Lzd-Lfx-Z (39 weeks)
* **endTB regimen 5:** Dlm-Cfz-Mfx-Z (39 weeks)

**Stream 2 Trial**

* **Regimen C:** 40 weeks of Bdq, Cfz, E, Z, Lfx, supplemented by H and Pto for the first 16 weeks

Programs do not have to use all-oral STRs that are being studied in RCTs. Examples of regimens that are not used in RCTs but are good candidates for use under operational research conditions are provided below:

* Lfx-Bdq-Lzd-Cfz (a common all-oral LTR, which can be used as an all-oral STR under operational research conditions)
* Lfx-Bdq-Lzd-Cfz-Dlm (adds a fifth bactericidal drug, delamanid, to a potent and common backbone of drugs. A disadvantage of this regimen is it has three QT prolonging drugs)
* Lfx-Bdq-Lzd-Dlm (similar to endTB regimen 3 but no pyrazinamide).

The authors lean against regimens that use more than 5 drugs, or if multiple drugs used in the regimen are commonly resistant in strains of MDR-TB (i.e. ethambutol, pyrazinamide and isoniazid). The authors also recommend avoiding drugs in STRs that are poorly tolerated (i.e. prothionamide, cycloserine and injectables). The authors of this guide strongly recommend against using injectables in STRs that treat FQ-susceptible MDR-TB.

## Choosing an all-oral STR based on the epidemiological and programmatic conditions of the country

There are a number of factors to be taken in consideration when deciding the final composition of an all-oral STR:

* There is extensive safety and efficacy data on the FQs. All-oral STRs designed to treat FQ-susceptible MDR-TB and contain an FQ as one of the backbone drugs.
* There is an expanding knowledge base on the use of bedaquiline[[19]](#footnote-20),[[20]](#footnote-21),[[21]](#footnote-22),[[22]](#footnote-23) in the treatment of MDR-TB. The drug performed very well in the WHO sponsored individual patient database (IPD) meta-analysis. However, bedaquiline has not completed a Phase III clinical trial. Bedaquiline prolongs the QT interval and can elevate liver enzymes. It is not mandatory that all-oral STRs always contain bedaquiline but it a common choice and may be the second-best option of a second-line TB drug after the FQs.
* Linezolid performed very well in the WHO sponsored IPD meta-analysis but has a poor safety profile. It should not be used in programs that cannot guarantee regular monitoring for full blood counts, optic neuritis, and peripheral neuropathy.
* Delamanid has an excellent safety profile, which was confirmed in a Phase III clinical trial.There was also better culture conversion in the secondary analyses of the Phase III trial, but no significant effect on final treatment outcome. 16  The Phase II trial of Dlm demonstrated a higher percentage of culture conversion.15 Delamanid has less drug-drug interaction with drugs metabolized by the cytochrome P450 enzymes like CYP3A4. Delamanid has no significant drug-drug interactions with ART. Delamanid appears helpful in treatment of highly resistant strains. [[23]](#footnote-24),12
* Clofazimine does not have abundant high-quality data on its efficacy and safety. There is some in vitro observed cross-resistance between clofazimine and bedaquiline; however, the clinical significance of this is not known. Clofazimine did perform well in the WHO-sponsored IPD meta-analysis (Table 2a) and there is one RCT from China that showed it use in the LTR improved outcomes (Table 2a).
* Many strains of MDR-TB may also have pyrazinamide resistance, especially in areas where the is a high amount of second-line resistance (like areas eastern Europe or Central Asian).
* Besides the theoretical cross-resistance with clofazimine and bedaquiline there is no known cross-resistance between any of the drugs used in all oral STRs.

The following are examples of all-oral STRs being used or planned in different areas of the world. All examples are based on real country decisions on all-oral STRs; however, the examples have been simplified and may vary from the actual plan in the country or may represent just a small pilot project in the country and not the NTP’s national plan. For this reason, the specific country’s name is not mentioned. They are meant to serve as general illustrative examples. Multiple options are often possible for a specific situation; often the regimen chosen is partially based on local expert preferences.

ATTENTION: THE FOLLOWING EXAMPLES ARE NOT MEANT TO SUGGEST THAT ALL COUNTRIES IN A SPECIFIC AREA USE THE SAME ALL-ORAL STR. THE EXAMPLES GIVE ONE POSSIBLE PRIMARY REGIMEN DESIGN ALONG WITH THE ADVANTAGES AND DISADVANTAGES OF CHOOSING THAT REGIMEN. FOR ANY GEOGRAPHICAL AREAS THERE ARE MANY ACCEPTABLE ALL-ORAL SHORTER REGIMENS THAT ARE LIKELY TO PRODUCE GOOD RESULTS.

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| --- | --- |
| **EXAMPLE 1: COUNTRY IN WEST AFRICA** | |
| **Epidemiological situation** | In strains of MDR-TB there is approximately < 2% resistance to FQs, and approximately 30% resistance to Z. |
| **Access to DST** | In-country rapid second-line DST is under development for FQs and no DST is planned for Z. Phenotypic DST is sent to a supra-national reference laboratory with a two-month turn-around time for FQs, injectables, E, Eto, and Z. |
| **Primary all-oral STR regimen** | **Lfx-Bdq-Lzd-Cfz-Z** |
| **Advantages** | * Uses all three Group A drugs and at least one Group B drug. * Moderate costs for the drugs in the regimen. * Z is effective in 70% of patients and can be dropped at the 2-month mark if resistance is documented. * It is a regimen being used in an RCT (endTB Clinical Trial). |
| **Disadvantages** | * Has two moderate QT prolonging drugs (Bdq and Cfz); however, both drugs are endorsed to be used together as an option for LTR by the WHO. * May have drug-drug interactions with some ARTs. |

|  |  |
| --- | --- |
| **EXAMPLE 2: COUNTRY IN SOUTHERN AFRICA** | |
| **Epidemiological situation** | In strains of MDR-TB there is approximately < 5% resistance to FQs, and approximately 60% resistance to Z. 80% HIV prevalence in TB patients. |
| **Access to DST** | In-country rapid second-line DST for FQs in available and no DST is planned for Z. Second-line phenotypic DST is available for FQs. |
| **Primary all-oral STR regimen** | **Lfx-Bdq-Lzd-Cfz-Dlm** |
| **Advantages** | * Uses all three Group A drugs and at least one Group B drug * Z is avoided as it is more than 50% resistant. * Since the regimen has five likely effective drugs, if intolerability develops in one drug, the drug can usually be stopped with no need for substitution in most circumstances. |
| **Disadvantages** | * The regimen is not being used in a registered RCT. * Has two moderate QT prolonging drugs (Bdq and Cfz) and one mild QT prolonging drug (Dlm). * May have drug-drug interactions with some ARTs. |

|  |  |
| --- | --- |
| **EXAMPLE 3: COUNTRY IN EASTERN EUROPE OR CENTRAL ASIA** | |
| **Epidemiological situation** | In strains of MDR-TB in the country there is approximately 10% resistance to FQs, and approximately 60% resistance to Z. |
| **Access to DST** | In-country rapid DST is available for FQs and in liquid culture for FQs and Z. |
| **Primary all-oral STR regimen** | **Lfx-Bdq-Lzd-Dlm-Z**  (Z will be continued whether susceptible or resistant). |
| **Advantages** | * Uses all three Group A drugs. * Has only one moderate QT prolonging drug. * It is a regimen being used in an RCT (endTB Clinical Trial). |
| **Disadvantages** | * Does not use any of the Group B drugs (this is due to the personal preference of some TB experts to use Dlm over Cfz or Cs). * Uses Z that is likely ineffective in most MDR-TB strains circulating in the area. * May have drug-drug interactions with some ARTs. |

|  |  |
| --- | --- |
| **EXAMPLE 4: COUNTRY IN EASTERN EUROPE OR CENTRAL ASIA** | |
| **Epidemiological situation** | In strains of MDR-TB in the country there is approximately 20% resistance to FQs, and approximately 80% resistance to Z. |
| **Access to DST** | In-country rapid DST is available for FQs and in liquid culture for FQs and Z. |
| **Primary all-oral STR regimen** | **Lfx-Bdq-Lzd-Cfz-Cs** |
| **Advantages** | * Uses all three Group A drugs and both Group B drugs * Does not use Z, which is resistant in most MDR-TB strains circulating in the area |
| **Disadvantages** | * Not used in any registered RCT * Uses Cs which has a poor side-effect profile and may have overlapping toxicities with Lzd * May have drug-drug interactions with some ARTs |

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| --- | --- |
| **EXAMPLE 5: COUNTRY IN SOUTH ASIA** | |
| **Epidemiological situation** | In strains of RR/MDR-TB, there is approximately 30-49% resistance to Z. Resistance to FQs in MDR-TB strains is 30 to 50% (most of the FQ resistance in the area is low-level FQ resistance). |
| **Access to DST** | In-country rapid DST is available for FQs and in liquid culture for FQs, injectables, Eto, E, and Z. |
| **Primary all-oral STR regimen** | **Option 1: Lfx-Bdq-Lzd-Cfz**  **Option 2: Lfx (or high-dose Mfx)-Bdq-Lzd-Dlm-Z** |
| **Advantages** | * Both Options include all three Group A drugs. * Option 1 allows a four-drug regimen in FQ-susceptible MDR-TB and avoids the use of Z as many areas have a high-prevalence of Z resistance. * Option 2 allows to employ high-dose Mfx in patients with strains that have low-level FQ resistance. This regimen uses Dlm (less QT prolongation) instead of Cfz. Note, Z is effective in only 50-70% of patients and can be dropped at the 2-month mark if resistance is documented. (Option 2 employs Lfx, instead of high-dose Mfx, in cases susceptible to the FQ, as serves as a second option). |
| **Disadvantages** | * Option 1 has two moderate QT prolonging drugs (Bdq and Cfz), however this combination is acceptable by the WHO. * Option 2 has two moderate QT prolonging drugs (Bdq and high-dose Mfx), there is limited experience using this combination. * Both options may have drug-drug interactions with some ARTs |

## Practical considerations and pearls for using all-oral STRs

The all-oral regimen is not a one-size fits all regimen; often the regimen needs to be adjusted because the patient is infected with a strain that is resistant to one of the drugs or the patient cannot tolerate one of the drugs in the regimen. The following are some practical tips and pearls for using all-oral STRs.

* **What to do if the patient has significant toxicity to a drug in the regimen?** 
  + If significant toxicity develops early in the regimen, before one can determine if the patient has converted, it is generally recommended to replace the drug.
  + For patients with minimal to moderate disease on chest X-ray and who are doing well clinically, if significant toxicity develops after the patient’s sputum has culture converted, the drug can be stopped and not replaced. For patients with severe disease the authors of this guide recommend replacing the drug even if the patient has converted.
  + If significant toxicity develops and the treatment regimen is failing or suspected of failing, then restart a new regimen (and never add a single drug to a failing regimen).
* **Can a patient with moderate to severe anemia prior to the start of treatment receive a regimen that contains linezolid?**

In most cases the patient can be given linezolid at the start of treatment if they are closely monitored with weekly full blood counts for any worsening of the anemia or other effects of linezolid on the blood ( decreased platelets or white blood cells). Despite its hematological effects, linezolid appears not to have an increased risk of hematological adverse effects in patients with preexisting hematological abnormalities.[[24]](#footnote-25) The underlying cause of the anemia should be determined and treated. Often patients with tuberculosis may have a low-grade anemia of chronic disease that will respond to TB treatment and good nutrition. If the hemoglobin falls significantly while on linezolid in a patient with baseline anemia (or falls into a level of severe anemia), the linezolid should be promptly stopped and managed according to Table 15. While pyridoxine (vitamin B6) does not appear to prevent the neuropathy associated with linezolid, it may be helpful in preventing anemia induced by linezolid, although the evidence is limited and effect small. [[25]](#footnote-26) Vitamin B6 is a low-cost supplement with few adverse effects; a dose of 50 mg per day for an adult can be given with linezolid.

* **What can be done if the patient has a contraindication to a drug in the primary all-oral STR that is being used in the country?**

In most cases where a patient cannot take a drug due to contraindication the drug can be substituted with another effective drug. For example, in a patient with severe peripheral neuropathy where 9 months of Lfx-Bdq-Lzd-Cfz-Z is the primary all-oral STR being used, programs can still offer the patient an all-oral STR by replacing the linezolid with delamanid (9 months of Lfx-Bdq-Dlm-Cfz-Z). Because this regimen now uses three drugs that can potentially prolong the QT interval more frequent QT monitoring may be needed for the first 2 months (for example every 2 weeks) until it is documented that the regimen is well tolerated.

* **When to consider that the all-oral STR is not effective and should be changed?**

Possible indications that the regimen is not effective include:

* + Lack of culture conversion: patients should be monitored with monthly cultures to monitor response to treatment. If the culture results do not go from positive to negative by month 4 of treatment this may indicate that the treatment is not effective and you should consider stopping the STR and starting a new LTR, especially if the patient is not clinically improving. If the patient is doing clinically well, the all-oral STR can be continue and monitored closely, including seeing if culture conversion occurs month 5 or 6. In general, patients still culture positive are considered to have failed the STR.
  + Lack of clinical response to treatment: given the delay in receiving culture results (especially in a contexts where transporting samples for culture delays the turnaround time of the results), clinicians can make a judgement that a regimen is not effective based on clinical criteria and smear microscopy. For example, the worsening of symptoms, continued weight loss, increase of cough and fever, lack of sputum microscopy conversion or worsening chest X-ray all indicate possible treatment failure. Not all need to be present and clinical failure is a judgement decision. Before a regimen is declared a failure, adherence and tolerance of treatment should be verified, as well verification that other comorbidities are well treated, and that there is not another unrecognized disease that is mimicking failure.
  + Delayed knowledge of an exclusion criteria: If a patient is found to have one of the exclusion criteria after starting the all-oral STR, then the patient should stop the regimen and start an individualized LTR. For example, LPA is not a perfect test and one can get a false negative FQ-susceptible and the phenotypic test demonstrating FQ-resistance. Other initial exclusion criteria may occur during treatment and in some cases a decision may be made on a case-by-case basis to continue the oral short treatment despite the exclusion criteria, taking into consideration the length of treatment the patient has already had, the response to treatment and the risk of the STR in this patient.
* **What regimen should be used when an all-oral STR fails?**

In patients in whom the all-oral STR fails or the patient has recurrent TB, an individualized LTR should be started based on the principles described in Appendix 2.

## Adult dosing of the TB drugs used in all oral STRs

This guide uses a limited set of drugs to compose all-oral STRs. The dosing is weight based, Table 6 describes adult dosing, age greater than 14 years.

### Table 7 Dosing of the TB drugs used in all-oral STRs for patients older than 14 years

|  |  |  |
| --- | --- | --- |
| **Drug** | **Weight group** | |
| **30-45 kg** | **More than 45 kg** |
| Levofloxacin (250 mg or 500 mg tablets) | 750 mg | 1000 mg |
| Moxifloxacin (400 mg tablets) | 600 mg | 800 mg |
| Bedaquiline (100 mg tablets) | 400 mg once daily for two weeks, then 200 mg three times per week afterwards | |
| Linezolid (600 mg tablets) | 600 mg once daily until 4-month of therapy (then 300 mg once daily or intermittently 600 mg every other day during 5 months) | |
| Clofazimine | 100 mg once daily | |
| Delamanid (50 mg tablets) | 100 mg twice daily (200 mg total daily dose) | |
| Pyrazinamide (400 mg tablets) | 30 to 35 kg: 1200 mg  36 to 45 kg: 1600 mg | 46 to 70 kg: 1600 mg  > 70 kg: 2000 mg |

## Children

Children—defined as individuals ages 0-18 years of age—are an ideal group to prioritize when implementing all-oral short-course regimens for a number of reasons. First, the WHO has recommended that children with non-severe forms of RR-TB be treated with all-oral regimens since 2016, and in the 2018 updated guidelines, they emphasize that “the avoidance of an injectable-containing regimen is particularly desirable in children.”2  Second, safety and dosing data on bedaquiline are available for children ages six years and above and on delamanid for children ages three years and above, and the WHO has recommended these new drugs for children in these age ranges. Data on dosing and safety of these novel agents in children of all ages will likely be available by early 2020 to guide optimal use in children. Third, expert groups have released a consensus statement supporting the use of all oral regimens in children given that the risks associated with injectable use—most notably hearing loss—have a more profound impact on children than adults and outweigh the benefits in the pediatric population.[[26]](#footnote-27) Finally, unlike in randomized clinical trials where children might be excluded for safety reasons, operational research must espouse the principles of equity. Children must be included in operational research protocols unless there is a compelling reason for their exclusion, and operational research is often the ideal way to collect systematic data on programmatic outcomes in pediatric populations.[[27]](#footnote-28)

In general, the principles of regimen design/selection in children should follow the same principles as outlined for adults, with some key exceptions which are defined below:

* Dosing and safety data on bedaquiline in children ages 6 years and above have been reviewed and the WHO recommends bedaquiline can be used in children with RR-TB who are ages 6 years and older. Thus, bedaquiline-containing regimens should be used in this population.
* Dosing and safety data on delamanid in children ages 3 years and above have been reviewed and the WHO recommends delamanid can be used in children with RR-TB who are ages 3 years and older. Thus delamanid containing regimens should be used in this population and delamanid is the preferred novel drug for children between the ages of 3 and 6 years.
* Linezolid dosing and safety has been established in children of all ages. Young children on linezolid will need special monitoring for neuropathy and optic neuritis associated with this drug, including monofilament testing for peripheral neuropathy and object tracking for visual acuity.
* Clofazimine dosing and safety has been established in children of all ages. The availability of clofazimine tablets should make pediatric dosing of this medication more straightforward compared with the use of the gelcaps.
* For children under the age of 3 years, data on the dosing of bedaquiline and delamanid are being assessed and are anticipated by 2020. Depending on the disease severity, bedaquiline and/or delamanid could be used with doses extrapolated from the adult population. Bedaquiline can be crushed and mixed with liquid and this does not affect the bioavailability of the drug. Delamanid can also be crushed and mixed with liquid, although this likely reduces the bioavailability by 85%. A pediatric formulation of delamanid is available via compassionate use from the company, and assistance accessing this agent can be requested from the Sentinel Project on Pediatric Drug-Resistant TB ([tbsentinelproject@gmail.com](mailto:tbsentinelproject@gmail.com)). Alternative agents to use in all-oral regimens for children under the age of 3 years could include PAS or ethionamide.
* Children with clinically diagnosed RR-TB who do not have bacteriologic confirmation should be treated based on the drug susceptibility test results of their known contacts.
* Children with CNS RR-TB or osteoarticular RR-TB should be treated with a minimum of 12 months of therapy.
* Severe disease has been defined by the WHO by the presence of cavities or bilateral disease on chest radiography or extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression. In children the occurrence of advanced malnutrition (defined by syndrome or by metrics) or advanced immunosuppression or positive TB bacteriology (smear, Xpert MTB/RIF, culture) may also be considered when determining disease severity.

Detailed clinical guidance on the management of children with RR-TB can be found in the Fourth Edition of the Field Guide on the Management of Multdrug-Resistant Tuberculosis in Children from the Sentinel Project (<http://sentinel-project.org/wp-content/uploads/2019/02/Updated_DRTB-Field-Guide-2019-V3.pdf>). Detailed dosing tables for the second-line drugs in children based on the WHO 2018 recommendations are included in Appendix 1 of this guide. Advice on the treatment of children with all-oral, short regimens can be obtained from the Sentinel Project on Pediatric Drug-Resistant Tuberculosis (contact [tbsentinelproject@gmail.com](mailto:tbsentinelproject@gmail.com)).

## Pregnancy or lactation

*Pregnancy*

Limited data exist on the optimal management of RR-TB in pregnancy, with fewer than 100 cases ever reported in the literature. It is well-established, however, that injectable agents cause fetal ear toxicity and for this reason, injectable agents should not be used during pregnancy. Because of this, all pregnant women should be treated with all-oral regimens, and thus they are an ideal population to include in observational research on all-oral shorter regimens. While it may be common to exclude pregnant women from early stages of clinical trials, the same principles of equity described for children also apply to this population. Thus, they must be included in operational research protocols unless there is a compelling reason for their exclusion, and operational research is often the ideal way to collect systematic data on programmatic outcomes in women who become pregnant while on RR-TB treatment or who are diagnosed with RR-TB during their pregnancies.[[28]](#footnote-29)

In MDR-TB patients who are pregnant, the main objective is to design a regimen that is effective and likely to cure the mother. The highest risk to both mother and fetus is from inadequately treated MDR-TB. For this reason, medications that have been associated with decreased mortality (i.e. bedaquiline, linezolid, and the third-generation fluoroquinolones) and improved outcomes (i.e. clofazimine, cycloserine) should be prioritized in the treatment of pregnant women.

The use of a specific treatment regimen in a pregnant woman must include a careful discussion of the risks and benefits for the woman and her unborn child. Given that most second-line medications have not been systematically used or assessed in pregnant women, animal studies are often used as a proxy for treatment regimen design. While drugs with identified teratogenic risks may be not primary choices, the potential teratogenic impact of these drugs should be considered in perspective of the risks to the mother/baby/family/community of not treating the mother with an appropriate regimen.

The following table summarizes the limited evidence about the safety of the TB drugs used in all-oral STRs in pregnant and lactating women.

### Table 8 Treatment of pregnant or lactating women with new and repurposed drugs

|  |  |
| --- | --- |
| **Drugs** | **Summary** |
| Lfx or Mfx | Use with caution. No teratogenic effects seen in humans when used for short periods of time (two to four weeks). Long-term use in gravid patients is limited, but given bactericidal activity, benefits often outweighs the risks. |
| Bdq | Animal studies have not revealed any evidence of harm to the fetus or any effects on fertility in females; some males treated with high doses failed to produce offspring. There are no controlled data in human pregnancy.[[29]](#footnote-30)  Pharmacokinetic data in rats treated with doses 1-2 times the human clinical dose have shown 6- to 12-fold higher Bdq concentrations in milk than the maximum concentrations observed in maternal plasma. |
| Dlm | In rabbit reproductive studies, embryo-fetal toxicity was observed at maternally toxic dosages. Avoid in pregnancy; however, the benefits in patients with no other options may outweigh the risks.  Pharmacokinetic data in animals have shown excretion of Dlm/metabolites into breast milk. In lactating rats, the Cmax for Dlm in breast milk was 4-fold higher than that of the blood. |
| Lzd | Animal studies have failed to reveal evidence of teratogenicity, but embryofetal toxicity was observed at maternotoxic doses. Placental transfer of this drug and/or its metabolites was observed in rats. There are no controlled data in human pregnancy. |
| Cfz | There are no studies of Cfz use in pregnant women. Few cases of Cfz use during pregnancy have been reported in the literature.  Embryofetal toxicity studies were conducted in rats, rabbits and mice. In mice, Cfz-induced embryotoxicity and fetotoxicity was evident. |
| Z | Experience in gravid patients suggests safety; however, there is less data than other first-line anti-TB drugs. WHO recommends its routine use. |

*Lactation*

For a variety of reasons, breastfeeding is still the ideal strategy for women and their infants. This is true for women with RR-TB on treatment as well. Little is known about the safety of most second-line medications during breastfeeding, although the doses of medications that can be passed along in the breast milk are usually quite low. Appropriate infection control measures should be followed during breastfeeding.

## Extrapulmonary TB

There is limited experience for the use of bedaquiline and delamanid in extrapulmonary TB. Both drugs are thought to have poor central nervous system (CNS) penetration. Many all-oral STRs heavily depend on bedaquiline or delamanid and it is not known if certain types of extrapulmonary TB, such as TB osteomyelitis or TB meningitis, can be treated with shorter treatment durations. Therefore, regimens for extrapulmonary TB are often individualized based on the type of extrapulmonary TB. Most forms of extra-pulmonary TB, such as TB of the lymph nodes and plural effusions, can likely be treated with all-oral STRs under operational research conditions. TB osteomyelitis or TB meningitis should be treated for at least 12 months under operational research conditions or by a full LTR (18-20 months). Table 9 describes the drugs commonly used in all oral STR and the knowledgebase of their use in extrapulmonary TB.

### Table 9 Extrapulmonary TB and the drugs commonly used in all-oral STR

|  |  |
| --- | --- |
| **Drugs** | **Comments** |
| Lfx or Mfx | Penetration of the FQ’s into the CNS only occurs in the presence of meningeal inflammation. Mfx is thought to have better penetration based on animal studies. |
| Bdq | Very limited experience with Bdq in TB meningitis or TB osteomyelitis. One patient with meningitis had undetectable levels of Bdq in CSF.[[30]](#footnote-31) Drug is protein bound and likely has low penetration into the CSF. It is not been adequately studied if Bdq has significant penetration in inflamed meninges as do many drugs. |
| Dlm | Very limited experience with Dlm in TB meningitis or TB osteomyelitis. Drug is protein bound and likely has low penetration into the CSF. It is not been adequately studied if Dlm has significant penetration in inflamed meninges as do many drugs. |
| Lzd | Excellent bone and soft-tissue penetration; commonly used for osteomyelitis due to gram-positive bacteria. Good CNS penetration.[[31]](#footnote-32) |
| Cfz | Cfz has been used extensively to treat leprosy lesions in soft tissue, though it is unclear if this means that bone and soft tissue penetration is adequate. |
| Z | Z has good penetration in bone, soft tissues and CNS. |

## Co-morbidities (HIV, chronic renal disease and insufficiency, hepatitis C)

### Table 10 Special populations

|  |  |
| --- | --- |
| **Situation** | **Recommendations** |
| HIV | * Antiretroviral therapy (ART) should be given to any HIV co-infected MDR-TB patient without delay. * ART can be started as soon as MDR-TB treatment is tolerated—usually within a few days. The risk of immune reconstitution syndrome can be mitigated by designing an appropriate MDR-TB regimen. * Bdq has important interactions with ART that will affect the choice of ART (see section 3.3.2). |
| Chronic renal insufficiency | * Bdq and Dlm are not renally excreted and no dose adjustment is required in mild/moderate renal insufficiency. There is no data on the use of either of these drugs in patients with severe renal impairment. * No dose adjustment of Lzd is required in patients with renal impairment; however, the two primary metabolites of Lzd accumulate in patients with renal impairment and the clinical significance of this is unknown. * No dose adjustment of Cfz is required in patients with renal impairment. |
| Hepatitis C | * MDR-TB is strongly correlated with hepatitis C infection in many countries. * Active hepatitis C is a risk factor for MDR-TB treatment failure. * Direct-acting antivirals (DAAs) are well-tolerated when given with MDR-TB treatment, although experience is limited. |
| Diabetes | * Diabetes is a risk factor for renal disease, peripheral neuropathy and eye disease. * Close monitoring for peripheral neuropathy is warranted in diabetic patients on Lzd with a low threshold for lowering the dose or stopping the drug if peripheral neuropathy develops or exacerbates while on treatment. * Treatment of diabetes with normalization of theHgA1C should occur concurrently with MDR-TB treatment. |

## Definitions: culture conversion, treatment outcome definitions and recurrence

Culture conversion and reversion are defined as the following:

**Conversion** (to negative)

Culture is considered to have converted to negative when two consecutive cultures taken at least 15 days apart are found to be negative. In such case, the specimen collection date of the first negative culture is used as the date of conversion.

**Reversion** (to positive)

Culture is considered to have reverted to positive when after an initial conversion, two consecutive cultures taken at least 30 days apart are found to be positive.

Outcomes are based on *Definitions and reporting framework for tuberculosis (2013 revision)* released by WHO in 2013. The outcome is assigned on the principle of "first outcome met" and is not revised during the follow up period.

**Treatment Outcomes:**

**Cured**

Treatment completed without evidence of failure AND three or more consecutive cultures taken at least 30 days apart at the end of treatment.

**Treatment completed**

Treatment completed without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative at the end of treatment.

**Treatment failed**

Treatment terminated or need for permanent regimen change of ≥2 anti-TB drugs because of:

lack of conversion.

bacteriological reversion after conversion to negative.

evidence of acquired resistance to drugs in the shorter regimen.

adverse drug reaction.

**Died**

A patient who dies for any reason during the course of treatment.

**Lost to follow-up**

A patient whose treatment was interrupted for 2 consecutive months or more.

**Not evaluated**

A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown, or where the shorter regimen was not available.)

**Withdrawn**

A patient is taken off the all-oral STR for any reason other than treatment failure (for example, an exclusion criterion was discovered after the start of the regimen, withdrawn patient informed consent or for other reasons) and referred to the PMDT program for routine care. (This outcome definition is not part of the standard WHO programmatic definitions).

**Treatment success** is defined as the sum of cured and treatment completed.

**Recurrent TB**

Defined as having either (1) or (2) after cure or completion of treatment:

1. Two positive cultures (taken on different days), irrespective of the presence of clinical signs and symptoms of TB.
2. One positive culture with clinical signs and symptoms or radiographic deterioration (an isolated positive smear or culture without clinical or radiographic deterioration after treatment completion provides insufficient evidence to define recurrent TB).

If genotyping is available, recurrent TB may be further classified as relapse, reinfection, or undetermined as defined below:

* **Relapse**: isolates of the recurrent episode share the same genotype pattern with isolates of the first episode of MDR-TB.
* **Reinfection**: isolates of the recurrent episode and isolates of the first episode of MDR-TB have different genotype patterns.
* **Undetermined:** there is insufficient information to determine whether the recurrent episode is due to relapse or reinfection.

# Treatment education and patient consent

## Treatment education material

Patient education materials should be provided to all patients undergoing MDR-TB treatment. Often the very same material used by the NTP can be used with minor modifications to educate the patient on the shorter duration of the regimen and novel nature of it. Examples of patient education materials are provided in the endTB Toolkit on implementation of the all oral shorter regimen under operational research.3

## Patient consent

Patient consent forms should be part of the study protocol that is approved by an ethics committee, the ministry of health, or both. For all patients starting all-oral STRs, written consent must be obtained. The consent process will ensure the patient is:

* Aware of the novel nature of the all-oral STRs;
* Understands the reason(s) why the all-oral STR is being proposed as an option for the treatment of MDR-TB;
* Recognizes the possible benefits and potential harms, including the uncertainty that surrounds outcomes.

Examples of informed consent are provided in the endTB Toolkit on implementation of the all oral shorter regimen under operational research.3

Additionally, for patients that meet the definition of a minor or “incapacitated” by national law, consent from the legal representative is required.

All patients should have the option of withdrawing consent at any time. The study protocol should describe what happens to patients who withdraw their consent. In most programs they are transferred to the all-oral LTR used in the national program. Depending on the time on treatment with the all-oral STR and clinical status at the time of withdrawal, a new regimen may be started or time in the all-oral STR can be counted towards an all-oral LTR.

# Baseline evaluation and monitoring treatment

## Monitoring schedule for patient follow-up

Patient should undergo appropriate baseline screening and monitoring during and after treatment, including clinical evaluation, bacteriological and laboratory testing as described in Table 11.

Additional remarks:

* The laboratory and ECG follow-up should be continued at monthly intervals for the first six months and then if indicated (because of palpitations, syncope, or cardiac symptoms).
* Clinical judgement is warranted; this guide advises to err on the side of caution, with more frequent monitoring in fragile patients or patients with co-morbidities.
* For cases of electrolyte disturbances or ECG abnormalities, more frequent monitoring should be performed as described in the section on clinical management of adverse events of interest (Section 6).
* Monitoring with audiometry does not need to be performed in patients on all-oral STRs.
* Urea, creatinine, and electrolytes should be performed at baseline and then repeated if clinically indicated. No need for routine monitoring of the urea, creatinine, and electrolytes.

### Table 11 ***Monitoring schedule***

|  | **Baseline Visit** | **Week 2** | **Month 1** | **Month 2** | **Month 3** | **Month 4** | **Month 5** | **Month 6** | **Until end of treatment** | **End of treatment** | **3 months post-end-of-treatment** | **6 months post-end-of-treatment** | **9 months post-end-of-treatment** | **12 months post-end-of-treatment** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***Clinical evaluation*** | | | | | | | | | | | | | | |
| Vital signs | X |  | X | X | X | X | X | X | Monthly | X | X | X | X | X |
| Brief peripheral neuropathy screen (BPNS) if on Lzd. | X |  | X | X | X | X | X | X | Monthly | X |  |  |  | X |
| Visual acuity and colorblindness screen | X |  | X | X | X | X | X | X | Monthly | X |  |  |  | X |
| Post-end-of- treatment consultation |  |  |  |  |  |  |  |  |  | X | X | X | X | X |
| Assessment and follow-up of adverse events | X | X | X | X | X | X | X | X | At each scheduled /unscheduled visit | X | X | X | X | X |
| Weight | X | X | X | X | X | X | X | X | Monthly | X | X | X | X | X |
| ***Bacteriological testing*** | | | | | | | | | | | | | | |
| Smear | X |  | X | X | X | X | X | X | Monthly | X |  | X |  | X |
| Culture | X |  | X | X | X | X | X | X | Monthly | X |  | X |  | X |
| Freeze baseline culture (if possible) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Xpert MTB/RIF | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| LPA (Hain GenoType MTBDRsl) | X |  |  | If smear- or culture-positive check for amplification of resistance | | | | | | | | | | |
| Culture-based first-line DST | X |  |  | If smear- or culture-positive check for amplification of resistance | | | | | | | | | | |
| Culture-based second-line DST | X |  |  | If smear- or culture-positive check for amplification of resistance | | | | | | | | | | |
| ***Laboratory testing*** | | | | | | | | | | | | | | |
| ECG | X | X | X | X | X | X | X | X | If indicated |  |  |  |  |  |
| Full blood count (hemoglobin, white blood cells and platelets) if on Lzd | X | X | X | X | X | X | X | X | Monthly  (if on Lzd) | X |  |  |  |  |
| Liver function tests (AST, ALT) | X | X | X | X | X | X | X | X | If indicated | X |  |  |  |  |
| Serum creatinine (at baseline and then only if clinically indicated) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serum potassium  (at baseline and then only if clinically indicated) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hepatitis Bs Antigen | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hepatitis C Antibody | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| HbA1c  (repeated every 3 months if elevated) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pregnancy test (females) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| HIV testing | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CD4 (repeated every 6 months if HIV+) | X |  |  |  |  |  |  | X |  |  |  |  |  |  |
| HIV Viral load (repeated every 6 months if HIV +) | X |  |  |  |  |  |  | X |  |  |  |  |  |  |
| Chest X-Ray | X |  |  |  |  |  |  | X |  |  |  |  |  |  |

# Drug safety and the management of adverse events

## Scope of safety data collection and definitions

There are three levels of monitoring in the aDSM Framework;7

* Core package: requiring monitoring for and reporting of all SAEs (in cases where this is not possible, then at least report SUSARs);
* Intermediate package: includes SAEs as well as AEs of special interest;
* Advanced package: includes all AEs of clinical significance.

The minimum requirements for safety data collection in operational research conditions are the same as those for programmatic use of MDR-TB regimens, which is the WHO’s aDSM framework core package. This framework includes a core package of requirements for the monitoring and management of adverse events, as well as the reporting of all serious adverse events (SAEs). SAEs are defined below. Many countries will have local pharmacovigilance (PV) requirements for TB drugs and may need to go beyond these core PV requirements.

However, some countries may not have a functioning PV system and hence will have to decide what they can collect in terms of SAEs and where to report them. The WHO maintains a global database for TB active drug-safety monitoring and management (aDSM) and encourages countries to contribute to it.[[32]](#footnote-33) The WHO global database for aDSM is a very good option for countries that do not have a functional PV system.

Unlike a number of years ago, the common SAEs are now fairly well described for bedaquiline, delamanid, clofazimine, and linezolid. This guide suggests as an alternative to the minimum package of reporting (especially for countries with a fragmented or no formal PV system) to routinely report any SAE they suspect to be odd or out of the ordinary, and due to a drug. There is a special term for this which is “suspected unsuspected SAE” or “**SUSAR**” for short.

An **adverse event (AE)** is defined as any untoward medical occurrence in a patient administered a pharmaceutical product, 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 it may be related to this medicinal product.

All patients are monitored and assessed clinically for AEs (including lab abnormalities) at all visits during treatment (see monitoring schedule, Table 11 ) and any detected AE is managed accordingly. Refer to the next section in this clinical guide.

It is also preferable to record pregnancies (and neonatal follow-up) and medical errors as serious adverse events.

**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 judgement 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 jeopardize the patient or 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.

In addition to SAEs, programs should report the following to regulatory authorities:

* **Pregnancy.** Pregnancymust be avoided during MDR-TB treatment and effective contraception is recommended. If despite all precautions, if a patient is found to be pregnant, the recommendations in Section 4.9 should be followed. Infants born from exposed pregnancies should be followed-up until they reach 12 months of age. Pregnancies on MDR-TB treatment (including both STRs and LTRs) are often required to be reported to the country’s PV unit.
* **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. Medical errors in MDR-TB treatment, including both STRs and LTRs, are often required to be reported to the country’s PV unit.

The clinician is responsible for appropriately managing all AEs, drug-exposed pregnancies, and potential medication errors in accordance with the local standards-of-care, as well as 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 SAEs, pregnancy exposure, abnormal lab results, etc). Specific clinical management suggestions are available in Section 7.3.

## Grading SAEs and assigning causality

SAEs are commonly graded based on severity. This guide recommends using the Severity Grading Scale described in Table 14 -Table 22 (grades 1-4[[33]](#footnote-34)). For those AEs not described in the Severity Grading Scale, the general definition of clinical severity should apply, as described below. Grading AEs is not only used for reporting, but can be helpful in determining the action needed for managing the AE.

### ***Tabl******e*** 12 ***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; minimal or no medical intervention/ therapy required. | Marked limitation in activity\*, some assistance usually required; medical intervention/therapy required, hospitalization(s) 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. | | | |

Reported SAEs 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 such as medical history, risk factors, past drug use, concomitant procedures, TB progression, etc.

### ***T******able 13 Causality categories definition***

| **Causality Category** | **Description** |
| --- | --- |
| **Related** | There is a reasonable possibility that the AE may be related to the drug(s). Elements in favor of a reasonable causal relationship include:   * A favorable temporal relationship, * A positive de-challenge and/or re-challenge, * 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. |

## Clinical management of adverse events of interest

***Peripheral neuropathy***

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

**Possible other causes: d4T, ddI**

* Peripheral neuropathy is a common adverse event of MDR-TB treatment caused by drug toxicity to the nerves of the peripheral nervous system.
* All patients taking isoniazid should receive 50 mg of pyridoxine daily; all patients taking Cs/Trd should receive 50 to 100 mg of pyridoxine (doses greater than 100 mg of pyridoxine may cause peripheral neuropathy and therefore lower doses than previously recommended are now the norm).
* 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.
* Peripheral neuropathy can be difficult to assess in young children. Symptoms of peripheral neuropathy in young children may include crying when walking or using hands, rubbing or slapping of hands and feet, crying when putting on sock and/or shoes, and difficult walking, grasping, or handling toys. Younger children should have monofilament or pin testing of their hands and feet at each visit and reflexes should be assessed as well.
* After a diagnosis of peripheral neuropathy, the subjective sensory neuropathy score from the BPNS (See Step 1 of the BPNS description) should be used for grading ( Table 14 ).

### Table 14 ***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/Trd, high-dose H, 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/Trd or high-dose H are not essential to the regimen, consider suspending these drugs. | Stop Cs/Trd, high-dose H, and Lzd. If symptoms improve, and if the drugs are essential to the regimen, consider restarting Cs/Trd or high-dose H. 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 the 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 co-infected patients, avoid use of d4T or ddI in combination with cycloserine/terizidone or linezolid because of an increased risk of peripheral neuropathy.
* Symptomatic relief:
* Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms.
* Tricyclic antidepressants have traditionally been used to treat neuropathic pain; however, due to their QT prolonging characteristics (and because they may increase the risk of arrhythmias) are best avoided when using all-oral regimens that contain drugs that may also prolong the interval. Tricyclic antidepressants should also be avoided in patients taking linezolid to avoided due to potential risk of serotonergic syndrome.
* 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 patient to rate the severity of each symptom on a scale from 01 (mild) to 10 (most severe) for both 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 patient 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). However, only the subjective sensory neuropathy score (BPNS step 1) is used for grading.

***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 more rare.
* Myelosuppression is very common in patients receiving linezolid. In one clinical trial of linezolid, approximately 18% of patients taking linezolid experienced clinically significant myelosuppression.
* 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 15 ***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 | 99,999 - 75,000 /mm³ | 74,999 - 50,000 /mm³ | 49,999 - 20,000 /mm³ | < 20,000 /mm³ |
| White blood cells decreased | <LLN - 3,000/mm3 | <3,000 - 2,000/mm3 | <2,000 - 1,000/mm3 | < 1,000 /mm3 |
| Absolute neutrophil count low | 1,500 – 1,000/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).  For Grade 2 neutropenia, stop Lzd immediately. | Stop Lzd immediately.  For Grade 3 anemia, consider erythropoietin (if available) .  Restart Lzd at reduced dose once toxicity has decreased to Grade 1. | Stop Lzd immediately. Consider hemo-transfusion 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 for Grades 3 or 4; consider dose reduction for Grades 1 or 2.
2. If iron-deficiency anemia is suspected to be contributing to the anemia where linezolid toxicity is involved, check iron stores and treat if iron-deficiency is diagnosed. Empiric treatment with iron can be done if testing for iron-deficiency is not possible. Note, oral iron may bind with the FQ and decrease the absorption of the FQ. Dose iron at least 3 hours apart from the FQ.
3. Monitor full blood counts regularly.
4. If erythropoietin is available, consider using for anemia Grades 3. (Most programs manage anemia secondary to linezolid toxicity without erythropoietin, with good antidotal outcomes).
5. Hospitalize the patient and consider transfusion (or erythropoietin) if the myelosuppression is severe.
6. Consider additional anti-TB drugs to reinforce the regimen if linezolid is being permanently stopped.

***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. Erythropoietin is not effective if there is significant iron deficiency present.

*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 pre-filled 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.

***Prolonged QT interval***

**Possible anti-TB drug causes: Cfz, Bdq, Mfx, Dlm, Lfx**

**Possible other causes: Many other drugs can cause QT prolongation. For example: erythromycin, clarithromycin, quinidine, ketoconazole, fluconazole, and antipsychotics – all have some risk including haloperidol, chlorpromazine, and risperidone. Many anti-nausea drugs (ondansetron/granisetron, domperidone), methadone, and some antiretrovirals, in addition to genetic causes such as long QT syndrome and hypothyroidism can also cause QT prolongation.**

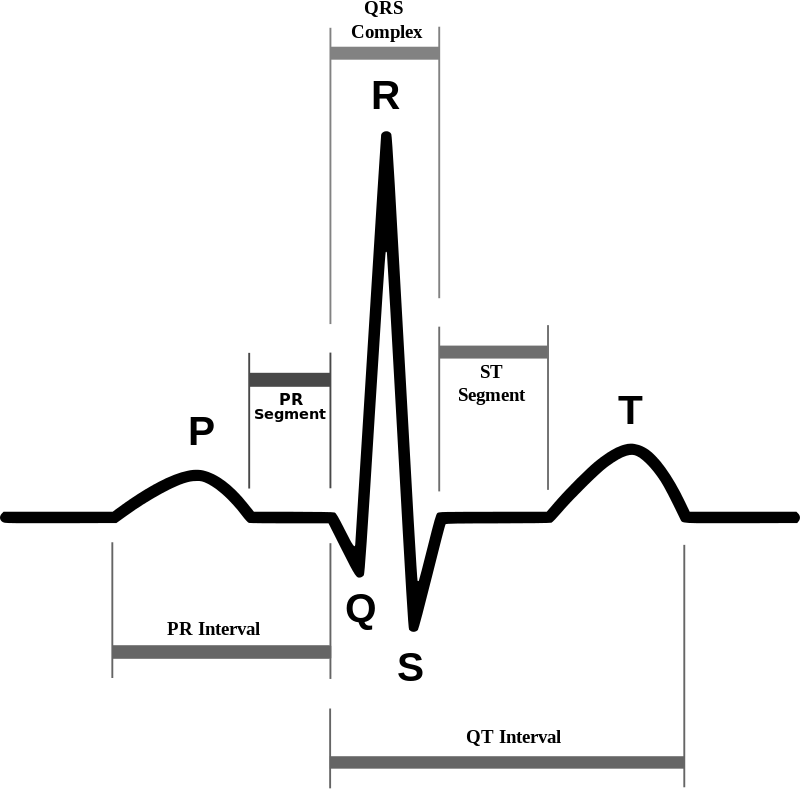
* Check an ECG if the patient has clinical symptoms (tachycardia, syncope, palpitations, or weakness or dizziness) of cardiotoxicity. Check the QT interval and rule out an arrhythmia.
* The QTc will be calculated using the Fridericia's formula which corrects for the heart rate and has been shown to be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

Where:

QTcF = the corrected QT interval

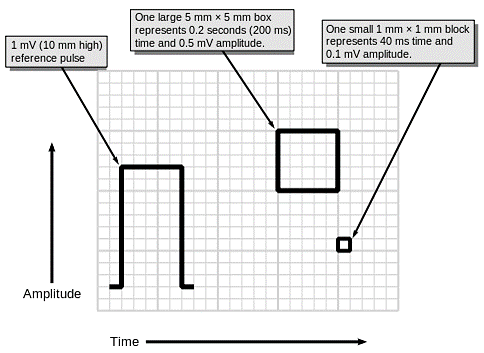
QT = the time between the start of the QRS complex and the end of the T wave

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



**Figure 1**

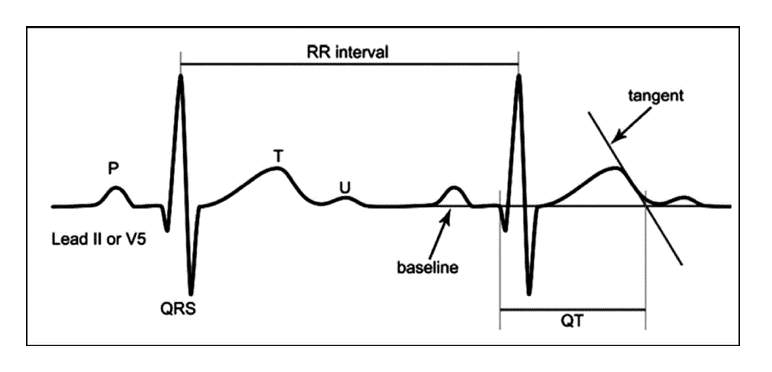
* The ECG machine should be calibrated to ensure that the following voltage and speeds apply:



**Figure 2**

**Procedure for measuring RR and QT interval**

* Obtain the 12-lead ECG:
* 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.
* Ensure the sweep speed is set to 25 mm/sec. This will allow for standard calibration and measurement of the QT interval.
* Measure the RR and QT intervals manually (Figure 1 illustrates the intervals):
* 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.
* Often, leads II or V5 may best show the end of the T wave. Try to measure the QT interval in these leads first.
* 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.
* The QT interval should be measured from the beginning of the QRS complex to the end of the T wave.
* 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.
* 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.
* 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.



**Figure 3**

* Correct the QT interval for the heart rate:
* 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.
* The QTcF can also be determined by using a calculator and using the Fridericia's formula; however, it is recommended for clinicians to use the other methods as it is less prone to error. One way is to use the QTcF nomogram below.
* Even simpler and quicker than the nomogram, are several applications (apps) available on mobile phones (e.g. Android, iPhone) that are designed to calculate the QTcF with a minimum of effort. For example - the QTc Calculator for Android phones (Google Play). These apps require the user to enter the QT interval and the RR interval, after which the QTc will be calculated according to several formulas. The correct units should be selected (e.g. mm or msec), as well as the correct formula.
* 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".
* Record RR interval, heart rate, and the QTcF interval in the patient’s chart:
* The RR interval is measured in seconds.
* 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).
* 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 16 ***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** |
| --- | --- | --- | --- | --- |
| Electrocardiogram QT Corrected Interval Prolonged | QTcF 450 – 480 ms# | QTcF 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. In the event that ionized calcium and magnesium is not able to be checked, give empiric magnesium whenever hypokalemia (low potassium) is found.
* Abnormal electrolytes in all oral STRs are most commonly due to vomiting or diarrhea, as the injectable is not used. The vomiting or diarrhea should be assessed and treated.
* Whenever a low potassium is found to be Grade 3 or 4, it should trigger urgent management with replacement and frequent repeat potassium testing (often daily or multiple times a day) to document if potassium is moving in the correct direction.

**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 TSH and treat any hypothyroidism found.
5. Once stable (QTCF 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 prolong the QT interval, consider suspending them.
* If the patient is on moxifloxacin, consider using levofloxacin instead.
* If the patient is 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).

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

**Possible anti-TB drug causes: Lzd, E, Eto/Pto, 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.
* Visual acuity may be difficult to formally assess in young children and age-appropriate visual screening tests should be used. Visual acuity can also be assessed with object tracking, especially using bright objects or toys. Symptoms of diminished visual acuity in children may include bumping into walls or objects, tripping, and inability to grasp or find objects.

### Table 17 ***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 in the affected eye:  20/200 [6/60] or worse |
| 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.

### 

***Elevated liver enzymes (hepatotoxicity)***

**Possible anti-TB drug causes: Z, H, Cfz, PAS, Eto/Pto, Bdq, FQ, Amx/Clv**

**Possible other causes: viral hepatitis (A, B, C), NVP, many other drugs, alcohol**

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, hepatotoxicity due to medications resolves upon discontinuation of suspected drug.
* In HIV co-infection, 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 re-challenged.
* Chronic alcoholism is a major cause of hepatotoxicity in patient with RR-/MDR-TB.

### Table 18 ***Clinical management of elevated liver enzymes according to severity grading***

| **Severity grade\*** | **Grade 1 Mild** | **Grade 2 Moderate** | **Grade 3 Severe** | **Grade 4 Life-threatening** |
| --- | --- | --- | --- | --- |
| ALT (SGPT) | >ULN – 3.0 x ULN | >3.0 – 5.0 x ULN | >5.0 – 20.0 x ULN | >20.0 x ULN |
| AST (SGOT) | >ULN – 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. |
| \* NCI Common Terminology Criteria for Adverse Event, v.4.03 14-Jun-2010. | | | | |

**Suggested management strategy:**

* 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.
* If alcohol is considered to be contributing to the hepatotoxicity, treatment for alcohol addiction may be need in order to help the patient abstain from alcohol.

***Hypokalemia***

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

**Possible ART causes: TDF (rare)**

**Other causes: Vomiting, diarrhea**

* 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). None of the commonly used drugs in the all-oral STR cause electrolyte wasting or renal tubular toxicity
* 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 are good sources of supplementation.

### Table 21 ***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 mmol/L | 2.9 - 2.5 mmol/L | 2.4 - 2.0 mmol/L or intensive replacement therapy or hospitalization required | < 2.0 mmol/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia |
| Action | Start oral potassium replacement therapy. Check serum magnesium and replace if necessary. | Start aggressive oral potassium replacement therapy. Replace magnesium as necessary. | Start IV potassium replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary. | 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. | | | | |

### Table 22 ***Clinical management of hypomagnesemia according to severity grading***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Severity grade\*** | **Grade 1 Mild** | **Grade 2 Moderate** | **Grade 3 Severe** | **Grade 4 Life-threatening** |
| Hypomagnesemia | 0.70-0.60 mmol/L | 0.59-0.45 mmol/L | 0.44-0.30 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. | | | | |

**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.

* Hypokalemia may be refractory if concurrent hypomagnesemia is not also corrected.
* If unable to check serum magnesium, give empiric oral replacement therapy in all cases of hypokalemia with magnesium gluconate 1000 mg twice daily.

1. In all cases of detected serum electrolyte disturbances (Grades 1-4) obtain an electrocardiogram as soon as possible and then weekly until potassium and other electrolytes return to normal.
2. Drugs that prolong the QT interval should be discontinued in patients with evidence of QT interval prolongation in the presence of Grade 2 or above hypokalemia.

### Table 23 ***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: 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). Potassium chloride 10% (100mg/ml) ampoules = 1g per ampoule = 13.4 mmol. Potassium chloride controlled release tablets of 600mg = 8mmol/tablet. | | |

### Table 24 ***Magnesium replacement therapy***

| **Magnesium level (mmol/L)** | **Total daily dose** | **Monitoring frequency** |
| --- | --- | --- |
| > 0.70 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). | | |

***Hypothyroidism***

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

**Possible ART causes: d4T**

* None of the drugs commonly used in the all-oral STR are associated with thyroid toxicity; however, patient may have a history of receiving TB drugs that are thyroid toxic.
* 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 T4, T3) 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 25 ***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 instrumental ADL | 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.

* Young healthy adults can be started on 75 to 100 mcg daily.
* Older patients should begin treatment with 50 mcg daily.
* Patients with significant cardiovascular disease should start at 25 mcg daily.

1. Children clear thyroxine faster than adults, so daily replacement doses may be higher.

* Children (4-15 years): 4 mcg/kg/day (maximum dose is 200 mcg).
* Infants (1-3 years): 10-15 mcg/kg/day (maximum dose is 200 mcg).

1. Monitor TSH every 1 to 2 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.
2. 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.

## Frequent adverse events

This table is extracted from the full Severity Grading Scale, which is available at <http://endtb.org/resources/pharmacovigilance>. The following table does not include the adverse events of interest; for those grading scales, refer to the relevant section.

### Table 26 List of most frequent adverse events

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Adverse event** | **Definition** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| **Cardiovascular disorders** | | | | | |
| Cardiac rhythm | Abnormality in cardiac rhythm other than QT Interval Prolongation. | N/A | Asymptomatic, transient signs, no treatment required | Recurrent/persistent; symptomatic treatment required | Unstable dysrhythmia; hospitalization and treatment required |
| **Chemistry** | | | | | |
| Lactate increased (lactic acidosis) | Increase in blood lactate accompanied or not with blood acidification. | ULN to < 2.0 x ULN without acidosis | ≥ 2.0 x ULN without acidosis | Increased lactate with pH < 7.3 without life threatening consequences | Increased lactate with pH < 7.3 with life threatening consequences |
| ***Ear Disorders*** | | | | | |
| Hearing Impaired | An audiogram that demonstrates hearing loss | Adult 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.  Minor enrolled on a monitoring program (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.  Minor enrolled on a monitoring program (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.  Minor enrolled on a monitoring program (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. | Adult: profound bilateral hearing loss (threshold >80 dB HL at 2 kHz and above); nonservicable hearing  Minor: audiologic indication for cochlear implant and additional speech-language related services indicated. |
| 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 |
| 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 |
| **General Disorders** | | | | | |
| 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 |
| **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 |
| **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 |
| 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; and/or Hamilton Anxiety Rating Scale score 1-17 | Moderate symptoms; limiting instrumental ADL; and/or Hamilton Anxiety Rating Scale score 18-24 | Severe symptoms; limiting self-care ADL; hospitalization not indicated; and/or Hamilton Anxiety Rating Scale score 25-30 | Life-threatening; Hamilton Anxiety Rating Scale score >30; and/or hospitalization indicated |
| Depression | A disorder characterized by melancholic feelings of grief or unhappiness. | Mild depressive symptoms; and/or PHQ9 depression score 1-9 | Moderate depressive symptoms; limiting instrumental ADL; and/or PHQ9 depression score 10-14 | Severe depressive symptoms; limiting self-care ADL; hospitalization not indicated; and/or PHQ9 depression score 15-19 | Life-threatening consequences, threats of harm to self or others; PHQ9 depression score 20-27; and/or 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 |
| **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 |
| Acute Kidney Injury | A disorder demonstrated by decreased renal function | 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 |
| **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, maculopapular 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 |

# References

Relevant references to produce this guide include:

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* [*PIH Guide to the Medical Management of MDR-TB, 2nd Edition*](https://drtbnetwork.org/pih-guide-medical-management-multidrug-resistant-tuberculosis-eBook). Partners In Health, Boston, USA. USAID TB CARE II. 2013.
* *Report of the Guideline Development Group Meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis: A review of available evidence (2016)* (WHO/HTM/TB/2017.01). WHO, Geneva. 2017.
* [*Tuberculosis: practical guide for clinicians, nurses, laboratory technicians and medical auxiliares. 2014 Edition*](http://refbooks.msf.org/msf_docs/en/tuberculosis/tuberculosis_en.pdf). Médecins Sans Frontières and Partners In Health.
* [*The use of bedaquiline in the treatment of MDR-TB: interim policy guidance*](http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf?ua=1) (WHO/HTMTB/2013.6). WHO, Geneva. 2013.
* [*The use of delamanid in the treatment of MDR-TB: interim policy guidance*](http://apps.who.int/iris/bitstream/10665/137334/1/WHO_HTM_TB_2014.23_eng.pdf?ua=1&ua=1) (WHO/HTM/TB2014.23). WHO, Geneva. 2014.
* *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.
* *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update* (WHO/HTM/TB/2016.04). WHO, Geneva. 2016.
* *WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis* (WHO/HTM/TB/2017.20). WHO, Geneva. 2017.

#### Appendix 1: Pediatric Dosing Recommendations

## Weight-Based Dosing in Children

**GROUP A DRUGS**

The following dosing tables (1a-1n) are meant to assist in optimal treatment of children with MDR-TB. The dosing ranges are based on the latest available pharmacokinetic data. However, it is important to realize that dosing recommendations can change quickly as additional studies are completed, and these recommendations could change. The weight-based dosing coincides with what is recommended by the WHO in their 2018 MDR-TB guidance. Some of the weight bands, however, are different and the WHO starts their weight-bands at 5 kg. This is because when the dispersible tablets are used, more precise dosing can be achieved within more narrow weight bands.

###### Table 1a: Levofloxacin

|  |  |  |  |
| --- | --- | --- | --- |
| **Levofloxacin 100 mg scored, dispersible tablets**  Recommended dosing: 15-20 mg/kg/day  Weight-based dosing | | | |
| **Weight Band (kg)** | **Dose** | **Number of 100 mg tablets** | **Number of 250 mg tablets** |
| 1 kg | 20 mg | Mix 100 mg tablet in 10 ml of water and administer 2 ml of mixture immediately | - |
| 2 kg | 40 mg | Mix 100 mg tablet in 10 ml of water and administer 4 ml of mixture immediately | - |
| 3 kg | 50 mg | 0.5 | - |
| 4-6 kg | 100 mg | 1 | 0.5 |
| 7-9 kg | 150 mg | 1.5 | 0.5 |
| 10-12 kg | 200-250 mg | 2.0 to 2.5 | 1 |
| 13-15 kg | 300 mg | 3 | 1-1.5 |
| 16-18 kg | 300-350 mg | 3-3.5 | 1.5 |
| 19-20 kg | 400 mg | 4 | 1.5 |
| 21-23 kg | 400-450 mg | 4-4.5 | 2 |
| 24-25 kg | 500 mg | 5 | 2 |
| 26-35 kg | 750 mg | - | 3 |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

###### Table 1b: Moxifloxacin

|  |  |  |  |
| --- | --- | --- | --- |
| **Moxifloxacin**  Recommended dosing: 10-15 mg/kg/day  Weight-based dosing | | | |
| **Weight Band (kg)** | **Dose** | **Number of 100 mg tablets** | **Number of 400 mg tablets**  **(dissolve in 10 ml water)** |
| 1 kg | 10 mg | Mix 100 mg tablet in 10 ml of water and administer 1 ml of mixture immediately | - |
| 2 kg | 20 mg | Mix 100 mg tablet in 10 ml of water and administer 2 ml of mixture immediately | - |
| 3 kg | 30 mg | Mix 100 mg tablet in 10 ml of water and administer 3 ml of mixture immediately | - |
| 4-6 kg | 50-80 mg | 0.5-0.75 | 2 ml |
| 7-9 kg | 150 mg | 1.5 | 3 ml |
| 10-15 kg | 200 mg | 2.0 | 4 ml |
| 16-19 kg | 300 mg | 3 | 0.5-.75 of a 400 mg tablet |
| 20-25 kg | 400 mg | 4 | 1 |
| 26-35 kg | 400 mg | - | 1 |

###### Table 1c: Linezolid

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Linezolid**  Dose: 10-12 mg/kg/day > 16kg; 15 mg/kg once daily in children < 16 kg  Weight-based dosing | | | | |
| **Weight Band (kg)** | **Dose** | **150 mg tablets (not yet available)** | **600 mg tablet** | **20 mg/ml suspension** |
| 1 kg | 15 mg once daily | Mix 150 mg tablet in 15 ml of water and administer 1.5 ml of mixture immediately | - |  |
| 2 kg | 30 mg once daily | Mix 150 mg tablet in 15 ml of water and administer 3 ml of mixture immediately | - |  |
| 3 kg | 45 mg once daily | Mix 150 mg tablet in 15 ml of water and administer 4.5 ml of mixture immediately | - |  |
| 4 kg | 60 mg once daily | Mix 150 mg tablet in 15 ml of water and administer 6 ml of mixture immediately | - |  |
| 5 kg | 75 mg once daily | 0.5 of 150 mg tablet | - | 4 ml |
| 6 kg | 90 mg once daily | Mix 150 mg tablet in 15 ml of water and administer 9 ml of mixture immediately | 0.25 | 4 ml |
| 7-9 kg | 75-150 mg once daily | 0.5-1.0 tablet | 0.25 | 6 ml |
| 10-15 kg | 150-225 mg once daily | 1-1.5 tablet | 0.25 | 8 ml |
| 16-20 kg | 225-250 mg once daily | 1.5-2 tablet | 0.5 | 11 ml |
| 21-25 kg | 300 mg once daily if < 12 years of age | 2 | 0.5 | 14 ml |
| 36-35 kg | 300 mg once daily if < 12 years of age | - | 0.5 | - |

###### Table 1d: Bedaquiline

|  |  |  |
| --- | --- | --- |
| **Bedaquiline**  Dose: 6 mg/kg/day for 14 days followed by 3-4 mg/kg thrice weekly  (dose extrapolated from adult dosing for those less than 16 kg)  Weight-based dosing | | |
| **Weight band** | **Dose** | **100 mg tablet** |
| 1-10 kg | Consult with specialist[[34]](#footnote-35) |  |
| 10-15 kg | Consult with specialist  *Likely recommended dose is 100 mg daily for 14 days followed by 50 mg thrice weekly* | 1 tablet daily for 14 days followed by 0.5 tablet thrice weekly (i.e. M/W/F) |
| 16-23 kg | 200 mg daily for 14 days followed by 100 mg thrice weekly (i.e. M/W/F) | 2 tablets daily for 14 days followed by 1 tablet thrice weekly (i.e. M/W/F) |
| 24-30 kg | 200 mg daily for 14 days followed by 100 mg thrice weekly (i.e. M/W/F) | 2 tablets daily for 14 days followed by 1 tablet thrice weekly (i.e. M/W/F) |
| 31-34 kg | 400 mg daily for 14 days followed by 200 mg thrice weekly (I.e. M/W/F) | 4 tablets daily for 14 days followed by 2 tablets thrice weekly (i.e. M/W/F) |
| > 34 kg | 400 mg daily for 14 days followed by 200 mg thrice weekly (i.e. M/W/F) | 4 tablets daily for 14 days followed by 2 tablets thrice weekly (i.e. M/W/F) |

**GROUP B DRUGS**

###### Table 1e: Clofazimine

|  |  |  |  |
| --- | --- | --- | --- |
| **Clofazimine**  Dosing: 2-5 mg/kg/day  Weight-based dosing | | | |
| **Weight Band (kg)** | **Dose** | **50 mg gelcaps** | **100 mg gelcaps** |
| <5 kg | 15 mg | Give 1 gelcap M/W/F | Consult a specialist |
| 5-6 kg | 10-30 mg | Give 1 gelcap on alternative days | 1 gelcap M/W/F |
| 7-9 kg | 15-30 mg | Give 1 gelcap on alternative days | 1 gelcap M/W/F |
| 10-15 kg | 20-75 mg | Give 1 gelcap either daily or on alternative days | 1 gelcap alternative days |
| 16-23 kg | 32-115 mg | Give 1 gelcap per day | 1 gelcap on alternative days |
| 24-35 kg | 100 mg | Give 2 gelcap daily | 1 gelcap daily |

###### Table 1f: Cycloserine

|  |  |  |  |
| --- | --- | --- | --- |
| **Cycloserine**  Recommended dose: 15-20 mg/kg/day  Weight-based dosing | | | |
| **Weight Band (kg)** | **Dose** | **125 mg minicapsule** | **250 mg capsule** |
| 1 kg | 20 mg | Mix 125 mg capsule in 12 ml of water and administer 2 ml of mixture immediately | - |
| 2 kg | 40 mg | Mix 125 mg capsule in 12 ml of water and administer 4 ml of mixture immediately | - |
| 3-4 kg | 62.5 mg | Mix 125 mg capsule in 12 ml of water and administer 5 ml of mixture immediately | - |
| 5-9 kg | 125 mg | 1 | - |
| 10-15 kg | 250 mg | 2 | 1 |
| 16-23 kg | 375 mg | 3 | 2 |
| 24-35 kg | 500 mg | 4 | 2 |
|  |  |  |  |

**GROUP C DRUGS (in order of how they should be used)**

###### Table 1g: Delamanid

|  |  |  |
| --- | --- | --- |
| **Delamanid**  Recommended dosing 3-4 mg/kg/day  (dose extrapolated from adult dosing for those less than 10 kg) | | |
| **Weight band** | **Dose** | **50 mg tablet** |
| 1-6 kg | Consult with specialist[[35]](#footnote-36) |  |
| 7-23 kg | 25 mg twice daily | ½ tablet twice daily |
| 24-34 kg | 50 mg twice daily | 1 tablet twice daily |
| > 34 kg | 100 mg twice daily | 2 tablets twice daily |

Note that the 50mg tablet of delamanid when it is crushed, manipulated, or mixed does not result in the same blood levels as the 25 mg pediatric formulation. Until the 25 mg pediatric formulation is available, the 50 mg tablet should be used with caution. Split tablets should not be saved for later administration for time periods longer than 12 hours.

According to recent WHO guidelines (2018), delamanid is preferred to bedaquiline in children <6 years, but bedaquiline can be considered in settings in which there is limited access to delamanid. However, there are no data to guide the dosing of bedaquiline in this population and it would be considered an “expanded indication” (sometimes referred to as “off-label use”).

###### Table 1h: Ethambutol

|  |  |  |  |
| --- | --- | --- | --- |
| **Ethambutol 100 mg**  Recommended Dosing: 15-25 mg/kg/day  Weight-based dosing | | | |
| **Weight Band (kg)** | **Dose** | **100 mg tablets** | **400 mg tablets** |
| 1 kg | 20 mg | Mix 100 mg tablet in 10 ml of water and administer 2 ml of mixture immediately | - |
| 2 kg | 40 mg | Mix 100 mg tablet in 10 ml of water and administer 4 ml of mixture immediately | - |
| 3 kg | 70 mg | Mix 100 mg tablet in 10 ml of water and administer 7 ml of mixture immediately | - |
| 4-6 kg | 100 mg | 1 | - |
| 7-9 kg | 200 mg | 2 | - |
| 10-12 kg | 250 mg | 2.5 | - |
| 13-15 kg | 300 mg | 3 | - |
| 16-18 kg | 350 mg | 3.5 | - |
| 19-20 kg | 400 mg | 4 | 1 |
| 21-23 kg | 450 mg | 4.5 | 1 |
| 24-31 kg | 500 mg | 5 | 1.5 |
| 31-35 kg | 800 mg | - | 2 |

###### Table 1i: Pyrazinamide

|  |  |  |  |
| --- | --- | --- | --- |
| **Pyrazinamide**  Recommended dose: 30-40 mg/kg/day  Weight-based dosing | | | |
| **Weight Band (kg)** | **Dose** | **150 mg dispersible tablets** | **500 mg tablet** |
| 1 kg | 30 mg | Mix 150 mg tablet in 10 ml of water and administer 2 ml of mixture immediately | - |
| 2 kg | 60 mg | Mix 150 mg tablet in 10 ml of water and administer 4 ml of mixture immediately | - |
| 3 kg | 90 mg | Mix 150 mg tablet in 10 ml of water and administer 6 ml of mixture immediately | - |
| 4-6 kg | 150 mg | 1 | - |
| 7-9 kg | 225 mg | 2 | - |
| 10-12 kg | 375 mg | 2.5 | - |
| 13-15 kg | 450 mg | 3 | - |
| 16-18 kg | 525 mg | 3.5 | 1 |
| 19-20 kg | 600 mg | 4 | 1.25 |
| 21-23 kg | 675 mg | 4.5 | 1.5 |
| 24-30 kg | 750 mg | 5 | 1.5-2 |
| 31-35 kg | 1250 mg |  | 2.5 |

###### Table 1j: Ethionamide

|  |  |  |  |
| --- | --- | --- | --- |
| **Ethionamide**  Recommended dose: 15-20 mg/kg/day  Weight-based dosing | | | |
| **Weight Band (kg)** | **Dose** | **125 mg tablets** | **250 mg tablets** |
| 1 kg | 20 mg | Mix 125 mg tablet in 12 ml of water and administer 2 ml of mixture immediately | - |
| 2 kg | 40 mg | Mix 125 mg tablet in 12 ml of water and administer 4 ml of mixture immediately | - |
| 3-4 kg | 62.5 mg | 0.5 | - |
| 5-6 kg | 125 mg | 1 | 0.5 |
| 7-9 kg | 187.5 mg | 1.5 | 0.5 |
| 10-13 kg | 250 mg | 2 | 1 |
| 14-15 kg | 312.5 mg | 2.5 | 1 |
| 16-20 kg | 375 mg | 3 | 2 |
| 21-23 kg | 437.5 mg | 3.5 | 2 |
| 24-30 kg | 500 mg | 4 | 2 |
| 31-35 kg | 500 mg | - | 2 |

###### Table 1k: PAS

|  |  |
| --- | --- |
| **Para-aminosalicylic acid (PAS either acid or sodium salt)** 200-300 mg/kg divided into 2 daily doses  *Some clinical centers give PAS 200 mg/kg as a single daily dose and this could be considered*  Should be used with dosing spoon for more accurate dosing | |
| **Weight Band (kg)** | **Dose** |
| 1 kg | 150 mg twice daily |
| 2 kg | 300 mg twice daily |
| 3-4 kg | 500 mg twice daily |
| 5-6 kg | 0.5-0.75 g twice daily |
| 7-9 kg | 0.75-1.0 g twice daily |
| 11-13 kg | 1 g twice daily |
| 14-15kg | 2 g twice daily |
| 16-20 kg | 2.5 g twice daily |
| 21-23 kg | 3 g twice daily |
| 24-30 kg | 3.5 g twice daily |
| 31-35 kg | 4 g twice daily |

PASER® (PAS Acid) is stable for up to 8 weeks at 40°C and 75% humidity, and therefore can be distributed to the patient on a monthly basis in most environments with no cold chain. If storage of longer than 8 weeks is needed, refrigeration below 15°C is required.

###### Table 1l: Meropenem

|  |  |  |
| --- | --- | --- |
| **Meropenem/Amoxicillin-clavulanate** | | |
| **Drug** | **Daily dose** | **Maximum daily dose** |
| **Amoxicillin-clavulanate\*** | 40 mg/kg given twice daily based on the amoxicillin component | 4000 mg amoxicillin and 500 mg clavulanate |
| **Meropenem** | 20–40 mg/kg IV every 8 hours | 6000 mg |

\*Amoxicillin-clavulanate should only be given in combination with meropenem. It should be given 30 minutes prior to the IV infusion of meropenem or imipenem.

###### Table 1m: Amikacin

|  |  |  |
| --- | --- | --- |
| **Amikacin** | | |
| **Drug** | **Daily dose** | **Maximum daily dose** |
| **Amikacin** | 15-20 mg/kg once daily | 1000 mg |

Amikacin should only be used in settings where susceptibility has been confirmed and where monthly, formal monitoring of hearing can be done (i.e. otoacoustic emissions in children <5 years of age, pure tone audiometry in children ages 5 years and above).

###### Table 1n: Isoniazid

|  |  |  |  |
| --- | --- | --- | --- |
| **Isoniazid 100 mg\***  Recommended dosing: 15-20 mg/kg  Weight-based dosing | | | |
| **Weight Band (kg)** | **Dose** | **100 mg dispersible tablets** | **300 mg tablet** |
| 1 kg | 15 mg | Mix 100 mg tablet in 10 ml of water and administer 1.5 ml of mixture immediately | - |
| 2 kg | 30 mg | Mix 100 mg tablet in 10 ml of water and administer 3 ml of mixture immediately | - |
| 3 kg | 50 mg | 0.5 | - |
| 4-6 kg | 100 mg | 1 | - |
| 7-9 kg | 150 mg | 1.5 | - |
| 10-15 kg | 200 mg | 2 | - |
| 16-18 kg | 250 mg | 2.5 | - |
| 19-20 kg | 300 mg | 3 | 1 |
| 21-23 kg | 350 mg | 3.5 | 1 |
| 24-30 kg | 400 mg | 4 | 1.5 |
| 31-35 kg | 600 mg | - | 2 |

\*The role of HD-INH in the treatment of MDR-TB is still unclear but the drug could be considered in children with inhA mutations if there are no other options to construct an adequate regimen.

Pyridoxine should always be given with high dose isoniazid in children (12.5 mg daily in children <5 year old and 25 mg daily in children >4 y old).

#### Appendix 2. Designing longer treatment regimens (LTRs)

In 2019, the WHO regrouped the TB medicines being used for RR- and MDR-TB. The grouping order is used for the design of LTRs.

###### Table 2a: Hierarchical grouping of medicines recommended for the treatment of RR-/MDR-TB (adapted from WHO 2019 treatment guidelines for DR-TB)

|  |  |
| --- | --- |
| **Group A:**  Include all three medicines | Lfx OR Mfx  Bdq  Lzd |
| **Group B:**  Add one or both medicines | Cfz  Cs OR Trd |
| **Group C:**  Add to complete the regimen and when medicines from Groups A and B cannot be used | E  Dlm  Z  Imp/Cln OR Mpm  Am OR S  Eto OR Pto  PAS |

In cases where the all-oral STR failed or did not produce a sustained cure, an individualized LTR will be needed. LTRs are designed according to the following principles:

* In general, LTRs are designed with at least four effective TB medicines, including three from Group A and one from Group B.
* If this combination cannot be used, a minimum of five effective drugs is preferred and drugs from Group C have to be added to bring the total to at least five likely effective drugs. Regimens may contain more than five drugs if there is uncertainty of effectiveness in some of the drugs being used.
* All drugs in the regimen are used throughout the whole treatment if well tolerated.
* In the case one or more drugs has to be stopped (e.g. for toxicity reasons), the regimen should contain no less than three drugs, and preferably four drugs, if less than two Group A drugs are included.

The definition of a "likely effective TB drug" includes both laboratory DST results and the patient's TB treatment history. Clinical judgement is often necessary to decide whether a specific drug counts as an effective TB medicine and all five criteria are not always able to be ascertained. A TB drug is considered likely to be effective if:

1. The drug has not been used in a regimen that failed to cure the individual patent.
2. DST performed on the patient’s strain indicates susceptibility to the drug.
3. If DST is not available:
   1. There is no resistance to drugs with known cross-resistance.
   2. There are no known close contacts with resistance to the drug or contact with a patient who had treatment failure of an MDR-TB regimen that contained the drug.
   3. Drug resistance surveys demonstrate that resistance to the drug is rare in patients with a similar TB history. For example, most circulating MDR-TB strains are also resistant to ethambutol and in most settings cannot be counted as a “likely effective TB drug” in the regimen.

In addition to the likelihood of effectiveness as defined above, other important characteristics include:

* The side effects of individual drugs and the overlapping toxicities they may have with other drugs in the regimen.
* Whether the patient has any comorbidity that might make an individual drug or a certain combination more likely to result in toxicity.
* Whether the patient is taking any drug which may interact with anti-TB drugs.
* Whether the patient is pregnant.

Table 2B describes the steps to build a longer regimen for MDR-TB treatment.

###### Table 2b: Steps for building an LTR

|  |  |  |
| --- | --- | --- |
| **STEP 1** | **Use as many Group A drugs as possible (considering FQ susceptibility, previous exposure, contraindications, and concomitant treatment)** | |
| **1.1. Use a later-generation fluoroquinolone**   * Avoid Mfx if possible when using Bdq or multiple QT-prolonging drugs. * If there is only low-level resistance to the FQ, high-dose Mfx (MfxH) can be used but should not be counted as an effective drug (see Table 2c). * When drug options are extremely limited, MfxH may be implemented despite using multiple QT-prolonging drugs (the risk/benefits should be carefully weighed and discussed with the patient).   **1.2. Use bedaquiline**   * As it is one of the most potent anti-TB drugs, Bdq is added to all regimens unless there is resistance or intolerance. * DST to Bdq is not commonly available. Resistance to Bdq is still highly unlikely in most settings.   **1.3. Use linezolid**   * + Monitoring for myelosuppression, optic neuritis, and peripheral neuropathy must be in place to use Lzd in the regimen. DST to Lzd is not commonly available. Resistance to Lzd is still highly unlikely in most settings. | Lfx, Mfx  Bdq  Lzd |

|  |  |  |
| --- | --- | --- |
| **STEP 2** | **Use as at least one Group B drug** | |
| **2.1. Clofazimine**   * Resistance to Cfz is still unlikely in most parts of the world, although this may change in some areas with wider use of the shorter MDR-TB regimen. * There may be cross-resistance between Cfz and Bdq. * Cfz in most scenarios is the preferred Group B drug to use due to a good safety profile.   **2.2. Cycloserine or terizidone**   * DST to Cs or Trd is not reliable. * Cs or Trd is associated with CNS toxicity and peripheral neuropathy. Toxicity may be more common in HIV-positive patients. | Cfz  Cs/Trd |

|  |  |  |
| --- | --- | --- |
| **STEP 3** | **When the combination of three Group A and at least one Group B cannot be used, Group C drugs are added to bring the regimen to five likely effective drugs (more than five may be needed if certainty of effectiveness in any of the five is in doubt).** |  |
|  | **3.1. Consider adding first-line drugs**   * First-line TB drugs are generally of limited utility due to high prevalence of resistance in MDR-TB. * DST to E is not reliable and, if used, E should never be counted as an effective drug. * If DST from a reliable lab demonstrates susceptibility to Z, this drug may be counted as an effective drug.   **3.2. Consider adding delamanid**   * Dlm is often the first choice of a Group C drug in cases of resistance or intolerance to a Group A or B drug. * DST to Dlm is not commonly available. Resistance to Dlm is still highly unlikely in most settings.     **3.3. Consider Carbapenem (imipenem/cilastatin or meropenem) plus amoxicillin/clavulanate**   * Imp/Cln and Mpm are the two carbapenems with the most experience of use in TB treatment. * Meropenem is preferred for use in children. * The difficulty in administration limits the use of carbapenems to centers with skilled staff and minor surgery capacities.   **3.4. Consider adding Amikacin (or streptomycin in rare circumstances)**   * The aminoglycoside of choice is Am; because of its toxicity, it should only be given when other effective options do not exist and if drug susceptibility has been confirmed. * If Am is added, close monitoring of hearing, renal function, and electrolytes is essential. If close monitoring cannot be performed, use alternative drugs. * Resistance to S is very frequent in MDR-TB; however, if phenotypic DST (rarely available) demonstrates susceptibility and there are no other options, S can be used. * The LPA to second-line drugs (Hain MTBDR*sl*) can provide an indication on susceptibility to Am but not to S.   **3.5. Consider adding ethionamide or prothionamide**   * Eto and Pto are very weak bacteriostatic and poorly tolerated drugs. If a regimen with five likely effective drugs is not possible otherwise, consider using Eto or Pto (with aggressive management of nausea and vomiting). They should not be included in the regimen if the *inhA* mutation is detected by first-line LPA or if phenotypic resistance is detected.   **3.5 Consider PAS**   * PAS is a very weak bacteriostatic and poorly tolerated drug. If a regimen with five likely effective drugs is not possible otherwise, consider using PAS (with aggressive management of nausea and vomiting).   **3.6 Consider high-dose H (HH)**   * HH should never be counted as a likely effective drug. * Do not use HH if the *katG* mutation is detected by first-line LPA. * Avoid using HH with Lzd because of potential additive toxicity of peripheral neuropathy. | E, Z  Dlm  Imp/Cln,  Mpm  (+Amx/Clv)  Am  Eto/Pto  PAS  HH |

***Table 2. Steps for building a longer MDR-TB treatment regimen (continued)***

All patients diagnosed with RR-/MDR-TB should have a molecular rapid DST to isoniazid and to second-line TB drugs. Commercial tests are available for isoniazid, the FQs and second-line injectable drugs. This is particularly important if the patient comes from an area with a high prevalence of FQ-resistant MDR-TB.

###### Table 2c: Interpretation of phenotypic and genotypic DST results

|  |  |
| --- | --- |
| **Drug** | **Notes** |
| **H** | * Resistance to H is classified as either high-level (MIC ≥2 µg/mL) or low-level (MIC 0.2–1 µg/mL) resistance. * A *katG* mutation confers high-level resistance to H; an *inhA* mutation confers low-level resistance to H. * Some clinicians may choose to use high-dose H when DST shows low-level resistance, but there is very limited clinical evidence to support this practice. |
| **Z** | * Sequencing the *pncA* gene may be helpful in determining Z resistance. * Phenotypic testing of Z can be done in qualified laboratories. |
| **E** | * Commercially available genetic testing is not available. * Both the phenotypic and genotypic tests are considered unreliable. |
| **FQ (Lfx, Mfx)** | * Some of the *gyrA* mutations (D94G, D94N/Y, D94H) confer high-level resistance across the class of FQ. FQ (including MfxH) should not be used in such cases. (An easy way to remember which mutations are associated with high resistance is all D94 mutations cause high-level resistance except D94A).  |  |  | | --- | --- | | **Mutation** | **Name of mutation with Hain MTBDR*sl* LPA** | | *gyrA* D94G | *gyrA* MUT3C | | *gyrA* D94N/Y | *gyrA* MUT3B | | *gyrA* D94H | *gyrA* MUT3B |  * The definitions of low- and high-level resistance can also be determined by phenotypic testing: * Low-level resistance to the FQ is defined as resistance in MGIT to Ofx at 2.0 mg/L or Lfx at 1.0 mg/L or Mfx at 0.25 mg/L. MfxH may be used in such cases but should not be counted as an effective drug. * High-level resistance to the FQ is defined as resistance to Mfx in MGIT at 1.0 mg/L. MfxH is unlikelyto be effective in such cases. |
| **Injectable (Am, S)** | * The *rrs* mutation is thought to confer cross-resistance to all injectables, including moderate resistance to Cm. * An *eis* promoter mutation is thought to confer low-level resistance to Am. Some clinicians will use Am in the presence of the *eis* promoter mutation while others are of the opinion that the side effect profile and the low-level resistance associated with the *eis* mutation does not justify the use of Am. In such cases, Am should not be counted as an effective drug. * The LPA to second-line drugs (Hain MTBDR*sl*) does not provide information on S resistance and no commercially available rapid tests provide genetic information on S resistance. |
| **Eto/Pto** | * The *inhA* mutation confers cross-resistance to H and Eto/Pto; the *katG* mutation confers resistance to H but not to Eto/Pto. If an *inhA* mutation is present, then Eto/Pto should not be used. In the absence of an *inhA* mutation, the clinical history should be taken into consideration, since there are other mutations that confer resistance to Eto/Pto (e.g. *ethA*) that are not tested in commercially available LPA. * Phenotypic testing of Eto/Pto can be done in qualified laboratories. |
| **Cs/Trd, PAS** | * Phenotypic DST of PAS and Cs/Trd are not considered reliable tests, even if done at a highly qualified laboratory. |
| **Bdq, Lzd, Cfz, Dlm** | * Phenotypic testing of these drugs is limited to supranational laboratories and is generally considered reliable. The clinical significance of these results, however, is still unclear. |

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33. 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. [↑](#footnote-ref-34)
34. [tbsentinelproject@gmail.com](mailto:tbsentinelproject@gmail.com) [↑](#footnote-ref-35)
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