WHO operational handbook on tuberculosis

Module 4: Treatment

Drug-resistant tuberculosis treatment

2022 update

Web Annexes

World Health Organization

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Design by Inis Communication

Contents

Web Annex 1. Tuberculosis medicines – information sheets 1

Web Annex 2. Management of adverse events in MDR/RR-TB treatment 53

Web Annex 3. Active TB drug-safety monitoring and management for treatment of drug-resistant TB 83

Web Annex 1. Tuberculosis medicines – information sheets

A1.1 Sources of information

These information sheets on drugs for the treatment of tuberculosis (TB) represent an update of the sheets first published in the World Health Organization (WHO) document, *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (1)*, which was based on an adaptation of the publication *Drug resistant tuberculosis: a survival guide for clinicians (2)*. The information has been updated and expanded through a review of multiple sources, including available information on new drugs, recent trials, pharmacokinetics, pharmacodynamics and safety studies. Formulations and dosages have been updated and are in line with the Annex of the *WHO operational handbook on tuberculosis. Module 4: Treatment – drug-resistant tuberculosis treatment, 2022 update*. These formulations are available in quality-assured forms, and have been approved by Stringent Regulatory Authorities, prequalified by WHO or approved by the Expert Review Panel of the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund). WHO recommends using formulations that have been quality assured based on international standards.

Information on drug interactions was sourced primarily from online resources from the United States Food and Drug Administration and the European Medicines Agency.

A1.2 Key concepts in specific situations

In addition to detailed drug information, the information sheets present several specific situations, including drug safety during pregnancy and the permeability of TB drugs used to treat drug-resistant TB (DR-TB) through the blood–brain barrier for the treatment of TB involving the central nervous system (CNS).

Drug safety during pregnancy

TB disease during pregnancy is associated with adverse maternal and neonatal outcomes (including eclampsia and pre-eclampsia, maternal anaemia, caesarean delivery, increased risk of preterm birth, low birth weight, birth asphyxia and perinatal death). The drug safety profile during pregnancy is described for each of the TB medicines in these information sheets.

Penetration of TB medicines through blood–brain barrier for treatment of TB involving the CNS

Not all drugs cross the blood–brain barrier and penetrate the cerebrospinal fluid (CSF) with an optimum concentration in the different intracranial compartments. The ideal compound to treat CNS infections should be a small, moderately lipophilic molecule that presents a low level of plasma protein binding (among other features).

Another way to improve the exposure and concentration of drugs at the CNS is by increasing the drug dosage, with close monitoring of side-effects; this has been shown to be beneficial in the case of rifampicin and isoniazid. However, case series using intrathecal infusion of TB drugs have presented variable results.

The value of TB medicines for the treatment of TB involving the CNS *(3)* depends on their ability to cross the blood–CSF barrier. Available information on the penetration capacity of each TB medicine is included in the drug information sheets. In all individuals with TB meningitis, the use of corticosteroids is recommended to prevent disability and improve survival. In cases of reduced levels of consciousness, use of nasogastric tube (using dispersible formulations if possible) or intravenous (IV) delivery may be considered.

Frequency of adverse events

An overall tolerance profile is included for each drug based on the frequency of adverse events and potential acceptability by patients. The adverse events related to each drug have been included here with a brief explanation, classified according to their frequency as common (>10%), frequent (1–10%), occasional (<1%) and rare (<1%). Occasional and rare adverse events that are severe and could cause disability are also included. Frequency of adverse events can vary according to study and circumstances; therefore, it should be considered as a proxy measure that may vary in different settings or subgroups of patients.

Amikacin (Am)

Amikacin (Am) **Drug class: aminoglycosides**	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** *M. tuberculosis* inner metabolism. Inhibits protein synthesis. Irreversibly binds to bacterial 30S ribosomal subunits. Leads to misreading of t-RNA (meaning that bacteria are unable to synthesize proteins) and hence interferes with bacterial growth. **Activity**: Mainly bactericidal, high early bactericidal activity. **Half-life and excretion:** Half-life is usually 2–3 hours. Primarily excreted unchanged through the kidney by glomerular filtration.
Cross-resistance	Cross-resistance with capreomycin and kanamycin has been reported.
Dose[a]	**Amikacin is recommended by WHO only in adults aged >18 years.** • **Adults:** 15–20 mg/kg/day in a single daily dose, 6–7 days per week (upper daily dose is 1 g). • **Adults > 60 years old:** Lowering of amikacin dosage is advised. A lower starting dose of 10 mg/kg/day (max 750 mg) 5–7 times a week may be used. Alternatively, a 15 mg/kg/dose may be administered thrice weekly. • **Renal failure or dialysis:** Consider replacing amikacin with another agent. Otherwise, a 12–15 mg/kg/dose after dialysis, twice or thrice weekly (not daily) may be considered. Amikacin should be used with caution.
Administration	IV or IM. Intraperitoneal and intrathecal administrations have been reported; however, intrathecal administration is not advised provided there are oral TB medications with high CSF penetration.
Formulation and Preparation	Available as 500 mg/2 mL solution for injection, ampoules and vials. For **IV solution**, mix with 100 mL or 200 mL of sterile diluent (e.g. D5W) or any other compatible solution. In paediatric patients, the volume of diluent used will depend on the amount of amikacin tolerated by the patient. The solution should be infused over 30–60 minutes for adults. It should not be mixed with any other parenteral medicine administered concurrently. **IM** absorption is complete within 4 hours and peak concentrations are achieved in 1–2 hours; however, absorption can be delayed if the same site is used repeatedly.
Storage	The solution in the original vial is stable at room temperature (15–25 °C). Reconstituted solutions can be stored at 2–8 °C for not more than 12 hours. Once at room temperature, it should be used within 24 hours.
Oral absorption	There is no significant oral absorption.
CSF penetration	Penetration is more effective in inflamed meninges.

Special circumstances	**Use during pregnancy or breastfeeding:** Should be avoided during pregnancy because of documented cases of congenital deafness. It is excreted into human milk; it is considered compatible with breastfeeding but should be used with caution (i.e. monitor for infant thrush and diarrhoea). **Use in renal disease:** Should be used with extreme caution; where possible, concentrations should be monitored in patients with impaired renal function. Interval adjustment is recommended for renal impairment or dialysis (see under Dose section, above). The drug is variably cleared by haemodialysis. **Use in hepatic disease:** Drug concentrations are not affected by hepatic disease (except a larger volume of distribution for patients with ascites due to cirrhosis). It is presumed to be safe in severe liver disease; however, it should be used with caution because patients with severe liver disease may progress rapidly to hepato-renal syndrome. **Diuretic use:** Co-administration of loop diuretics and aminoglycoside antibiotics carries an increased risk of ototoxicity. **Older people:** There is increased risk of ototoxicity and nephrotoxicity owing to potential baseline damage in both organs.
Adverse reactions	**Overall tolerance:** It is badly tolerated, giving local pain with IM injections or lengthy infusions. Toxicity is associated with prolonged use and dose accumulation. **Common:** Proteinuria. **Occasional:** Nephrotoxicity (9% for general population, may be lower with thrice weekly administration), ototoxicity (hearing loss, increased risk with advanced age and prolonged use) and vestibular toxicity (vertigo, ataxia and dizziness); and electrolyte abnormalities, including hypokalaemia (which may prolong the QTc interval), hypocalcaemia and hypomagnesaemia. **Uncommon:** Neuropathy and rash.
Contraindications	**Hypersensitivity to aminoglycosides.** **Renal, hepatic, vestibular or auditory impairment**: In such cases, it should be used only with extreme caution.
Drug interactions	**Loop diuretics:** Co-administration of furosemide and aminoglycoside antibiotics carries an increased risk of ototoxicity and hypokalaemia.
Food interactions	None.

Monitoring	Monitoring of renal function should include: • creatinine at least monthly (more frequently if there is renal or hepatic impairment); • creatinine clearance if there is baseline renal impairment or any concerns; and • electrolytes: baseline follow-up with monthly minimum potassium, magnesium and calcium if possible. Audiology examination: document baseline and monthly results. Vestibular examinations: question patient regularly about vestibular symptoms and perform serial vestibular exams. If possible, in patients aged over 60 years or with altered renal function, peak serum concentrations should be monitored.
Patient instructions and alerting symptoms	**Patients should be instructed to inform their health care provider immediately if any of the following occur:** • problems with hearing, dizziness or vertigo; • rash or swelling of the face; • trouble breathing; • swelling, pain or redness at the IV site; or • muscle twitching or weakness.

CSF: cerebrospinal fluid; D5W: dextrose 5% in water; IM: intramuscular; IV: intravenous; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis; t-RNA: transfer ribonucleic acid; WHO: World Health Organization.

[a] See the handbook Annex for revised weight-based dosing.

Bedaquiline (B or Bdq)

Bedaquiline (B or Bdq) **Drug class: diarylquinoline**	
Activity against *M. tuberculosis,* mechanism of action and metabolism	**Target**: *M. tuberculosis* inner metabolism. Inhibits ATP synthesis, leaving the bacteria without sources of energy that are needed for replication and also for latency. **Activity**: High bactericidal activity, but it may take 7–14 days to manifest a bactericidal effect. **Sterilizing activity**: Significant; able to support reduction in duration of treatment. **Half-life and excretion**: has a 5.5-month half-life, with slow release of bedaquiline from peripheral tissues, which may have implications in toxicity and in cases of loss to follow-up (sustained monotherapy). Is hepatically metabolized by CYP3A4 (cytochrome p450) leading to the formation of its main metabolite M2, which does not contribute significantly to antimycobacterial activity compared with the parent compound. Bedaquiline is mainly eliminated in faeces. The renal clearance of the unchanged drug is insignificant.
Cross-resistance	Cross-resistance has been reported between bedaquiline and clofazimine, through efflux pump-mediated resistance and other mechanisms.
Dose[a]	• **Adults:** 400 mg once daily for 2 weeks, followed by 200 mg once daily, thrice weekly for 22 weeks. The maximum daily dose is 400 mg. For patients treated with the BPaLM/BPaL regimen (>14 years), bedaquiline can also be administered 200 mg once daily for 8 weeks, followed by 100 mg once daily until the end of treatment. • **Children:** There is no age restriction (see the handbook Annex for weight bands). • **Renal failure or dialysis:** No dose adjustment is needed for mild-to-moderate renal insufficiency. It should be used with caution in patients requiring renal dialysis (see the handbook Annex for weight-based dosing in adults and children).
Administration	Oral. In children, 100 mg tablets can be administered whole, or crushed and suspended in water without affecting bioavailability. Vigorous stirring or shaking is needed before administration. The 20 mg tablets can be administered whole, or crushed and dispersed in <1–3 mL of water per tablet (maximum of 5 tablets in 5 mL of water), or crushed and mixed with food.
Formulation and preparation	20 mg scored, dispersible tablet. 100 mg uncoated tablets.
Storage	Tablets can be stored at room temperature (15–30 °C). Tablets removed from the original packaging should be stored in a tight, light-resistant container and labelled with an expiration date that should not exceed 3 months.
Oral absorption	Administration with food (ideally high-fat meals) leads to a twofold increase in bioavailability.

CSF penetration	Studies[b] involving a small number of participants indicate that bedaquiline and M2 (main metabolite) penetrate well into the CSF of patients with pulmonary TB with a presumably intact blood–brain barrier.
Special circumstances	**Use in pregnancy or breastfeeding:** No fetal harm was found in animal studies. The drug accumulates significantly in breast milk, and breastfed infants receive doses of bedaquiline equivalent to maternal doses.[c] **Use in renal disease:** No dosage adjustment is required in patients with mild-to-moderate renal impairment. It should be used with caution in patients requiring peritoneal dialysis or haemodialysis. Therapeutic drug monitoring may be useful, if available. **Use in hepatic disease:** Bedaquiline should be used with caution because it is metabolized in the liver. No dosage adjustment is required in patients with mild-to-moderate hepatic impairment. It has not been studied in patients with severe hepatic impairment and should be used with extreme caution in such patients, and only when benefits outweigh risks. Clinical monitoring for bedaquiline-related adverse reactions is recommended.
Adverse reactions	**Overall tolerance:** Well tolerated. **Occasional:** Nausea, arthralgia (joint pain) and headache (~10%). QTc prolongation (estimated QTc increased by 10–15 msec, maximal at week 15). Overall QTc prolongation in cohorts using bedaquiline and other QTc-prolonging drugs was 2.7%, with median appearance at 2.5 months. **Uncommon:** Hyperuricaemia, phospholipidosis (accumulation of phospholipids in the body tissues) and elevated transaminase are an early signal for increased risk of pancreatitis.
Contraindications	Hypersensitivity to bedaquiline. Taking other medications that are strong inducers of CYP3A (e.g. rifamycins and carbamazepine). **Use with caution in potential situations that may increase QT interval:** Such situations are patients aged >60 years, heart failure, long QT syndrome, history of TdP, hypokalaemia, untreated hypothyroidism, low BMI, HIV infection, concomitant use of other QT-prolonging drugs. Any syncopal event (such as fainting) or palpitations should prompt an immediate medical evaluation and ECG. In several retrospective cohort studies on the incidence of QTc prolongation and cardiac events, the increase was modest, and no arrhythmias or related deaths were reported even when bedaquiline and delamanid were co-administered. **Discontinue or do not use in the presence of:** • clinically significant ventricular arrhythmia; • a QTcF interval of >500 msec (confirmed by repeat ECG); • severe liver disease; or • abnormal electrolytes.

Drug interaction	Metabolized by CYP3A4 (cytochrome p450). • Co-administration with rifamycins (e.g. rifampicin, rifapentine and rifabutin) significantly reduces concentrations of bedaquiline (<50%). Other strong CYP3A4 inducers (e.g. efavirenz, phenytoin and glucocorticoids) may also require caution and dose adjustment.[d] • CYP3A4 inhibitors (e.g. azole antifungal drugs, some macrolides and PIs) can increase the level of bedaquiline. Substitution of the PI with an integrase inhibitor (e.g. dolutegravir or raltegravir) is suggested. If a ritonavir-boosted PI must be used, an ECG should be performed every 2 weeks for the first 8 weeks. • Use with other medicines that direct or indirectly prolong the QT interval may cause additive prolongation that requires caution and monitoring. Such medicines include TB drugs (fluoroquinolones, clofazimine and delamanid) and ancillary and common drugs (azoles, macrolides, metoclopramide, efavirenz, furosemide, hydrochlorothiazide, citalopram, escitalopram, methadone, antiarrhythmics and others).
Food interactions	Administered with food; ideally, with high-fat meals (which increases the oral bioavailability).
Monitoring	Ideally, an ECG should be obtained before initiation of treatment, and at least 2, 12 and 24 weeks after starting treatment. Bedaquiline should be stopped if the QTc >500 msec, and ECGs and potassium levels should be monitored regularly until the QTc returns to normal. More frequent monitoring is recommended if cardiac conditions, hypothyroidism or electrolyte disturbances are present. Liver function tests should be done at baseline, then monthly.
Patient instructions and alerting symptoms	Medication is to be taken with food. Alcohol should be avoided. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • baseline heart problems, fast or irregular heartbeat, or if the patient faints; or • liver problems (hepatotoxicity): severe nausea or vomiting, stomach pain, jaundice, fever, weakness, itching, unusual tiredness, loss of appetite, light-coloured stool, dark-coloured urine, and yellowing of the skin or the whites of the eyes.

ATP: adenosine triphosphate; BMI: body mass index; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; CSF: cerebrospinal fluid; ECG: electrocardiograph; HIV: human immunodeficiency virus; *M. tuberculosis*: *Mycobacterium tuberculosis*; PI: protease inhibitor; TB: tuberculosis; TdP: torsade de pointes.

[a] See the handbook Annex for weight bands.

[b] Upton CM, Steele CI, Maartens G, Diacon AH, Wiesner L, Dooley KE. Pharmacokinetics of bedaquiline in cerebrospinal fluid (CSF) in patients with pulmonary tuberculosis (TB). J Antimicrob Chemother. 2022;77:1720–4. doi: https://doi.org/10.1093/jac/dkac067.

[c] Court R, Gausi K, Mkhize B, Wiesner L, Waitt C, McIlleron H et al. Bedaquiline exposure in pregnancy and breastfeeding in women with rifampicin-resistant tuberculosis. Brit J Clin Pharm. 2022;88:3548–58. doi: https://doi.org/10.1111/bcp.15380.

[d] Sirturo (bedaquiline) label. Maryland: United States Food and Drug Administration; 2012 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf). (See Section 7).

Clofazimine (C or Cfz)

Clofazimine (C or Cfz) **Drug class: iminophenazine**	
Activity against *M. tuberculosis,* mechanism of action and metabolism	**Target:** *M. tuberculosis* cell wall; clofazimine is highly lipophilic and it interferes with the proton-motive force, leading to membrane-destabilizing effects and, ultimately, ATP production. **Activity:** Studies suggest bactericidal and sterilizing effect. **Half-life and excretion:** Tissue half-life is estimated to be around 25–70 days. Metabolized by the liver and very slowly eliminated, mainly by bile in the faeces.
Cross-resistance	Cross-resistance has been reported between bedaquiline and clofazimine through efflux pump-mediated resistance and others.
Dose[a]	• **Adults:** 100 mg daily (upper daily dose is 100 mg). • **Children:** See handbook Annex for weight bands. • **Renal failure or dialysis:** No adjustment required. See handbook Annex for weight-based dosing in adults and children.
Administration	Oral. Capsules should be taken whole. Tablets can be taken whole or dispersed. Clofazimine tablets dissolve slowly (~5 minutes) in water (5 mL and 10 mL for the 50 mg and 100 mg tablets, respectively). The suspension should be stirred before administration.
Formulation and preparation	50 mg tablets or capsules. 100 mg tablets or capsules.
Storage	Should be stored below 30 °C. Capsules should be protected from moisture.
Oral absorption	70% absorption after an oral dose.
CSF penetration	There are limited data available regarding CNS penetration.
Special circumstances	**Use during pregnancy or breastfeeding:** There are limited data; recommended during pregnancy when benefits outweigh risk. The drug passes into human breast milk. Infants exposed to it in utero or during breastfeeding may appear more deeply pigmented. **Use in renal disease:** No dosage adjustment required. **Use in hepatic disease:** Partially metabolized by the liver; use caution or adjust the dose for severe hepatic impairment.

Adverse reactions	**Overall tolerance**: Well tolerated. **Common:** In 75–100% of patients receiving clofazimine there will be an orange, pink or brownish-black discolouration of the skin, conjunctivae and bodily fluids (owing to deposits, primarily in fatty tissues). The drug is often rejected by adolescents or in societies where body image is highly important. Also causes dry skin (ichthyosis and xerosis) and itching. **Frequent:** QT prolongation (10–20 msec). **Uncommon:** Photosensitivity, abdominal pain and obstruction or bleeding, due to the deposition of drug and formation of crystals in the intestinal mucosa.
Contraindications	Allergy to clofazimine.
Drug interactions	Use with other medicines that direct or indirectly prolong the QT interval may cause additive prolongation that requires caution and monitoring: • anti-TB drugs: fluoroquinolones, bedaquiline and delamanid; and • ancillary and common drugs: azoles, macrolides, metoclopramide, efavirenz, furosemide, hydrochlorothiazide, citalopram, escitalopram, methadone, antiarrhythmics and others.
Food interactions	To be administered with a meal, to avoid stomach upset and improve absorption.
Monitoring	Monitor clinical signs and symptoms. Perform ECG if other QT interval-prolonging agents are given concomitantly.
Patient instructions and alerting symptoms	To be taken with food to avoid stomach upset and improve absorption. May discolour skin and body secretions to orange, pink or brownish-black. This effect goes away after stopping the medicine but may take a long time to do so (months to years). Patients should avoid the sun and use strong sunscreens. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • abdominal pain, severe nausea, vomiting, black stools or diarrhoea.

ATP: adenosine triphosphate; CNS: central nervous system; CSF: cerebrospinal fluid; ECG: electrocardiography; *M. tuberculosis*: *Mycobacterium tuberculosis;* TB: tuberculosis.

[a] See the handbook Annex for revised weight-based dosing.

Cycloserine (Cs) or terizidone (Trd)

Cycloserine (Cs) or terizidone (Trd) **Drug class: analogue of D-alanine**	
Activity against *M. tuberculosis,* mechanism of action and metabolism	**Cycloserine (Cs) or terizidone (Trz)** are considered equivalent drugs and are commonly used interchangeably. Terizidone is formed by two molecules of cycloserine combined. There is no significant safety difference between the two drugs. **Target:** *M. tuberculosis* cell wall. These drugs block the formation of the peptidoglycan layer (which has a structural role, especially in the Gram-positive cell wall). **Activity:** Bactericidal or bacteriostatic (low bactericidal activity), depending on concentration. **Half-life and excretion:** Has a half-life of 10 hours. Renally excreted.
Cross-resistance	There is no cross-resistance with other drugs.
Dose[a]	• **Adults:** 10–15 mg/kg/day (upper daily dose is 1 g). • **Children:** See handbook Annex for weight bands. • **Renal failure or dialysis:** 250 mg once daily or 500 mg, thrice weekly; monitor drug concentrations, if possible, to keep peak concentrations <35 mcg/mL. **Pyridoxine (vitamin B6):** commonly used to limit cycloserine toxicity but there are insufficient data to support systematic administration of vitamin B6 to adults or children on these drugs. See the handbook Annex for weight-based dosing in adults and children.
Administration	Oral. Capsules should be taken whole. However, dissolving the content of the capsules in 10 mL of water and administering the volume corresponding to the correct milligram dose may facilitate administration in younger children, although bioavailability is uncertain.
Preparation	125 mg mini capsule (only available for cycloserine). 250 mg capsule.
Storage	Should be stored at room temperature (15–25 °C) in an airtight container. Protect from moisture.
Oral absorption	Modestly decreased by food (best to take on an empty stomach); not significantly affected by antacids or orange juice.
CSF penetration	Concentrations in CSF approach those in serum.

Special circumstances	**Use during pregnancy or breastfeeding:** Not well studied; there is exposition in utero and these drugs are present in milk but no teratogenicity has been documented. **Use in renal disease:** Cycloserine is cleared by the kidney and requires dose adjustment for renal failure (see under Dose section, above). Use with caution. **Use in hepatic disease:** These drugs are considered to be liver friendly, but hepatotoxicity and jaundice have been reported.
Adverse reactions	**Overall tolerance:** Variable; poorly tolerated by many patients due to common neuropsychiatric toxicity. **Common:** Inability to concentrate, lethargy, neuropathy (30%) and depression (10%). **Frequent:** Psychosis (7.6%). **Occasional:** Seizures (3%), jaundice, suicidal ideation and skin problems. Severe CNS side-effects can be associated with peak concentrations >35 mcg/mL, but may also be seen in the normal therapeutic range, especially in patients with pre-existing mental health conditions.
Contraindications	Pre-existing significant neurological or mental health conditions including seizure disorders, depression, anxiety, psychotic disease, personality disorder or alcohol and other substance abuse.
Drug interactions	Increased risk of CNS toxicity when given with isoniazid. Co-administration with delamanid may increase the risk of neuropsychiatric adverse events, especially in children.
Food interactions	Best taken on an empty stomach, with juice or antacids. If food is taken, large high-fat meals should be avoided, as should alcohol, which increases the risk of convulsions.
Monitoring	Baseline and monthly monitoring for depression should be done using a tool (e.g. the Beck Depression Index). If therapeutic drug monitoring is possible, peak concentrations should be obtained within the first 1–2 weeks of therapy and monitored serially during therapy. The peak concentration should be kept at <35 mcg/mL. When administering delamanid and cycloserine concurrently, monitoring for neuropsychiatric side-effects is important. These events should be reported through the national pharmacovigilance system.
Patient instructions and alerting symptoms	**Patients should be instructed to inform their health care provider immediately if any of the following occur:** • seizures; • shakiness, trouble talking or thinking or loss of memory; • depression or thoughts of hurting themselves or others; and • anxiety, confusion or personality changes (e.g. aggressive behaviour).

CNS: central nervous system; CSF: cerebrospinal fluid; *M. tuberculosis*: *Mycobacterium tuberculosis*.

[a] See the handbook Annex for revised weight-based dosing.

Delamanid (Dlm)

Delamanid (Dlm) **Drug class: nitro-dihydro-imidazooxazole (nitroimidazole)**	
Activity against *M. tuberculosis,* mechanism of action and metabolism	**Target:** *M. tuberculosis* cell wall. Inhibits the synthesis of methoxy-mycolic and keto-mycolic acid, which are mycobacterial cell wall components. **Activity:** Bactericidal, potent in vitro activity. Potential sterilizing activity as nitroimidazooxazole derivatives are thought to generate reactive nitrogen species, including nitrous oxide, which causes cell poisoning. **Half-life and excretion:** The prodrug is activated by mycobacterial nitroreductase and binds tightly to plasma proteins. It is metabolized mainly by albumin and to a lesser extent by the CYP3A4 isoenzyme in the liver (cytochrome P450). The half-life is 30–38 hours. It is excreted primarily in the faeces, with less than 5% excretion in the urine.
Cross-resistance	There is limited published information about resistant mutations, frequencies and their correlation with clinical relevance.
Dose[a]	• **Adults:** 200 mg daily (upper daily dose is 200 mg). • **Children:** No age restriction. Dispersible tablets are the preferred option. See the handbook Annex for weight bands. • **Renal failure or dialysis:** No dose adjustment needed for mild-to-moderate renal insufficiency; there are no data regarding use in patients with severe renal impairment. Initially, delamanid is not recommended for patients with severe renal impairment.
Administration	Oral. The use of the 25 mg dispersible tablet formulation is preferred in children. Delamanid adult tablets (50 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole, and they can be used in young children or people who cannot swallow tablets whole if the dispersible tablet formulation is not available.
Formulation and preparation	25 mg dispersible tablet. 50 mg film-coated tablets.
Storage	Should be stored at room temperature (15–25 °C) and in the original package, to protect from moisture.
Oral absorption	Absorption is increased with a standard meal (about 2.7-fold compared with fasting); 25–47% of the delamanid dose is absorbed following oral administration with food.
CSF penetration	One study suggests that, despite relatively low total CSF drug levels, delamanid achieves adequate concentrations in brain tissue and the oral formulation may be sufficient to have a role in treating TB meningitis.[b]

Special circumstances	**Use during pregnancy or breastfeeding:** Data on the use of delamanid in pregnancy are limited. Animal data show no evidence of teratogenicity. The manufacturer allows its use in pregnant women in their compassionate-use protocol. Although the case series of pregnant women on delamanid is small, all neonates had excellent birth outcomes, suggesting that pregnant women in need should not be denied access. In animals, delamanid and its metabolites appeared in breast milk. There is no information from studies in humans, but it is usually not recommended during breastfeeding. **Use in renal disease:** No dosage adjustment is required in patients with mild-to-moderate renal impairment, but delamanid is not recommended for patients with severe renal impairment. **Use in hepatic disease:** No dosage adjustment is required in patients with mild hepatic impairment, but delamanid is not recommended in patients with moderate-to-severe hepatic impairment. **Use in cardiac disease:** Patients with various cardiac risk factors, including QTc interval prolongation, should not receive delamanid unless the potential benefits of treatment are expected to outweigh the possible risks. For all patients, an ECG is recommended before starting treatment, and then monthly throughout treatment. Patients with serum albumin levels <3.4 g/mL (but at least 2.8 g/mL) or with cardiac risk factors should receive more frequent ECG monitoring. Serum electrolytes should be checked and corrected as needed. **Use in malnourished patients:** Delamanid is contraindicated in patients with serum albumin levels <2.8 g/mL. However, recent PD and PK studies suggest no alterations linked to albumin levels. **Use beyond 6 months and in combination with bedaquiline is considered safe**.
Adverse reactions	**Overall tolerance**: Well tolerated, low toxicity profile. **Occasional:** QTc prolongation (5–15 msec average, peak at 8 week). Overall QTc prolongation in cohorts using delamanid, bedaquiline and other QTc-prolonging drugs was 2.7%, with median appearance at 2.5 months, with no cardiac deaths reported. Other effects are nausea, vomiting, dizziness, insomnia, anxiety, hallucinations, night terrors and upper abdominal pain.

Contraindications	Hypersensitivity to delamanid. Serum albumin levels <2.8 g/mL. Use with caution in patients sensitive to lactose. **Discontinue or do not use in the presence of:** • clinically significant ventricular arrhythmia; • QTcF interval of >500 msec (confirmed by repeat ECG); • severe liver disease; or • abnormal electrolytes. **Use with caution in situations that may increase QT interval:** In patients aged >60 years, heart failure, long QT syndrome, history of TdP, hypokalaemia, untreated hypothyroidism, low BMI, HIV infection and concomitant use of other QT-prolonging drugs. Any syncopal event (e.g. fainting) or palpitations should prompt an immediate medical evaluation and ECG. In several retrospective cohort studies on the incidence of QTc prolongation and cardiac events, the increase is modest and no arrhythmias or related deaths were reported, even with bedaquiline and delamanid co-administration.
Drug interactions	Low potential for drug–drug interactions. Concomitant administration of strong CYP3A inducers (e.g. rifampicin and carbamazepine) should be avoided. Co-administration with strong CYP3A inhibitors (e.g. ritonavir and ketoconazole): frequent monitoring of ECG should be considered. No interactions have been found between delamanid, dolutegravir and the main antiretroviral drugs. Delamanid may attenuate vitamin K-dependent blood clotting, and increase prothrombin time and activated partial thromboplastin time. Use with other medicines that directly or indirectly prolong the QT interval may cause additive prolongation, which requires caution and monitoring: • anti-TB drugs: fluoroquinolones, clofazimine and bedaquiline; and • ancillary and common drugs: azoles, macrolides, metoclopramide, efavirenz, furosemide, hydrochlorothiazide, citalopram, escitalopram, methadone, antiarrhythmics and others. Co-administration with cycloserine may increase the risk of neuropsychiatric adverse events, especially in children.
Food interaction	Delamanid should be taken with food, and alcohol should be avoided.
Monitoring	Before initiating delamanid, it is important to ensure that the albumin level is 2.8 g/dL or higher. ECG and baseline electrolytes should be obtained whenever possible before the initiation of treatment, and repeated if necessary (e.g. documented QTc prolongation or multiple QTc-prolonging risk factors). When administering delamanid and cycloserine concurrently, monitoring for neuropsychiatric side-effects is important. These events should be reported through the national pharmacovigilance system.

Patient instructions and alerting symptoms	**Patients should be instructed to inform their health care provider immediately if any of the following occur:** • history of heart problems, heart attack, congenital long QT syndrome or problems with heart rhythm; • liver or kidney disease; • HIV; or • pregnancy or planning to get pregnant.

BMI: body mass index; CSF: cerebrospinal fluid; ECG: electrocardiography; HIV: human immunodeficiency virus; *M. tuberculosis*: *Mycobacterium tuberculosis*; PD: pharmacodynamic; PK: pharmacokinetic; TB: tuberculosis; TdP: torsades de pointes.

[a] See the handbook Annex for revised weight-based dosing.

[b] Tucker EW, Pieterse L, Zimmerman MD, Udwadia ZF, Peloquin CA, Gler MT et al. Delamanid central nervous system pharmacokinetics in tuberculous meningitis in rabbits and humans. Antimicrob Agents Chemoth. 2019;63:e00913–19. doi: https://doi.org/10.1128/AAC.00913–19.

Ethambutol (E)

Ethambutol (E) **Drug class: unspecified**	
Activity against *M. tuberculosis,* mechanism of action and metabolism	**Target:** *M. tuberculosis* cell wall. It inhibits the synthesis of arabinogalactan and lipoarabinomannan (special cell wall layer typically from *Mycobacterium* species), preventing division. **Activity:** Low bactericidal activity (bacteriostatic; bactericidal only at the high end of the dosing range). At doses used over long periods of time, ethambutol protects against further development of resistance to other drugs. **Half-life and excretion:** has a half-life of 3.3 hours; mainly renal excretion (20–22% of a dose is eliminated unchanged in the faeces).
Cross-resistance	Not reported.
Dose[a]	• **Adults:** 15–25 mg/kg/day. Upper daily dose 1200 mg. • **Children:** See the handbook Annex for weight bands. • **Renal failure or dialysis:** 15–25 mg/kg/dose, thrice weekly (not daily). See the handbook Annex for weight-based dosing in adults and children.
Administration	Oral.
Formulation and preparation	100 mg dispersible tablets. 400 mg film-coated tablets. Crushing and dissolving 400 mg tablets in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole, and avoids fractioning solid formulations, although the bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	Should be stored below 30 °C.
Oral absorption	Has 80% bioavailability, independent of food intake.
CSF penetration	Penetrates meninges poorly.
Special circumstances	**Use during pregnancy or breastfeeding:** Ethambutol is considered safe in pregnancy; it can be used while breastfeeding but may appear in breast milk. **Use in renal disease:** Should be used with caution; ethambutol is cleared by the kidneys. Dose adjustment is required (see under Dose section, above) because there is an increased risk of toxicity. **Use in obesity:** Risk of chronic overdose; dose adjustment is required (see under Dose section, above). **Use in hepatic disease:** Considered safe.

Adverse reactions	**Overall tolerance**: Well tolerated; side-effects are commonly related to chronic overdose (e.g. wrong prescription, renal failure or overdose in obesity). **Occasional**: Decrease in visual acuity and colour vision (retrobulbar neuritis). The effect may be related to dose and duration of treatment; ethambutol should be stopped in cases of optic neuritis because irreversible blindness has been reported. **Uncommon**: Liver toxicities.
Contraindications	Pre-existing optic neuritis or severe visual problems; visual changes after ethambutol use.
Drug interactions	Low potential for drug–drug interactions. No major interactions with CYP450. Concomitant use with aluminium hydroxide-containing antacid should be avoided for at least 4 hours after ethambutol administration.
Food interactions	No interaction; food may reduce gastrointestinal irritation.
Monitoring	Patients should be counselled to report any changes in vision. Baseline and monthly visual acuity and colour discrimination monitoring should be performed; particular attention should be given to individuals on higher doses or with renal impairment. Each eye must be tested separately and both eyes tested together.
Patient instructions and alerting symptoms	Can be taken with food or on an empty stomach. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** Any problems with vision changes, blurring, colour blindness, trouble seeing or eye pain.

CSF: cerebrospinal fluid; *M. tuberculosis*: *Mycobacterium tuberculosis*.

[a] See the handbook Annex for revised weight-based dosing.

Ethionamide (Eto) or prothionamide (Pto)

Ethionamide (Eto) or prothionamide (Pto) Drug class: carbothionamides group, derivatives of isonicotinic acid	
Activity against *M. tuberculosis,* mechanism of action and metabolism	Ethionamide and prothionamide (a propyl-analogue of ethionamide) are both thioamides; they have similar efficacy and are considered interchangeable; however, ethionamide is more widely available. As with pyrazinamide, they are nicotinic acid derivatives related to isoniazid. **Target:** *M. tuberculosis* cell wall. Ethionamide and prothionamide are pro-drugs. Following enzymatic activation by mycobacterial EthA, the active metabolite inhibits the inhA enzyme, which is responsible for mycolic acid synthesis (mycolic acid is an essential part of mycobacterium cell wall), with a similar mechanism to isoniazid. **Activity:** Weak bactericidal (depending on the concentration of the drug attained in tissues, mostly bacteriostatic). **Half-life and excretion:** Has a half-life of 2–3 hours. Excreted via hepatic metabolism.
Cross-resistance	There is complete cross-resistance between ethionamide and prothionamide. In the case of mutation in the *inhA* gene, there is cross-resistance with isoniazid (high-level ethionamide and prothionamide resistance, but low-level resistance to isoniazid).
Dose[a]	• **Adults:** 15–20 mg/kg/day; upper daily dose is 1 g. Once-daily dosing is advised but clinicians can use 2 divided doses if tolerance is a problem, or until tolerance improves. Many individuals require gradual ramping up of the dose and treatment due to gastrointestinal upset. • **Children:** See the handbook Annex for weight bands. • **Renal failure or dialysis:** No change. • **Pyridoxine (vitamin B6):** There are insufficient data to support the systematic administration of vitamin B6 to adults or children receiving ethionamide and prothionamide. See the handbook Annex for weight-based dosing in adults and children.
Administration	Oral. Crushing and dissolving 250 mg tablets in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; this avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Formulation and preparation	125 mg dispersible tablet (only ethionamide). 250 mg film-coated tablets (ethionamide and prothionamide).
Storage	Should be stored below 30 °C in a dry place.
Oral absorption	Has almost full oral bioavailability but there is potential for erratic absorption, possibly owing to associated gastrointestinal disturbances.

CSF penetration	Concentrations approach those in the serum; one paediatric study evaluating drug concentrations in the CSF suggested that ethionamide should be dosed at the higher end of the dose range for patients with meningitis.
Special circumstances	**Use during in pregnancy or breastfeeding:** These drugs are generally avoided during pregnancy owing to increased nausea and vomiting, risk of decreased TSH (fundamental for pregnant woman and the fetus) and limited reports of teratogenicity. TSH levels should be monitored and supplemented if necessary to prevent congenital hypothyroidism. There are few data about the use of these drugs during breastfeeding: it is estimated that 20% of the infant therapeutic dose will be passed on to the baby in breast milk (the infant should be supplemented with vitamin B6 if breastfed). **Children:** TSH levels should be monitored, and supplemented if necessary to avoid growth failure and permanent intellectual disability. **Use in renal disease:** No precautions are required for renal impairment. **Use in hepatic disease:** These drugs can cause hepatotoxicity similar to that seen with isoniazid; they should be used with caution in liver disease.
Adverse reactions	**Overall tolerance:** Poorly tolerated. **Common**: Most patients (adults and children) will experience dose-related gastrointestinal intolerance with ethionamide and prothionamide, resulting in nausea, vomiting, metallic taste, anorexia, abdominal discomfort, diarrhoea and weight loss. Symptoms are moderated by food or by taking the drugs at bedtime. Many individuals require gradual ramping up of the dose and treatment due to gastrointestinal upset. Premedication with an antiemetic is often helpful. Gastrointestinal upset may increase with concomitant use of para-aminosalicylic acid. **Occasional:** Hypothyroidism in adults is usually subclinical and reversible but has potential important consequences in pregnant woman and children, requiring monitoring of TSH and supplementation with levothyroxine. The risk of hypothyroidism increases when the drugs are used with para-aminosalicylic acid. Hepatotoxicity may occur, and the risk is increased by the concomitant use of rifampicin. Neurological side-effects (e.g. convulsions) may be exaggerated in patients also taking cycloserine. **Uncommon**: Gynaecomastia, hair loss, acne, impotence and menstrual irregularity.
Contraindications	Sensitivity to ethionamide and prothionamide or isoniazid.
Drug interactions	Temporarily raises serum concentrations of isoniazid. No major drug–drug interactions have been found but there is the potential for increased side-effects in the presence of other anti-TB medication (para-aminosalicylic acid, cycloserine, isoniazid and rifampicin).

Food interactions	Can be taken with or without food. Taking ethionamide and prothionamide with food may reduce gastrointestinal upset. Alcohol ingestion should be avoided because it may increase the risk of psychotic reactions.
Monitoring	TSH should be monitored for evidence of hypothyroidism requiring replacement therapy; therapeutic drug monitoring is required if malabsorption is suspected. Liver function tests should be monitored.
Patient instructions and alerting symptoms	Should be taken with food. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • convulsions, personality changes such as depression, confusion or aggression; • severe nausea and vomiting or dehydration; • yellowing of skin or eyes or dark-coloured urine; or • swollen breasts.

CSF: cerebrospinal fluid; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis; TSH: thyroid-stimulating hormone.

[a] See the handbook Annex for revised weight-based dosing.

Imipenem–cilastatin (Imp–Cln)

Imipenem–cilastatin (Imp–Cln) **Drug class: beta-lactam – carbapenem**	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** *M. tuberculosis* cell wall. Imipenem is a beta-lactam antibiotic belonging to the subgroup of carbapenems. It needs to be used in combination with clavulanic acid to block the β-lactamase secretion present in bacteria such as *M. tuberculosis*, which otherwise inactivates most penicillins. Carbapenems have several mechanisms of action, including inactivating the penicillin-binding proteins and transpeptidases, inhibiting the biosynthesis of the peptidoglycan layer of the bacterial cell wall (creating lysis) or interfering with cell wall formation. **Activity:** Bactericidal and probably sterilizing activity. **Half-life and excretion:** Imipenem is rapidly degraded by renal proximal tubule dipeptidases; therefore, it is used in combination with the dipeptidase inhibitor cilastatin. Following IV injection, imipenem has a half-life of 1 hour; following IM injection, it has a half-life of 1.3–5.1 hours. Cilastatin is partially metabolized renally. Imipenem is mainly excreted in the urine (70%).
Cross-resistance	Imipenem and meropenem may have cross-resistance, but evidence about *M. tuberculosis* is limited.
Dose[a]	These drugs should not be used in children aged <15 years. • **Adults: 1000 mg twice daily**. Upper daily dose 2000 mg. • **Renal failure or dialysis:** Adjustment in dose based on severity of renal failure; for example, 750 mg every 12 hours for creatinine clearance of 20–40 mL/min or 500 mg every 12 hours for creatinine clearance <20 mL/min. See the handbook Annex for weight-based dosing in adults.
Administration	No oral absorption. It can be administered IV or IM. Every dose is to be preceded by 30–60 minutes of administration of clavulanate (see amoxicillin–clavulanic acid medicine information sheet for dosing). **IV:** The infusion must be given slowly and can take 20–60 minutes to complete (or even longer in case of nausea). For long-term use as part of TB treatment, consider insertion of a peripherally inserted central catheter line.
Formulation and preparation	Powder for injection, 500 mg/500 mg in 10 mL vial.
Storage	The powder should be kept at room temperature (15–25 °C); the reconstituted product should be used within 2 hours and not frozen. Any unused product or waste material should be disposed of in accordance with local requirements.
Oral absorption	–
CSF penetration	Good CSF penetration. Meropenem is usually preferred for TB meningitis and for children because of the increased risk of seizures associated with use of imipenem.

Special circumstances	**Use during pregnancy or breastfeeding:** There is limited information regarding the use of this medicine in pregnancy; safety during breastfeeding is unknown. **Use in renal disease:** Dose adjustment is required (see under Dose section above); dose after dialysis. **Use in hepatic disease:** Elevated liver function test levels have been noted in up to 6% of patients, but no definite liver damage has been documented.
Adverse reactions	**Overall tolerance**: Poorly tolerated, owing to the disruption of daily life from lengthy infusions and the care of a peripherally inserted central catheter line, which may be needed for many months. **Frequently**: Diarrhoea, nausea or vomiting; yeast infection (thrush). **Occasional**: Pseudomembranous colitis (overgrowth of *Clostridioides difficile*). **Uncommon**: Seizures (noted with CNS infection), palpitations.
Contraindications	Carbapenem intolerance. **Meningitis** (use meropenem rather than imipenem–cilastatin).
Drug interactions	Low potential for drug–drug interactions. Ganciclovir: Increased risk of convulsions. Valproate: Imipenem reduces serum concentrations of valproate. Avoid concomitant use.
Food interactions	None.
Monitoring	Monitor clinical signs and symptoms.
Patient instructions and alerting symptoms	Ask patient about concomitant medication with ganciclovir or history of allergy to penicillins or cephalosporins. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • severe diarrhoea (watery or bloody); • seizures or epilepsy; or • fast or irregular heartbeat.

CNS: central nervous system; CSF: cerebrospinal fluid; IM: intramuscular; IV: intravenous; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis.

[a] See the handbook Annex for revised weight-based dosing.

Isoniazid high dose (Hh)

Isoniazid high dose (Hh) **Drug class: isonicotinic acid hydrazide**	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** The *M. tuberculosis* cell wall. Isoniazid is a prodrug that after activation by the enzyme katG (bacterial catalase), blocks the action of the inhA enzyme that is responsible for the biosynthesis of mycolic acids, a major component of mycobacterial cell walls. Isoniazid is a first-line TB medicine that may be an effective as a second-line agent if used at high doses in the absence of high-level resistance. **Activity:** Strongly bactericidal against actively growing intracellular and extracellular *M. tuberculosis*. To date, isoniazid is considered the most bactericidal of the first-line and second-line drugs. **Half-life and excretion**: Primarily hepatic metabolism (*N*-acetyl transferase). The half-life is 0.5–1.6 hours in fast acetylators and 2–5 hours in slow acetylators (the acetylation rate in humans is genetically determined). Isoniazid is 50–70% excreted in the urine.
Cross-resistance	Mutations in the *inhA* promoter region may cause low-level resistance to isoniazid and resistance to thionamides.
Dose[a]	In DR-TB, a higher dose of isoniazid may be used as part of a shorter 9-month regimen. • **Adults**: 10–15 mg/kg/day. Standard daily dose is 300 mg/kg; high dose is 600 mg. • **Children:** See the handbook Annex for weight bands. • **Renal failure or dialysis:** 300 mg once daily. • **Pyridoxine (vitamin B6):** Should be used when high-dose isoniazid is administered. Pregnant and postpartum women and exclusively breastfed infants should always receive vitamin B6 while taking isoniazid. See the handbook Annex for weight-based dosing in children.
Administration	Oral.
Formulation and preparation	50 mg/5 mL oral solution. 100 mg dispersible tablets. 100 mg scored and unscored tablets. 300 mg scored and unscored tablets. Crushing and dissolving uncoated tablets (100 mg and 300 mg) in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; it also avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	The oral solution should be stored below 25–30 °C. Tablets should be stored below 30 °C and protected from light. The dispersible tablets should be protected from moisture.
Oral absorption	Well absorbed orally or intramuscularly. Best absorbed on an empty stomach (there is a >50% reduction in peak concentration if taken with a high-fat meal).

CSF penetration	Being a moderately lipophilic small molecule, the concentration in CSF is equivalent to that in plasma in inflamed meninges, but to only 20% of plasma concentrations in noninflamed meninges.
Special circumstances	**Use during pregnancy or breastfeeding:** Such use is not contraindicated. When breastfeeding, both infant and mother should receive pyridoxine supplementation. **Use in renal disease:** No dose adjustment is necessary in cases of renal failure, but pyridoxine supplementation should be used. **Use in hepatic disease:** It may exacerbate liver failure and should be used with caution.
Adverse reactions	**Overall tolerance:** Well tolerated. **Frequently:** Peripheral neuropathy: numbness, weakness, tingling, or burning pain in the hands or feet; nausea, vomiting and upset stomach; and abnormal liver function test results (transaminitis). **Occasional:** Hepatitis (higher risk in older age, alcohol misuse, pregnancy, viral hepatitis, fatty liver disease or nonalcoholic steatohepatitis and liver TB); and fever, chills, joint pain (arthralgia) and mild CNS effects (enhanced by concomitant use of cycloserine). **Uncommon:** Severe hypersensitivity (allergic) reaction; serious and sometimes fatal liver problems (more frequent in isoniazid monotherapy, less in rifampicin–isoniazid concomitant use); and drug-induced lupus.
Contraindications	Patients with high-level isoniazid resistance for whom an isoniazid-containing regimen has failed. History of allergic reaction to isoniazid or ethionamide or prothionamide.
Food interactions	Should be taken on an empty stomach (1 hour before or 2 hours after meals); absorption and bioavailability are reduced when administered with food. In case of stomach upset, isoniazid can be taken with a snack. Should be taken separately from antacids (which reduce absorption). Alcohol should be avoided because it may increase the risk of induced hepatitis and neuropathy. Caffeine and chocolate intake should be avoided, as should foods and supplements containing histamine and tyramine.
Drug interactions	Low potential for drug–drug interactions. Isoniazid is a weak CYP3A4 inhibitor and may increase the concentration of certain cytochrome P450 enzyme substrates such as phenytoin (increase concentration) and carbamazepine (risk of hepatotoxicity). Alcohol can lead to an increased risk of convulsions. There is an increased risk of CNS toxicity when isoniazid is given concomitantly with cycloserine.
Monitoring	Clinical monitoring and liver function testing should be undertaken, ideally monthly. For patients receiving multiple TB drugs or other hepatotoxic drugs, or with underlying liver disease (including viral hepatitis), baseline liver function testing is recommended. Follow-up liver function testing is determined by baseline concerns and symptoms of hepatotoxicity.

Patient instructions and alerting symptoms	The medication should be taken on an empty stomach for better absorption. It should not be taken with a large fatty meal. In the case of stomach upset, isoniazid can be taken with a snack. The liquid suspension should not be refrigerated. Patients should avoid alcohol, antacids, chocolate, caffeine, and foods and supplements containing histamine and tyramine while taking this medicine. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • convulsions (seizures) or behavioural change; • flushing, sweating or headaches; • numbness, pain or tingling or burning of fingers or toes; • blurred vision or eye pain; • loss of appetite, tiredness, weakness, yellow skin or eyes or dark-coloured urine; or • fever and skin rash that spreads and causes blistering and peeling.

CNS: central nervous system; CSF: cerebrospinal fluid; DR-TB: drug-resistant tuberculosis; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis.

[a] See the handbook Annex for revised weight-based dosing.

Levofloxacin (Lfx)

Levofloxacin (Lfx) **Drug class: fluoroquinolone**	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** Inner *M. tuberculosis* cell metabolism. A third-generation fluoroquinolone (along with moxifloxacin), it inhibits enzymes that are crucial for bacterial DNA replication. In *M. tuberculosis* it appears that DNA gyrase is the sole topoisomerase targeted. DNA gyrase is a tetrameric A_2B_2 protein (two A subunits and two B subunits). Inhibiting DNA gyrase (in any subunit) results in a blockade of DNA replication, inhibiting cell division and resulting in cell death of replicative and nonreplicative *M. tuberculosis*. The antimycobacterial activity of this fluoroquinolone depends on the molecule's affinity to target enzyme and efflux pumps, and the naturally low permeability of the *M. tuberculosis* cell wall. **Activity:** Levofloxacin is considered both highly bactericidal (excellent early bactericidal activity) and highly sterilizing. **Half-life and excretion:** The half-life of levofloxacin is 6–8 hours. It is mainly excreted unchanged in the urine.
Cross-resistance	In general, there is a class effect of cross-resistance among fluoroquinolones in vitro. Data suggest that levofloxacin and moxifloxacin may continue to demonstrate some activity, even against strains that have in vitro resistance to second-generation fluoroquinolones, such as ofloxacin. The pattern of resistance or susceptibility to the different fluoroquinolones depends on specific point mutation and is the subject of ongoing research.
Dose[a]	• **Adults:** 750–1125 mg/day (oral or IV); usually at least 750 mg/day, and the standard upper daily dose is 1.5 g. • **Children**: See the handbook Annex for weight bands. • **Renal failure or dialysis:** 750–1000 mg/dose, thrice weekly for creatinine clearance <30 mL/min. See the handbook Annex for weight-based dosing in adults and children.
Administration	Oral.
Formulation and preparation	100 mg dispersible tablet. 250 mg, 500 mg, 750 mg tablets film coated (may be scored in some markets). Crushing and dissolving film-coated tablets (100 mg and 300 mg) in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; it also avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	Should be stored below 30 °C, in a dry place, protected from light.

Oral absorption	Excellent oral absorption. Absorption can be reduced by ingestion of aluminium or magnesium antacids, sucralfate, metal cations (e.g. iron and multivitamin preparations with zinc). When use of these products is necessary, they should be administered at least 2 hours before or 2 hours after the fluoroquinolone.
CSF penetration	In general, fluoroquinolones achieve an effective concentration in the brain and meninges. Levofloxacin concentrations are at least 65% of the concentration in serum. Levofloxacin is also widely bioavailable in other organs and body fluids. It has been successfully used in the treatment of TB meningitis.
Special circumstances	**Use during pregnancy or breastfeeding:** It has been associated with arthropathy in canine models. There have been multiple case reports of fluoroquinolones being used safely in humans during pregnancy and breastfeeding. **Use in renal disease:** Dosage adjustment is recommended if creatinine clearance is <50 mL/min. The drug is not cleared by haemodialysis; supplemental doses after dialysis are not necessary. **Use in hepatic disease:** Drug concentrations are not affected by hepatic disease. It is presumed to be safe in severe liver disease. **Marfan syndrome, Ehlers–Danlos syndrome or steroid use:** Increased risk of tendon or aorta lesions • **Diabetes:** Increased risk of hypoglycaemia. • **Long QT syndrome (patient or family member), hypokalaemia, malnutrition, hypothyroidism in those aged >60 years, multiple QT-prolonging drugs:** Increased risk of QTc prolongation.
Adverse reactions	**Overall tolerance**: Generally well tolerated, with low potential for acute toxicity. **Common**: Diarrhoea, nausea and bloating, and arthralgia. **Occasional:** QTc interval prolongation (levofloxacin is considered safer than moxifloxacin); may decrease or alter glycaemia (this is true of all third-generation fluoroquinolones); and tendon rupture, especially Achilles tendon. **Uncommon**: Peripheral neuropathy, mood or behaviour changes, insomnia and aortic dissection.

Contraindications	Fluoroquinolone intolerance. It should be used with caution in situations that may increase the QT interval: patients aged >60 years, heart failure, long QT syndrome, history of TdP, hypokalaemia, untreated hypothyroidism, low BMI, HIV infection and concomitant use of other QT-prolonging drugs. Any syncopal event (e.g. fainting) or palpitations should prompt an immediate medical evaluation and ECG. In several retrospective cohort studies on the incidence of QTc prolongation and cardiac events, the increase was modest, and no arrhythmias or related deaths were reported even with co-administration of bedaquiline and delamanid. **Discontinue or do not use in the presence of:** • clinically significant ventricular arrhythmia; • a QTcF interval of >500 msec (confirmed by repeat ECG); or • abnormal electrolyte levels.
Drug interactions	Low potential for drug–drug interactions. Concomitant steroid use may increase risk of tendon rupture. Multivalent cation-containing products including antacids and metal cations may decrease absorption. The intravenous formulation should not be co-administered through the same IV line as a multivalent cation, such as magnesium. Warfarin: The effect of this drug may be enhanced. Prothrombin time and INR should be monitored, and the patient should be monitored for bleeding. Antidiabetic agents: Carefully monitor blood glucose.
Food interactions	Can be taken with or without food, without a clinically significant impact on absorption or bioavailability. There are no major interactions between milk or dairy products and third-generation fluoroquinolones. Antacids (especially those containing aluminium), mineral supplements (e.g. iron or magnesium) or multivitamins should be taken more than 2 hours before or after this medication.
Monitoring	No specific laboratory monitoring is required. Ideally, an ECG should be obtained before initiation of treatment, and at least 2, 12 and 24 weeks after starting treatment. Levofloxacin should be stopped if the QTc >500 msec, and ECGs and potassium should be monitored frequently until the QTc returns to normal. More frequent monitoring is recommended if cardiac conditions, hypothyroidism or electrolyte disturbances are present.

Patient instructions and alerting symptoms	This medication should be taken with or without food. Antacids (especially aluminium-containing ones), mineral supplements (e.g. iron or magnesium), or multivitamins should be taken more than 2 hours before or after of this medication. This medicine may cause sun sensitivity; sunscreens should be used. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • pain, swelling or tearing of a tendon (such as the back of your ankle, elbow), or muscle or joint pain; • severe diarrhoea (watery or bloody); • seizures, epilepsy, change in mood or behaviour; or • low blood sugar symptom (i.e. headache, hunger, sweating, irritability, dizziness, nausea, fast heart rate, or feeling anxious or shaky).

BMI: body mass index; CSF: cerebrospinal fluid; DNA: deoxyribonucleic acid; ECG: electrocardiography; HIV: human immunodeficiency virus; INR: international normalized ratio; IV: intravenous; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis; TdP: *torsade de pointes*.

[a] See the handbook Annex for revised weight-based dosing.

Linezolid (L or Lzd)

Linezolid (L or Lzd) **Drug class: oxazolidinones**	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** Bacterial ribosome. Linezolid blocks protein synthesis at the bacterial ribosome. It interferes with translation of the bacterial mRNA into proteins by binding to the 23S ribosomal RNA component (part of the large ribosome subunit). Without the capacity to synthesize proteins, bacterial reproduction and subsistence is not possible. **Activity:** Has modest early bactericidal activity in vitro, and probable sterilizing and excellent bioavailability in tissues. **Half-life and excretion**: Maximum plasma concentrations are reached in about 1–2 hours after dosing. The half-life is estimated as 5–7 hours. About 31% binds to plasma proteins (mainly albumin). It is primarily metabolized by the liver (biotransformation routes are unclear) and subsequently eliminated by the kidneys, with minor faecal elimination.
Cross-resistance	Cross-resistance between linezolid and other oxazolidinones in *M. tuberculosis* is not fully documented.
Dose[a]	• **Adults:** 600 mg, once daily, upper daily dose is 1.2 g. • **Children:** See the handbook Annex for weight bands. • **Renal failure or dialysis:** No dose adjustment is required. However, accumulation of the two primary metabolites may occur; hence, it should be used with caution. • **Pyridoxine (vitamin B6):** There are insufficient data to support the systemic administration of vitamin B6 to adults or children on linezolid. However, some studies suggest an effect on myelotoxicity prevention and thrombocytopenia improvement. See the handbook Annex for weight-based dosing in adults and children
Administration	Oral.
Formulation and preparation	100 mg/5 mL powder for oral liquid. Following reconstitution, the solution should be mixed gently before administration; it should not be shaken. 150 mg dispersible tablet. 600 mg coated tablet. Crushing and dissolving film-coated tablets (600 mg) in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; also, it avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	The powder for the oral liquid should be stored below 25 °C, protected from light and moisture. The reconstituted suspension may be stored at room temperature for 21 days. Tablets should be stored below 25 °C, protected from light and moisture.
Oral absorption	It is extensively absorbed following oral administration and has an absolute bioavailability of about 100%.

CSF penetration	It has excellent CSF and brain penetration.
Special circumstances	In patients with pre-existing haematological conditions, it should be used with extreme caution. **Use during pregnancy or breastfeeding:** Studies in animals have shown evidence of an increased occurrence of fetal damage. There are limited data in humans but no reports of increased malformation or other direct or indirect harmful effects on the human fetus. Drug levels appear in breast milk at lower than the usual infant dose. **Use in renal disease:** No dose adjustment is recommended, but metabolites may accumulate. **Use in hepatic disease:** Despite hepatic metabolism, it is rarely associated with increased transaminases. **Use in diabetes mellitus:** There is increased risk of lactic acidosis in patients being treated with metformin. Hypoglycaemia has been reported in patients receiving insulin or oral hypoglycaemic agents and linezolid. **Use in patients with cerebrovascular or cardiovascular disease, pheochromocytoma, carcinoid syndrome or untreated hyperthyroidism:** Linezolid may exacerbate symptoms of those conditions. **Use in patient with depression:** Administration of linezolid concurrently with even common SSRIs can lead to serious reactions such as serotonin syndrome or neuroleptic malignant syndrome-like reactions. See the sections on Adverse reactions and Drug interactions.
Adverse reactions	**Overall tolerance:** Poorly tolerated. **Frequently/common:** • Nausea, vomiting and diarrhoea. • **Myelosuppression**, which may manifest within the first 2 months of treatment with decreased platelet or white blood cell counts and anaemia. • **Optic nerve toxicity and peripheral neuropathy** tend to develop after several weeks of treatment and may lead to irreversible blindness or disabling permanent neuropathy. Nerve toxicity is usually a reason to stop linezolid. **Occasional:** Pseudomembranous colitis, vaginal candidiasis, hypoglycaemia, serotonin syndrome and lactic acidosis; and arrhythmia (tachycardia), transient ischaemic attacks, pancreatitis, seizures. **Uncommon:** Stevens–Johnson syndrome, angioedema and alopecia.

Contraindications	• Hypersensitivity to oxazolidinones. • If patient is taking another MAO inhibitor medication or has used one in the past 14 days, linezolid should not be taken. • Should be used with extreme caution with antidepressants, antimigraine and other medications (see section on Drug interactions, and balance risk of serotonin syndrome versus benefit). • Should not be used concomitantly with stavudine or didanosine. • Should be used with extreme caution with lamivudine, zidovudine and abacavir. • Should be used with extreme caution if metformin is used at a high dose; in such cases, it is best to consider a change to other oral antidiabetic medication or insulin to limit the risk of lactic acidosis. • Should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis or carcinoid syndrome.
Drug interactions	There is a high potential for drug–drug interactions. There are no CYP450 enzyme system interactions but linezolid is an MAO inhibitor, and combination with other drugs may increase the risk of severe clinical conditions and linezolid-induced toxicities. **Increased risk of pancytopenia:** Zidovudine and co-trimoxazole. **Increased risk of lactic acidosis:** Metformin, stavudine, didanosine, lamivudine, zidovudine and abacavir. **Increased risk of serotonin syndrome:** Because linezolid is an MAO inhibitor, there is increased risk with SSRIs, SNRIs, TCAs, serotonin 5-HT1 receptor agonists, bupropion, anti-seizure medication, opioid analgesics, buspirone, antiemetics, anti-Parkinson's medication, sympathomimetic agents, vasopressive agents, dopaminergic agents and common medications used for influenza or congestion and bought over the counter such as dextromethorphan, pseudoephedrine , diphenhydramine or guaifenesin .
Food interactions	Oral absorption is not significantly affected by co-administration with food; thus, it may be taken with or without food, but taking with food may alleviate stomach irritation. **Increased risk of tyramine toxicity:** Patients should avoid tyramine-containing foods and supplements such as aged cheese, fava beans, cured foods, dried meats, pickled foods, sauerkraut, kimchi, soy sauce, teriyaki sauce, fish sauce and red wine, tap beers and liquors.
Monitoring	Patients should be monitored for: • peripheral neuropathy and optic neuritis, through visual eye acuity (both eyes) and Ishihara tests every 2 months or, if symptoms develop, clinical examination for peripheral neuropathy monthly; • complete blood count weekly during the initial period, then monthly, and thereafter as needed based on symptoms; and • pH, anion gap and lactate levels in case of suspected lactic acidosis (hyperlactatemia, if lactate >2.0 mmol/L and confirmed lactic acidosis at >4.0 mmol/L), hypotension, lethargy or clinical worsening without a clear explanation.

Patient instructions and alerting symptoms	The medication can be taken with or without food but patients should avoid tyramine-containing foods (see list in Food interactions section, above). Patients should be asked about any medicines or supplements taken, especially metformin, antidepressants and common cold medications (see Drug interactions section above). **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • pain, numbness, tingling or weakness in the extremities; • unusual tiredness, weakness, hypotension; • black, tarry stools or severe diarrhoea; • unusual bleeding or bruising; • changes in vision; or • headache, nausea or vomiting, sweating, rigidity, tremor, or change in mood, behaviour or consciousness.

CSF: cerebrospinal fluid; *M. tuberculosis*: *Mycobacterium tuberculosis*; MAO: monoamine oxidase; mRNA: messenger ribonucleic acid; RNA: ribonucleic acid; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant.

[a] See the handbook Annex for revised weight-based dosing.

Meropenem (Mpm)

Meropenem (Mpm) **Drug class: beta-lactam – carbapenem**	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** *M. tuberculosis* cell wall. Meropenem is a beta-lactam antibiotic belonging to the subgroup of carbapenems. It must be used in combination with clavulanic acid to block the β-lactamase secretion present in bacteria such as *M. tuberculosis*, which otherwise inactivates most penicillins. Carbapenems, through several mechanisms (e.g. inactivation of the penicillin-binding proteins and transpeptidases), inhibit the biosynthesis of the peptidoglycan layer of the bacterial cell wall, causing lysis or interfering with cell wall formation. **Activity:** Has bactericidal and probably sterilizing capacity. One study found a better efficacy profile with meropenem than with imipenem. **Half-life and excretion:** Meropenem is stable to renal dipeptidases and does not require cilastatin. It is mainly excreted in the urine (70%) and has a half-life of about 1–1.5 hours in adults and children.
Cross-resistance	Imipenem and Meropenem may have cross-resistance, but evidence with *M. tuberculosis* is very limited.
Dose[a]	• **Adults:** 1 g (20 mL) IV thrice daily or 2 g twice daily. Each dose is preceded by 125 mg clavulanate (administer clavulanic acid 60 minutes before each dose of meropenem). Upper daily dose is 6000 mg. • **Children:** See the handbook Annex for weight bands. • **Renal failure or dialysis:** The adjustment to the dose is based on the severity of renal failure; for example, 750 mg every 12 hours for creatinine clearance of 20–40 mL/min or 500 mg every 12 hours for creatinine clearance <20 mL/min. See the handbook Annex for weight-based dosing in adults and children.
Administration	IV only (no IM recommended); there is no oral absorption. Clavulanate should be given orally 30–60 minutes before an IV dose of meropenem (every 8 hours) For long-term use in TB, insertion of a peripherally inserted central catheter line should be considered.
Formulation and preparation	Powder for injection or infusion (1 g) is to be reconstituted (1 g in 20 mL) with water for injection or 0.9% sodium chloride or 5% glucose solution for infusion before administration.
Storage	Powder should be stored below 25–30 °C. Reconstituted solution storage conditions vary; hence, the specific product label should be checked.
Oral absorption	Not applicable
CSF penetration	Has adequate CSF penetration and is recommended in case of TB meningitis (where meropenem is preferred over imipenem).

Special circumstances	**Use during pregnancy or breastfeeding:** It is considered safe but there is little information regarding lengthy use in TB use during pregnancy. Meropenem is excreted into human milk, and its safety during breastfeeding is unknown. **Use in renal disease:** Dose adjustment is required in renal disease (see under Dose section, above); dose after dialysis. **Use in hepatic disease:** Liver disease does not alter the pharmacodynamics of meropenem.
Adverse reactions	**Overall tolerance:** It is poorly tolerated because of important disruption to daily life owing to IV administration and the need to care for a peripherally inserted central catheter line, sometimes for many months. **Frequently:** Headache, diarrhoea, nausea or vomiting, and yeast infection (thrush). **Occasional:** Anaemia and pseudomembranous colitis (overgrowth of *Clostridioides difficile*). **Uncommon:** Seizures (noted with CNS infection), but rare compared with imipenem; and elevated liver enzymes, haematologic toxicity and hypersensitivity.
Contraindications	Carbapenem intolerance.
Drug interactions	Low potential for drug–drug interactions. Co-administration of probenecid inhibits renal excretion of meropenem. Co-administration of valproic acid or divalproex sodium reduces the serum concentration of valproic acid, potentially increasing the risk of seizures.
Food interactions	None.
Monitoring	Monitoring of clinical signs and symptoms.
Patient instructions and alerting symptoms	The patient should be asked about concomitant medication with valproic acid and whether they are allergic to penicillins or cephalosporins. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • severe diarrhoea (watery or bloody); • skin rash, hives or itching; • pale skin, unusual tiredness; or • swelling in the face, throat or lips, wheezing or trouble breathing.

CNS: central nervous system; CSF: cerebrospinal fluid; IM: intramuscular; IV: intravenous; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis.

[a] See the handbook Annex for revised weight-based dosing.

Moxifloxacin (M or Mfx)

Moxifloxacin (M or Mfx) **Drug class: fluoroquinolone**	
Activity against *M. tuberculosis,* mechanism of action and metabolism	**Target:** Inner *M. tuberculosis* metabolism. A third-generation fluoroquinolone (the other is levofloxacin), which inhibits enzymes that are crucial for bacterial DNA replication. In *M. tuberculosis* it appears that DNA gyrase is the sole topoisomerase targeted. DNA gyrase is a tetrameric A_2B_2 protein (two A subunits and two B subunits). Inhibiting DNA gyrase (in any subunit) results in blockade of DNA replication, inhibiting cell division and resulting in cell death of replicative and nonreplicative *M. tuberculosis*. The particular antimycobacterial activity of the third-generation fluoroquinolones depends on their molecule affinity to target enzymes and efflux pumps, and the naturally low permeability of the *M. tuberculosis* cell wall. **Activity:** Moxifloxacin is considered both highly bactericidal (it has excellent early bactericidal activity) and highly sterilizing. Based on in vitro data, moxifloxacin anti-TB activity is higher than the other current fluoroquinolones. **Half-life and excretion:** The half-life of moxifloxacin is 11.5–15.3 hours. It is mainly metabolized via glucuronide and sulfate conjugation, and 45% is excreted as the unchanged drug in urine and faeces.
Cross-resistance	In general, there is a class effect of cross-resistance among fluoroquinolones in vitro. Data suggest that levofloxacin and moxifloxacin may continue to demonstrate some activity, even against strains that have in vitro resistance to second-generation fluoroquinolones such as ofloxacin. The pattern of resistance or susceptibility to particular fluoroquinolones depends on specific point mutations, which is the subject of ongoing research.
Dose[a]	• **Adults:** 400 mg daily (oral or IV). High dose is 600–800 mg daily, depending on weight band. • **Children:** See the handbook Annex for weight bands. • **Renal failure or dialysis:** No dose adjustment is required. See the handbook Annex for weight-based dosing in children and adults.
Administration	Oral.
Formulation and preparation	100 mg dispersible tablet (poor palatability; taste-masking studies are ongoing). 400 mg film-coated tablet. Crushing and dissolving film-coated tablets (400 mg) in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; also, it avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	Should be stored below 30 °C, protected from light. Dispersible tablets should be stored in a dry place.

Oral absorption	Has good oral absorption (90% bioavailable). It should be administered at least 4 hours before or 8 hours after antacids or other medications (e.g. iron, magnesium, calcium, zinc, vitamins and sucralfate), because they may interfere with absorption.
CSF penetration	In general, fluoroquinolones achieve an effective concentration in the brain and meninges. Moxifloxacin has good penetration in animal model studies and humans with TB meningitis, reaching high concentrations in the CSF in the presence and absence of meningeal inflammation. It has been used successfully in TB meningitis.
Special circumstances	**Use during pregnancy or breastfeeding:** Associated with arthropathy in canine models. there are multiple case reports of fluoroquinolones being used in humans safely during pregnancy and breastfeeding. **Use in renal disease:** Excretion is unchanged during renal failure; there are no data on the effect of dialysis. **Use in hepatic disease:** Moxifloxacin is rarely associated with hepatotoxicity, but should be used with caution. No dose adjustment is required for mild-to-moderate liver disease. **Marfan syndrome, Ehlers–Danlos syndrome or steroids use:** In these situations, there is increased risk of tendon or aorta lesions **Diabetes:** Increased risk of hypoglycaemia. **Long QT syndrome (in the patient or a family member), hypokalaemia, malnutrition, hypothyroidism in patients aged >60 years or taking multiple QT prolonging drugs:** Increased risk of QTc prolongation.
Adverse reactions	**Overall tolerance**: Generally well tolerated, with a low potential for acute toxicity **Common**: Diarrhoea, nausea and bloating, and arthralgia. **Occasional:** QTc interval prolongation (it is considered the most QTc-prolonging of the fluoroquinolones, causing an estimated QTc increase of 10–20 msec). Headache and dizziness. All third-generation fluoroquinolones may cause dysglycaemia. Tendon rupture, especially Achilles tendon. **Uncommon**: Peripheral neuropathy; mood or behaviour changes; insomnia; disturbances in mental abilities; aortic aneurysm rupture and aortic dissection.

Contraindications	Fluoroquinolone intolerance. **Use with caution in situations that may increase QT interval:** Patients aged >60 years, heart failure, long QT syndrome, history of TdP, hypokalaemia, untreated hypothyroidism, low BMI, HIV infection, concomitant use of other QT prolonging drugs. Any syncopal event (e.g. fainting) or palpitations should prompt an immediate medical evaluation and ECG. In several retrospective cohort studies on the incidence of QTc prolongation and cardiac events, the increase was modest and no arrhythmias or related deaths were reported, even with co-administration of bedaquiline and delamanid. **Discontinue or do not use in the presence of:** • clinically significant ventricular arrhythmia; • a QTcF interval of >500 msec (confirmed by repeat ECG); or • abnormal electrolyte levels.
Drug interactions	Low potential for drug–drug interactions (the cytochrome P450 system is not involved in metabolism). Concomitant steroid use may increase the risk of tendon rupture. Multivalent cation-containing products (including antacids and metal cations) may decrease absorption. Warfarin: The effect of moxifloxacin may be enhanced. Prothrombin time and INR should be monitored, as should bleeding. Antidiabetic agents: Blood glucose should be carefully monitored. Concomitant use with antiarrhythmics Class IA (e.g. quinidine, ajmaline and disopyramide) and Class III (e.g. amiodarone, dronedarone and sotalol) should be avoided because the proarrhythmic effect may be enhanced.
Food interactions	Can be taken with or without food; food has little effect on absorption. There are no major interactions with milk or dairy products in third-generation fluoroquinolones. Antacids (especially those containing aluminium), mineral supplements (e.g. iron or magnesium) or multivitamins should be taken more than 2 hours before or after of this medication.
Monitoring	Symptomatic monitoring. Ideally, an ECG should be obtained before initiation of treatment, and at least 2, 12 and 24 weeks after starting treatment. Moxifloxacin should be stopped if QTc >500 msec, and ECGs and potassium should be monitored frequently until the QTc returns to normal. More frequent monitoring is recommended if cardiac conditions, hypothyroidism or electrolyte disturbances are present.

Patient instructions and alerting symptoms	Can be taken with or without food. Antacids (especially those containing aluminium), mineral supplements (e.g. iron or magnesium) or multivitamins should be taken within 2 hours of this medication. **Patients should be instructed to inform their health care provider Immediately if any of the following occur:** • pain, swelling or tearing of a tendon (such as the back of your ankle, elbow), or muscle or joint pain; • severe diarrhoea (watery or bloody); • seizures, epilepsy, change in mood or behaviour; or • low blood sugar symptom (e.g. headache, hunger, sweating, irritability, dizziness, nausea, fast heart rate, or feeling anxious or shaky).

BMI: body mass index; CSF: cerebrospinal fluid; DNA: deoxyribonucleic acid; ECG: electrocardiography; HIV: human immunodeficiency virus; INR: international normalized ratio; IV: intravenous; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis; TdP: torsade de pointes.

[a] See the handbook Annex for revised weight-based dosing.

Para-aminosalicylic acid (PAS)

Para-aminosalicylic acid (PAS) **Drug class: salicylic acid – anti-folate**	
Activity against *M. tuberculosis,* mechanism of action and metabolism	**Target:** *M. tuberculosis* cell wall and inner metabolism. Probably inhibits folic acid synthesis and thus slows cell growth and multiplication. Para-aminosalicylic acid may inhibit the synthesis of mycobactin (a cell wall component) leading to a reduction of iron uptake by *M. tuberculosis* and inhibiting cell wall synthesis. **Activity:** Very low bactericidal (bacteriostatic) activity. It is used as a companion drug to prevent resistance to other medicines. **Half-life and excretion**: the half-life of PAS is 1.5 to 2 hours, within 24 hours, more than 80% is excreted in the urine. More than 50% of the excreted PAS is acetylated.
Cross-resistance	No data available.
Dose[a]	• **Adults:** 8–12 g/day in 2–3 divided doses; upper daily dose is 12 g. Doses are given twice daily; however, if tolerated, the same dose can also be administered at one time. • **Children:** See the handbook Annex for weight bands. • **Renal failure or dialysis:** No dose modifications. See the handbook Annex for weight-based dosing in children and adults.
Administration	Oral. The powder should be reconstituted in water (100 mL) before administration. It should be taken with food to limit gastrointestinal disturbances.
Formulation and preparation	Sodium powder is used for the oral solution: 5.52 g sachet (equivalent to 4 g para-aminosalicylic acid).
Storage	Para-aminosalicylic acid sodium salt may be stored at room temperature.
Oral absorption	Absorption is incomplete, and sometimes requires increased doses to achieve therapeutic concentrations. Absorption is unaffected by food.
CSF penetration	Para-aminosalicylic acid poorly penetrates the meninges, but penetrates better when the meninges are inflamed.
Special circumstances	**Use during pregnancy or breastfeeding:** The safety profile is unknown; however, it is used during pregnancy. There is limited information on its use while breastfeeding (a proportion goes into human milk). **Use in renal disease:** The inactive metabolite is cleared by the kidneys. It should be avoided in severe renal failure. **Use in hepatic disease:** It should be used with caution.

Adverse reactions	**Overall tolerance:** It is poorly tolerated. **Common:** Most patients experience gastrointestinal upset (although this is less with the Paser® formulation than with older preparations); nausea, vomiting, diarrhoea and abdominal pain. **Frequently:** Hypothyroidism in adults is usually subclinical and reversible but the consequences may be important in pregnant woman and children, necessitating TSH monitoring and levothyroxine supplementation. The risk of hypothyroidism increases when it is used with ethionamide and prothionamide. It reduces the absorption of vitamin B12; if significant erythrocyte abnormalities develop, vitamin B12 supplements should be considered. **Uncommon**: Hepatotoxicity and coagulopathy.
Contraindications	Allergy to aminosalicylic acid.
Drug interactions	There is a low potential for drug–drug interactions. Antacids cause fast dissolution of the acid-resistant coating, resulting in early release of para-aminosalicylic acid into the stomach. Ethionamide and prothionamide: If these are co-administered with para-aminosalicylic acid, it may intensify hypothyroidism and gastrointestinal effects (e.g. jaundice, hepatitis or hepatotoxicity, nausea, vomiting, diarrhoea, abdominal pain or anorexia). Rifamycins: Para-aminosalicylic acid reduces the absorption of rifamycins, and these drugs should be given 8–12 hours apart. Diphenylhydramine decreases the gastrointestinal absorption of para-aminosalicylic acid and should not be administered concomitantly.
Food interactions	The absorption is unaffected by food. Taking para-aminosalicylic acid with food may reduce gastrointestinal upset. To improve tolerance, it should be given sprinkled onto or stirred into yogurt or similar food.
Monitoring	Should monitor TSH, electrolytes, blood counts and liver function tests.
Patient instructions and alerting symptoms	It is better tolerated when taken with food. Gastrointestinal discomfort and diarrhoea usually improve over time. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • skin rash, severe itching or hives; • severe abdominal pain, nausea or vomiting; • unusual tiredness or loss of appetite; or • black stools or bleeding.

CSF: cerebrospinal fluid; *M. tuberculosis*: *Mycobacterium tuberculosis*; TSH: thyroid stimulating hormone.

[a] See the handbook Annex for revised weight-based dosing.

Pretomanid (Pa)

Pretomanid (Pa) Drug class: nitro-dihydro-imidazooxazole	
Activity against *M. tuberculosis*, mechanism of action and metabolism	**Target:** *M. tuberculosis* cell wall and inner cell metabolism. Pretomanid is a prodrug that is metabolically activated by the Ddn enzyme or F420 co-enzyme, producing various active metabolites responsible for its anti-TB effects: • A des-nitro derivative is responsible for the induction of nitric oxide, leading to cell poisoning even in anaerobic conditions, and thus killing active and also dormant or latent bacteria. • Other metabolites inhibit mycolic acid biosynthesis, resulting in the inhibition of the bacterial cell wall biosynthesis. This mechanism is not yet fully understood, but data suggest that it involves the *fasI* and *fasII*, *efpA* and *iniBAC cyd* genes. **Activity:** It is bactericidal and has potent in vitro activity to kill actively replicating bacteria. It has excellent sterilizing capacity, as demonstrated in trials studying BPaL/BPaLM regimens. **Half-life and excretion:** It is a prodrug that requires bioactivation. It binds tightly to plasma proteins (86.4%). It has a half-life of 18 hours. Hepatic metabolism is by different routes, and no single major metabolic pathway has been identified. CYP3A4 (cytochrome P450) is responsible for 20% of its metabolism. About 53% is excreted in urine and 38% in faeces.
Cross-resistance	To date, there is limited published information about mutations that may lead to cross-resistance, their frequency, distribution and correlation with clinical relevance.
Dose[a]	• **Adults:** 200 mg once daily with food (upper daily dose is 200 mg). See the handbook Annex for weight-based dosing in the BPaLM/BPaL regimens. **Pretomanid is not recommended by WHO for use in those aged <14 years.**
Administration	Oral (it is better absorbed with food). Tablets should be taken whole; they should not be broken, crushed or chewed.
Formulation and preparation	200 mg tablet.
Storage	Should be stored below 30 °C and in the original package.
Oral absorption	Absorption is increased when it is taken with high-calorie and high-fat food.
CSF penetration	No data.

Special circumstances	**Use during pregnancy or breastfeeding:** There are no studies available on pretomanid use in pregnant women, and no pregnancy category has been assigned. Animal studies (of prenatal and postnatal development) showed changes in the fetus at toxic doses but not at equivalent doses used in humans. Pretomanid passes into breast milk. It is currently not recommended during pregnancy or breastfeeding. **Use in renal disease:** Safety, effectiveness and pharmacokinetics are unknown. **Use in hepatic disease:** Safety, effectiveness and pharmacokinetics are unknown. **Use in cardiac disease:** It is a QTc prolonging drug; hence, it should be used with caution in patients with predisposing factors for QTc interval prolongation. **Use in malnourished patients:** Unknown. **Use beyond 6 months**: Unknown. Use with caution in case of confirmed or suspected resistance to delamanid (potential cross-resistance).
Adverse reactions	**Overall tolerance:** Well tolerated. The most common toxicities reported related to pretomanid were headache (32%), nausea (12%), contact dermatitis (11%), decreased haemoglobin level (11%), diarrhoea (9%) and dizziness (8%). **Adverse events of special interest:** In animal studies, toxic effects attributable to pretomanid were ocular disorders and male reproductive toxicity; however, a recent review of available evidence reported no changes in male hormones in four clinical trials, suggesting no association between pretomanid-containing treatment and testicular toxicity. Current evidence is considered sufficient to address the relative safety of pretomanid (although it is thought unlikely to affect male fertility). Other adverse events include: • convulsions; • ECG QT prolongation: 5 msec average, without significant clinical consequences; • hepatotoxicity (increase in GGT); and • myelosuppression (anaemia). There are several studies ongoing to further evaluate the efficacy and safety of pretomanid alone or in combination with other medicines.
Contraindications	It is currently contraindicated in patients for whom bedaquiline or linezolid is contraindicated.
Drug interactions	There is low potential for drug–drug interactions. No major interactions had been reported but data are limited. If possible, concomitant administration of strong CYP3A inducers should be avoided. In studies, rifampicin decreases the pretomanid AUC by 66%, and nevirapine decreases the pretomanid AUC by 35%. It should be used with caution with other QTc-prolonging medicines.

Food interaction	It should be taken with food; alcohol should be avoided owing to increased risk of hepatotoxicity.
Monitoring	Signs and symptoms of hepatotoxicity should be monitored, and liver function tests monitored at baseline, at 2 weeks and then monthly as needed. The BPaL regimen has been associated with hepatic adverse reactions. ECG and baseline electrolytes should be obtained whenever possible before the initiation of treatment and repeated if needed (e.g. documented QTc prolongation or multiple QTc-prolonging risk factors).
Patient instructions and alerting symptoms	It should be taken with food. The tablet should be swallowed whole and should not be crushed, chewed or broken. Alcohol should be avoided. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • history of heart problems, heart attack, congenital long QT syndrome or problems with heart rhythm; • liver or kidney disease; • HIV; or • pregnancy or planning to get pregnant.

AUC: area under the curve; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; CSF: cerebrospinal fluid; Ddn: deazaflavin-dependent nitroreductase; ECG: electrocardiography; GGT: gamma-glutamyl transferase; HIV: human immunodeficiency virus; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis; WHO: World Health Organization.

[a] See the handbook Annex for revised weight-based dosing.

Pyrazinamide (Z)

Pyrazinamide (Z) **Drug class: synthetic derivative of nicotinamide**	
Activity against *M. tuberculosis,* mechanism of action and metabolism	**Target:** Inner *M. tuberculosis* metabolism with potential multiple mechanisms. Pyrazinamide is a prodrug that, via the pyrazinamidase enzyme, is activated into pyrazinoic acid (active form); it is highly active in acidic conditions in which most drugs become inactive and bacilli enter into nonreplicating, or latent or dormant forms. Pyrazinamide is the prototype for drugs that specifically targets dormant or latent *M. tuberculosis* forms. Under acidic conditions (found inside macrophages and in inflammation and caseum), pyrazinoic acid enters the cell wall and may destroy *M. tuberculosis* by: • accumulating intracellularly, leading to acid bacterial cytoplasm; • accelerating energy consumption: bacilli efflux pumps on the cell wall are constantly pumping pyrazinoic acid out of the cell; • disrupting membrane potential and interfering with energy production of bacilli in acid medium; • potentially inhibiting fatty acid synthesis; and • binding to the ribosomal protein S1 (RpsA) and inhibiting trans-translation. **Activity:** Pyrazinamide has potent sterilizing capacity; it is able to kill dormant or latent bacilli; however, it has weak or no bactericidal activity, because the drug is only active against bacilli in acid media. **Half-life and excretion**: Peak plasma concentrations are attained within 2 hours, and the half-life is 9–10 hours (under normal conditions). About 10% binds to plasma proteins. It undergoes hepatic metabolism and 70% is excreted in the urine (mainly by glomerular filtration within 24 hours).
Cross-resistance	None reported.
Dose[a]	• **Adults:** 20–30 mg/kg/day. Upper daily dose 2000 mg. • **Children:** See the handbook Annex for weight bands. • **Renal failure or dialysis:** 25 mg/kg/dose, thrice weekly (not daily). See the handbook Annex for weight-based dosing in adults and children
Administration	Oral.
Formulation and preparation	150 mg dispersible tablet. 400 mg tablet. 500 mg tablet. Crushing and dissolving uncoated tablets (400 mg and 500 mg) in 10 mL of water may facilitate administration in younger children or those who cannot swallow tablets whole; also, it avoids fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (dispersible tablets are preferred).
Storage	Should not be stored above 25–30 °C. Dispersible tablets should be protected from moisture.

Oral absorption	Well absorbed from the gastrointestinal tract.
CSF penetration	Being a moderately lipophilic small molecule, concentrations in the CSF are equivalent to those in serum in patients with inflamed meninges.
Special circumstances	**Use during pregnancy or breastfeeding:** Has no known teratogenicity. It is distributed into breast milk but is commonly used while breastfeeding. **Use in renal disease:** It is cleared by the kidneys; dosage adjustment may be needed; for example, when changing to thrice weekly dosage and after dialysis. **Use in hepatic disease:** It should be used with caution. Patients with pre-existing liver disease (alcohol abuse, nonalcoholic steatohepatitis, chronic viral hepatitis or TB hepatitis) should be carefully monitored. It is associated with hepatotoxicity in about 1% of patients. Hepatotoxicity can be severe and can worsen treatment outcomes. **Use in patients with gout:** The drug to be avoided if the patient has frequent or ongoing gout. **Use in diabetes mellitus:** It should be used with caution.
Adverse reactions	**Overall tolerance:** Variable. **Common (>10%):** Asymptomatic hyperuricemia is an expected effect and should not be treated or considered pathologic. The drug should be discontinued only if hyperuricemia is accompanied by an acute gout-associated arthritis. Arthralgia (pain in large and small joints) and gastrointestinal effects (nausea, vomiting and anorexia). **Frequently (5–10%):** Arthralgia (pain in large and small joints that are not inflamed) and gastrointestinal effects (nausea, vomiting and anorexia). **Occasional (>1%):** Hepatotoxicity can occur at any time and appears to be dose related. Transient increase in ALT/AST (<4 times the ULN) is the most frequent presentation. However, severe liver injuries, including some fatalities, have been reported. The drug should be discontinued in symptomatic or asymptomatic patients with an ALT concentration >4–5 times the ULN, and in patients who have serum bilirubin concentrations above the ULN. Gout is described as sudden, severe attacks of pain, swelling, redness and tenderness in one or more joints, most often in the big toe, with or without hyperuricaemia. It may cause photosensitivity and dermatitis. **Rare (<1%):** Sideroblastic anaemia, hypersensitivity reactions and effects on blood clotting.
Contraindications	Hypersensitivity to pyrazinamide. Severe hepatic damage. Acute gout or frequent flares.
Drug interactions	There is low potential for drug–drug interactions. If used with other hepatotoxic drugs, the effects can accumulate.
Food interactions	The absorption is unaffected by food.

Monitoring	Liver function (AST, ALT, and bilirubin) should be monitored at baseline and monthly if possible. Patients should be closely monitored if they are at risk for drug-related hepatitis (e.g. alcohol abuse, nonalcoholic steatohepatitis or chronic viral hepatitis) and if signs or symptoms of hepatotoxicity occur.
Patient instructions and alerting symptoms	May be taken with or without food. Pyrazinamide may cause a rash after sun exposure (so sun exposure should be limited). It should not be used if there is active gout with frequent flares or if the patient presents with severe liver disease (e.g. alcohol abuse, nonalcoholic steatohepatitis or chronic viral liver infections). **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • skin rash, severe itching or hives; • pain or swelling in the joints; • yellowing of the skin or eyes or dark urine; or • unusual tiredness or loss of appetite.

ALT: alanine transaminase; AST: aspartate transaminase; CSF: cerebrospinal fluid; *M. tuberculosis*: *Mycobacterium tuberculosis*; TB: tuberculosis; ULN: upper limit of normal.

[a] See the handbook Annex for revised weight-based dosing.

Streptomycin (Sm)

Streptomycin (Sm) **Drug class: aminoglycosides**	
Activity against *M. tuberculosis,* mechanism of action and metabolism	**Target:** *M. tuberculosis* inner metabolism. Streptomycin binds to the bacterial ribosome small subunit (30 S or 16 S rRNA), leading to mistranslation of proteins and also disruption of the cytoplasmic membrane. **Activity:** It has important bactericidal activity (medium–high early bactericidal activity) and the potential for sterilizing activity. **Excretion and half-life:** Reaches peak serum concentration within 1 hour after IM administration, and 50% is eliminated in the urine within 24 hours after IV or IM administration.
Cross-resistance	Mutations at the *eis* gene may confer resistance to amikacin but not to streptomycin.
Dose[a]	**Streptomycin is recommended by WHO** only in adults aged >18 years. • **Adults:** 12–18 mg/kg/day in a single daily dose, upper daily dose is 1 g**.** • **Renal failure or dialysis:** 12–15 mg/kg/dose, twice or thrice weekly (not daily). It should be used with caution. See the handbook Annex for weight-based dosing. • **Markedly obese individuals (e.g. BMI >35):** The dose should be adjusted because of decreased distribution of extracellular fluids in adipose tissues. Dosing based on actual weight will give supratherapeutic concentrations. For dosing in obese adults who conform to weight bands corresponding to the following adjusted weights: – ideal body weight (men): 50 kg plus 0.9 kg/cm >1.52 m; and – ideal body weight (women): 45 kg plus 0.9 kg/cm >1.52 m. Serum concentrations should be monitored closely, if possible.
Administration	It is not absorbed orally. Aminoglycosides (amkacin and streptomycin) are administered parenterally as an IM injection, and in some cases may be administered IV. IM absorption may be delayed if the same site is used consistently. Intrathecal and intraperitoneal administration have been tried in the past.
Formulation and preparation	The powder for injection (1 g, vial) requires reconstitution with water for injection (at 200 mg/mL, 250 mg/mL or 400 mg/mL) before administration. For IV use, the concentration may be decreased.
Storage	The powder for injection should be stored below 30 °C. The reconstituted solution may be stored at room temperature for 1 week, protected from light.
Oral absorption	There is no significant oral absorption.
CSF penetration	Penetration is better in inflamed meninges.

Special circumstances	**Use during pregnancy or breastfeeding:** The drug should be avoided during pregnancy owing to documented cases of congenital deafness. It is excreted into human milk, and is considered compatible with breastfeeding but should be used with caution (the infant should be monitored for thrush and diarrhoea). **Use in renal disease:** It should be used with extreme caution. Concentrations should be monitored in patients with impaired renal function, if possible. Interval adjustment is recommended for renal impairment or dialysis (see under Dose section above for dosage under renal disease or dialysis). Clearance by haemodialysis is variable. **Use in hepatic disease:** Drug concentrations are not affected by hepatic disease (except for a larger volume of distribution for patients with ascites due to cirrhosis). It is presumed to be safe in liver disease; however, it should be used with caution because patients with severe liver disease may progress rapidly to hepato-renal syndrome. **Diuretic use:** Co-administration of loop diuretics and aminoglycoside antibiotics increases the risk of ototoxicity. **Older people:** There is increased risk of ototoxicity and nephrotoxicity due to potential baseline damage in both organs. **Children:** It should be used with extreme caution. There is a risk of ototoxicity with important consequences (e.g. effects on verbal communication, cognitive and emotional development linked to school performance and future disability).
Adverse reactions	**Overall tolerance:** Generally, it is poorly tolerated, due to local pain from IM injections or lengthy infusions. **Common:** IM injection pain, permanent hearing loss (10–12%) and vestibular toxicity including nausea, vomiting and vertigo. **Frequently:** Electrolyte abnormalities, including hypokalaemia, hypocalcaemia and hypomagnesaemia. Watery or bloody diarrhoea may occur months after the last dose; vaginal itching or discharge; and eosinophilia. **Occasional:** Nephrotoxicity (typically transient), paraesthesia of face and neuropathy, weakness and neuromuscular blockage.
Contraindications	Hypersensitivity to aminoglycosides. Pregnancy: Congenital deafness can occur with streptomycin and kanamycin use during pregnancy. Children: Owing to the important consequences of ototoxicity. Older people or adults with renal, vestibular or auditory impairment.
Drug interactions	There is low potential for drug–drug interactions. It should be used with caution with other drugs that might be nephrotoxic or may change the electrolyte balance (e.g. loop diuretics) or in clinical conditions such as dehydration. The ototoxic effects of aminoglycosides, including streptomycin, are potentiated by the co-administration of ethacrynic acid, furosemide, mannitol and other diuretics.
Food interactions	No alcohol or food interactions.

Monitoring	Patients should be carefully monitored for early signs of hearing loss and vestibular dysfunction, to prevent permanent damage to sensorineural cells. Baseline and monthly audiology exams should be documented. Renal function should be monitored by documenting creatinine at least monthly (and more frequently if there is renal or hepatic impairment). Serum concentrations should be monitored serially for patients with impaired renal function, if possible.
Patient instructions and alerting symptoms	The patient should be informed of the potential harm to the fetus, so should be advised on contraception methods and a pregnancy test should be administered before drug initiation. **Patients should be instructed to inform their health care provider immediately if any of the following occur:** • problems with hearing, dizziness or balance; • decreased urination; • watery or bloody diarrhoea; • swelling, pain or redness at IV site; or • muscle twitching or weakness.

BMI: body mass index; CSF: cerebrospinal fluid; IM: intramuscular; IV: intravenous; *M. tuberculosis*: *Mycobacterium tuberculosis*; WHO: World Health Organization.

[a] See the handbook Annex for revised weight-based dosing.

References for Web Annex 1

1 Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (WHO/HTM/TB/2014.11). Geneva: World Health Organization; 2014 (https://apps.who.int/iris/handle/10665/130918).

2 Curry International Tuberculosis Center, California Department of Public Health. Drug-resistant tuberculosis: a survival guide for clinicians. California: University of California San Francisco; 2016 (https://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition).

3 Nau R, Sorgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clin Microbiol Rev. 2010;23:858–83. doi: https://doi.org/10.1128/CMR.00007–10.

Web Annex 2. Management of adverse events in MDR/RR-TB treatment

A2.1 Introduction

Early identification, ongoing monitoring and proper management of adverse events (AEs) associated with anti-tuberculosis (TB) medications is crucial in relieving suffering and improving the quality of care of patients undergoing treatment for multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB). Awareness and optimal management of AEs are essential parts of a holistic approach to supporting patients to adhere to various treatment regimens. Such an approach requires comprehensive education and training for health care workers, and provision of appropriate information and counselling for patients and their treatment supporters. From the early stages of MDR/RR-TB treatment, patients and their care providers must be aware of the potential AEs associated with anti-TB drugs; how to prevent, manage or cope with common but non-serious AEs; how to recognize serious or severe signs and symptoms; and when and where to seek medical assistance or psychosocial support. Health care workers must be prepared to anticipate, prevent, monitor and manage common AEs, particularly those that may affect patients' adherence to treatment; rapidly identify serious AEs (SAEs) or potential SAEs and respond appropriately; record details of all AEs associated with MDR/RR-TB treatment; and know when to notify the responsible authorities.

National TB programmes (NTPs) should have established systems for active TB drug-safety monitoring and management (aDSM). Such systems involve the active and systematic clinical and laboratory assessment of patients being treated with new TB medicines or novel MDR/RR-TB regimens, to detect, manage and report suspected or confirmed drug toxicities *(1)*. The details of the aDSM framework are described in Web Annex 3. Countries where aDSM has been implemented are encouraged to contribute their national data to this database, to improve the collective knowledge of the safety of new TB medicines and regimens and to inform future TB treatment policies.

A2.2 AEs associated with MDR/RR-TB drugs and regimens

Several systematic reviews have summarized AEs associated with MDR/RR-TB treatment over the past decade; however, most of the reviews could not assign causal relationships between specific anti-TB drugs and the reported AEs. Furthermore, most meta-analyses were conducted at a time when injectables were commonly used within MDR/RR-TB treatment regimens. Other systematic reviews have focused on specific drugs and the AEs commonly associated with their use, but patients with MDR/RR-TB are usually treated with multidrug regimens; hence, attribution of causality can be difficult. In 2020, the Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB Treatment used the individual patient data (IPD) MDR database (created for the meta-analysis of MDR-TB treatment and outcomes that was published in 2018) to obtain individual patient-level data

on AEs leading to permanent discontinuation of anti-TB drugs from studies published between 2009 and 2016 *(2)*. The group also obtained patient-level data shared with the World Health Organization (WHO) following a public call in 2018; thus, the combined data from over 8000 patients with MDR/RR-TB in 28 countries were used to conduct an IPD meta-analysis to estimate the frequency of AEs leading to permanent discontinuation associated with 20 different anti-TB drugs. Of note, the analysis did not include high-dose isoniazid, rifabutin, gatifloxacin or delamanid because too few patients received these drugs across the included studies. Almost one quarter of patients had at least one drug permanently stopped because of an AE, and stopping of one or more drugs was significantly more likely among females, older people and those receiving treatment in high-income countries. Fluoroquinolones, clofazimine and bedaquiline had the lowest incidence of AEs leading to permanent drug discontinuation, whereas second-line injectable drugs, aminosalicylic acid and linezolid had the highest incidence *(2)*. Table A2.1 outlines the types of AEs associated with each of the 20 drugs from this analysis.

Table A2.1. Types of AEs resulting in permanent discontinuation of anti-TB drugs

	AEs[a]/ patients using the drug	Pooled incidence of AEs, random effect[b] (95% CI)	AEs type reported[c]	Type 1[d]	Type 2	Type 3	Type 4	Type 5
Levofloxacin	22/1012	1.3% (0.3–5.0)	14	Musculoskeletal (9, 64%)	Peripheral neuropathy (2, 14%)	Rash (2, 14%)	Hypoglycaemia (1, 7%)	–
Clofazimine	12/1712	1.6% (0.5–5.3)	12	Cardiovascular (4, 33%)	Hyperpigmentation (5, 42%)	Rash (2, 17%)	Gastrointestinal (1, 8%)	–
Bedaquiline	9/464	1.7% (0.7–4.2)	9	Cardiovascular (5, 56%)	Hepatotoxicity (2, 22%)	CNS toxicity (1, 11%)	Musculoskeletal (1, 11%)	–
Ethambutol	124/6089	1.8% (1.0–3.3)	59	Visual impairment (41, 70%)	Gastrointestinal (10, 17%)	Musculoskeletal (2, 3%)	Rash (2, 3%)	Hepatotoxicity (1, 2%)
Streptomycin	34/1208	2.9% (1.3–6.2)	6	Ototoxicity (5, 83%)	Peripheral neuropathy (1, 17%)	–	–	–
Moxifloxacin	30/904	2.9% (1.6–5.0)	24	Cardiovascular (5, 21%)	Hepatotoxicity (4, 17%)	Gastrointestinal (3, 13%)	Peripheral neuropathy (3, 13%)	Musculoskeletal (2, 8%)
Amoxicillin-clavulanate	21/695	2.9% (1.7–4.8)	9	Gastrointestinal (6, 67%)	Rash (1, 11%)	Musculoskeletal (1, 11%)	Peripheral neuropathy (1, 11%)	–
Clarithromycin	18/457	3.3% (1.5–7.0)	7	Gastrointestinal (4, 57%)	Hepatotoxicity (1, 14%)	Peripheral neuropathy (1, 14%)	Fatigue (1, 14%)	–
Imipenem and meropenem	9/158	4.9% (1.0–20.5)	6	Hepatotoxicity (3, 50%)	Rash (1, 17%)	Fatigue (1, 17%)	Pneumonia (1, 7%)	–

	AEs[a]/ patients using the drug	Pooled incidence of AEs, random effect[b] (95% CI)	AEs type reported[c]	Type 1[d]	Type 2	Type 3	Type 4	Type 5
Pyrazinamide	410/5141	5.1% (3.1–8.4)	142	Musculoskeletal (47, 33%)	Gastrointestinal (33, 23%)	Hepatotoxicity (29, 20%)	Rash (18, 13%)	Hyperuricaemia (8, 6%)
Cycloserine and terizidone	337/7547	5.7% (4.1–7.8)	140	Psychiatric (92, 66%)	CNS toxicity (35, 25%)	Gastrointestinal (5, 4%)	Peripheral neuropathy (2, 1%)	Rash (1, 1%)
Ethionamide, protionamide	376/4627	6.5% (4.1–10.1)	108	Gastrointestinal (52, 48%)	Hepatotoxicity (24, 22%)	Psychiatric (6, 6%)	Gynaecomastia (5, 5%)	Musculoskeletal (5, 5%)
Amikacin	235/4106	10.2% (6.3–16.0)	211	Ototoxicity (183, 87%)	Nephrotoxicity (22, 10%)	Gastrointestinal (2, 1%)	Intolerance (2, 1%)	Musculoskeletal (1, 1%)
Aminosalicylic	532/2929	11.6% (7.1–18.3)	120	Gastrointestinal (95, 79%)	Hypothyroidism (6, 5%)	Hepatotoxicity 5, 4%)	Rash (5, 4%)	Nephrotoxicity (4, 3%)

AE: adverse event; CI: confidence interval; CNS: central nervous system; TB: tuberculosis.

[a] AEs were defined as those that resulted in permanent discontinuation of a drug.

[b] Pooled incidence of AEs was estimated through meta-analysis of proportions.

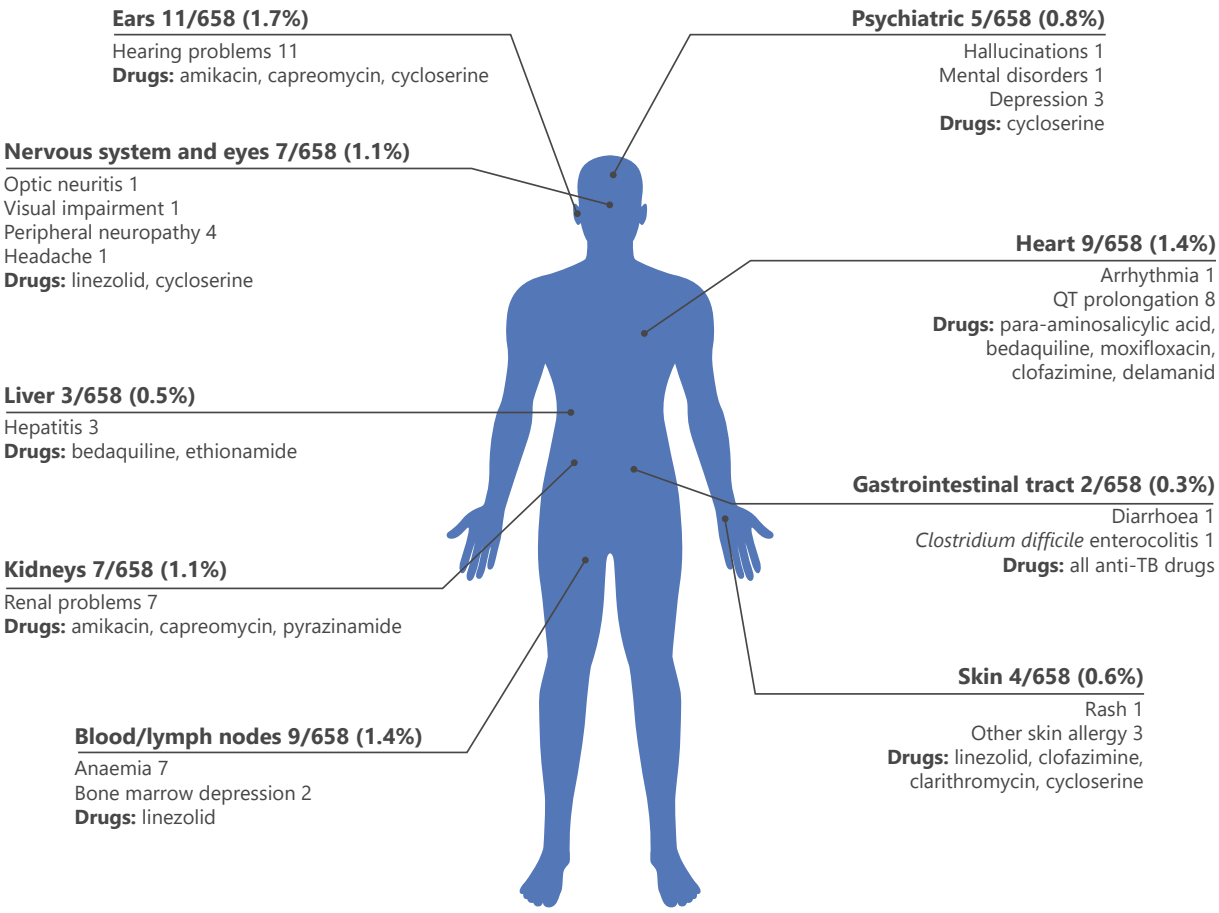
[c] This analysis included only studies that reported AE types.

[d] For each drug, simple pooling was done to calculate the number of each type of AE; the five most common AE types with the corresponding proportions were presented.

Source: Lan et al. (2020) (2).

In addition to the IPD-MDR analysis, the first global report from the WHO aDSM project presented an interim analysis of safety data reported between July 2017 and August 2019 for 658 patients receiving regimens based on bedaquiline or delamanid (or both) for treatment of MDR/RR-TB at participating centres across 26 countries *(3)*. Because the data were prospectively collected, it was possible to assign causal attribution of AEs to specific drugs through external assessment of reported events, discussion with reporting clinicians and consideration of the scientific evidence available for each drug during the study period. The drugs most commonly used in treatment regimens for this cohort, in addition to bedaquiline or delamanid, were linezolid, moxifloxacin, levofloxacin, clofazimine, capreomycin, amikacin and carbapenems. Fig. A2.1 illustrates the distribution of reported SAEs by organ or system.

Fig. A2.1. Summary of the distribution of 57 SAEs, by organ or system, among 658 patients treated for MDR/RR-TB across 26 countries between 2017 and 2019



MDR/RR-TB: multidrug-resistant or rifampicin-resistant TB; SAE: serious adverse event; TB: tuberculosis.

Source: Borisov et al. (2019) (3).

Longer treatment regimens for MDR/RR-TB often contain multiple drugs with overlapping toxicities; hence, the frequency of AEs will depend on the combination of drugs in the regimen. The drug information sheets in Web Annex 1 outline clinically significant AEs associated with each of the WHO-recommended anti-TB drugs. For the shorter regimens, the frequency of specific AEs may be more predictable because these regimens are standardized. Among 109 participants enrolled on the Nix-TB trial (and who received the bedaquiline, pretomanid and linezolid [BPaL] regimen), 57% experienced SAEs. More than 80% of all participants experienced peripheral neuropathy, reported as mostly mild or moderate symptoms, and 37% had anaemia *(4)*. Twelve (11%) participants had moderate to severe transaminitis; no participants had QT interval prolongation beyond 480 ms. The most common AEs associated with the 9-month all-oral regimen were anaemia (among patients receiving the linezolid-containing regimen), hepatotoxicity, QT prolongation, nausea and vomiting *(5)*.

Children generally experience fewer AEs from second-line TB treatment than adults, and most of the AEs are mild or moderate; however, treatment-related AEs appear to be more common among children who are HIV-positive *(6)*. Furthermore, monitoring and timely detection of AEs (e.g. repeated blood draws, clinical assessment of vision and neuropathies, and identification of emergent neuropsychiatric events) can be more challenging in children than in adults.

Data on AEs among people who are pregnant or breastfeeding and receiving shorter standardized treatment regimens for MDR/RR-TB are currently extremely limited. Pregnant and breastfeeding patients should continue to be monitored for the same AEs at least as frequently as non-pregnant patients receiving the same treatment *(7)*.

A2.3 Monitoring AEs associated with MDR/RR-TB treatment

Treatment monitoring schedules must include relevant clinical and laboratory parameters to detect, manage and prevent common and significant AEs in a timely manner. Many AEs are easy to recognize (e.g. skin hyperpigmentation due to clofazimine) and most adults, adolescents and older children can describe most of the symptoms they experience. However, some patients or caregivers may be reticent about reporting symptoms, or might only remember when asked about specific problems; thus, it is important to have a systematic approach when screening for potential AEs. Safety monitoring requirements will vary depending on the chosen treatment regimen, because some parameters apply to specific drugs (e.g. full blood counts during exposure to linezolid) whereas others (e.g. liver function tests) measure AEs associated with a wider variety of anti-TB drugs. The frequency of evaluation of specific safety monitoring parameters for various treatment regimens is outlined in the relevant chapters of the operational handbook.

Further information on key monitoring parameters is given below.

Haematological assessment

Because of the risk of myelosuppression associated with even relatively short exposures to linezolid, pre-treatment assessment of haemoglobin, neutrophils and platelets is crucial in patients considering treatment with a linezolid-containing regimen. Severe anaemia in patients with TB is a significant risk factor for poor treatment outcomes *(8)* and patients with a low baseline haemoglobin may be at higher risk of severe linezolid-induced haematological toxicity *(9)*. Linezolid should not be administered to patients with a pre-treatment serum haemoglobin below 8 g/dL that cannot be rapidly corrected (i.e. with a blood transfusion) before starting MDR/RR-TB treatment. Similarly, owing to the morbidity associated with severe neutropenia and thrombocytopenia, treatment with linezolid is not suitable in patients with neutrophil levels below 0.75×10^9/L or platelets below 150×10^9/L before starting treatment. Owing to the high risk of anaemia posed by linezolid, even among people with normal blood counts before starting treatment, haemoglobin must be checked fortnightly at least for the first month and then monthly for the duration of linezolid exposure. Complete blood counts should be performed if clinically indicated (i.e. signs and symptoms of myelosuppression, particularly if neutrophils or platelets were relatively low at the start of treatment).

Liver function tests

Drug-induced liver injury can result from pyrazinamide, pretomanid, high-dose isoniazid or bedaquiline, and less commonly from other second-line drugs. Chronic liver disease, secondary to alcoholic liver disease and infection with hepatitis B and C viruses, increases the risk of drug-induced liver injury among patients receiving MDR/RR-TB treatment *(10)*. It is advisable to screen for viral hepatitis B and C in patients who are due to receive regimens with multiple hepatotoxic drugs (e.g. bedaquiline, pretomanid, linezolid and moxifloxacin [BPaLM]/BPaL) because these patients may require

regular liver function monitoring through treatment. All patients starting MDR/RR-TB treatment must have serum liver enzymes (at least alanine transaminase [ALT]) checked at baseline, and liver enzyme tests should be repeated in all patients who experience signs and symptoms of hepatotoxicity through treatment. It is recommended to check serum liver enzymes once a month among people living with HIV who are receiving pyrazinamide.

QT interval monitoring

Many drugs, including multiple anti-TB medications, are known to prolong the QT interval as recorded on an electrocardiogram (ECG).[1] Severe QT prolongation may lead to a specific type of polymorphic ventricular tachycardia called torsade de pointes (TdP), which can result in sudden death. The absolute QT interval is measured from the onset of the Q-wave to the termination of the T-wave. Limb lead II or precordial lead V5 are best for measuring the QT interval; alternative leads may be used if T-wave termination is poorly visualized. The normal QT interval changes physiologically (e.g. depending on time of day, level of activity and emotional state) and several formulae may be used to correct the absolute QT interval for an individual's heart rate. The Fridericia correction (QTcF) measures the QT interval in milliseconds divided by the cubed root of the RR-interval in seconds; the Bazett correction (QTcB) measures the QT interval divided by the square root of the RR-interval. The "corrected QT interval" can be calculated manually with the aid of a calculator or through various online calculators or applications (apps). Automatic readings from the ECG machine are not as accurate as manual reading; therefore, manual measurement and calculation of QTc is advised if there is any concern about potential QT prolongation. In practice, both QTcB and QTcF yield similar results when the heart rate range is within 55 to 85 beats per minute, but QTcB tends to overestimate QTc at higher heart rates. Although QTcF is often the preferred QT interval correction method, clinicians are advised to at least use a consistent correction algorithm when serially following patients for QT prolongation. A corrected QT interval between 450 and 470 msec is considered borderline and QTcF of more than 480 ms warrants closer ECG monitoring in any individual. Other factors that may trigger closer ECG monitoring are symptoms of palpitations, dizziness, chest pain and syncope, and a QT interval increase of more than 60 msec from the pretreatment baseline; however, these are not in themselves reliable indictors of increased risk of TdP. A corrected QT interval of more than 500 ms is considered dangerous and increases the risk for TdP with possible arrhythmic death; this level of QT prolongation typically occurs when multiple QT-prolonging drugs are used, particularly in individuals with additional risk factors such as cardiac disease, hypokalaemia, hypomagnesaemia or hypocalcaemia.

Psychosocial assessment

Several TB medications (e.g. terizidone and delamanid) are known to have neuropsychiatric AEs (NPAEs), whereas other TB medications (e.g. clofazimine) have side-effects that may be socially unacceptable or stigmatizing in some settings. Furthermore, some patients may experience psychosis or depression during MDR/RR-TB treatment that is not directly related to specific drug AEs but may be due to underlying psychiatric disorders or other psychosocial stressors and catastrophic costs associated with the diagnosis and treatment of MDR/RR-TB. The psychosocial aspects of MDR/RR-TB must not be ignored and may have a considerable impact on patients' mental health and adherence to treatment.

Renal assessment

It is important to assess kidney function at baseline to determine whether a patient requires renal dosing of selected anti-TB drugs (i.e. levofloxacin, terizidone, pyrazinamide, ethambutol, carbapenems and para-aminosalicylic acid). Patients with a history of renal disease (including comorbidities such as HIV and diabetes), advanced age or any renal symptoms (or those with a low baseline glomerular filtration rate) should be monitored closely and regularly during treatment. If baseline renal function is

[1] The website https://crediblemeds.org/ lists drugs that have a QT-prolonging effect.

normal, then re-assessment of renal function during MDR/RR-TB treatment is only required if clinically indicated or if the patient starts taking nephrotoxic drugs.

Thyroid function assessment

Para-aminosalicylic acid or ethionamide/prothionamide (or both) can cause hypothyroidism, which may be suspected during clinical assessment and should be confirmed by testing levels of serum thyroid stimulating hormone (TSH). Goitres can develop due to the toxic drug effects, but symptoms can often be subtle and may be masked by TB symptoms or other AEs; hence, it is recommended that patients be screened for hypothyroidism (serum TSH levels) every 3 months, or sooner if symptoms arise, for the duration of exposure to either of these drugs. Dosing of thyroid replacement therapy should be guided by serum TSH levels every month until a stable dose of the thyroid replacement hormone is reached, and 3-monthly monitoring may resume. In areas where iodine deficiency goitres are endemic, treatment with iodine is indicated, in addition to assessment and treatment for hypothyroidism.

A2.4 Management of AEs

Most patients receiving MDR/RR-TB treatment experience at least one or more AEs associated with the TB medications. Therefore, ongoing education of patients and their caregivers or family members is crucial, to empower patients to anticipate and prepare for common AEs, and to be aware of signs and symptoms that may be serious and require urgent medical attention. Too much information at the start of treatment, especially just after receiving the diagnosis of MDR/RR-TB (a potentially life-threatening disease that the patient may not have heard of) can be overwhelming; therefore, information should be shared with as much detail and as often as the patient can cope with, in ways that the patient can understand. Some people may request information leaflets to read in their own time or referral to relevant websites and other sources of accurate information; others may prefer to receive the information through individual counselling sessions or patient support groups, where they can also learn helpful coping strategies.

Acknowledgement of patients' experiences and reassurance by the health care provider is sometimes all that the patient needs to cope with the AEs associated with treatment, particularly if they understand the importance of completing a full course of effective treatment. Patients who feel negated, belittled or unheard may decide to stop taking their TB medications, particularly if the AEs outweigh the perceived benefit of their treatment (e.g. as they start feeling better and TB symptoms resolve). Some AEs may disappear or diminish over time, even without intervention, and patients may be able to continue the drug if they are sufficiently motivated to tolerate the non-serious AEs. Some AEs (e.g. skin hyperpigmentation) may be absolutely unacceptable to some patients, despite health care providers not considering the AE to be clinically serious enough to withhold the offending agent from an otherwise effective treatment regimen. Additional medications to treat AEs can add to the patients' already heavy pill burden, and these ancillary medications come with their own side-effects. Clinicians must take patients' preferences into account and, wherever possible, should involve patients or their caregivers in decisions about whether to treat AEs with additional medications and when to withdraw TB medications in response to AEs, particularly if this might compromise the efficacy of their treatment regimen.

Table A2.2 summarizes the common AEs associated with MDR/RR-TB treatment, the likely responsible TB medications, suggested management strategies and other potentially useful information.

In general, clinicians should avoid lowering doses of TB medications to reduce the incidence or severity of AEs; however, it may be possible to split doses or change the frequency of some drugs. It is sometimes helpful to change the timing of the administration of certain drugs, to help patients cope with certain AEs, especially in relation to food intake and sleeping. Weight-banded dosing guidelines may allow for some medications (e.g. terizidone/cycloserine, ethionamide/prothionamide,

pyrazinamide and ethambutol) to be administered at the lower end of the recommended dose range for a specific weight band. Pharmacokinetic studies of TB medications are helpful in determining an acceptable dosing range and frequency that balances safety and tolerability without compromising efficacy.

Overlapping toxicities with TB medications and antiretroviral drugs must be considered in patients who are coinfected with HIV; for example, zidovudine should be avoided in patients receiving linezolid because of the increased risk of myelosuppression.

Table A2.2. AEs, suspected agents and management strategies

AE	Suspected agent	Suggested management strategies	Comments
Allergic reaction, anaphylaxis and rashes	Any drug	1. For severe rashes (i.e. peeling skin, mucous membrane involvement and the patient being systemically unwell) and serious allergic reactions, stop all therapy pending resolution of reaction. Manage anaphylaxis as per standard emergency protocols. 2. Eliminate other potential causes of allergic skin reactions (e.g. scabies and other environmental agents). 3. For non-severe skin reactions, continue TB medications and manage symptoms with relevant ancillary agents: • antihistamines and calamine lotion; • hydrocortisone cream (localized rash); • oral prednisone (low dose, short course); • sunscreen (to prevent phototoxicity); • moisturizing lotion for dry skin (common with clofazimine, and in diabetic patients); and • topical benzoyl peroxide for acneiform rashes. 4. Following resolution of severe adverse cutaneous drug reactions, reintroduce drugs one at a time, with the drug most likely to cause the reaction being given last; consider avoiding or substituting drugs that are highly likely to have caused a severe reaction, and do not reintroduce non-essential TB medications – this may necessitate a change in regimen if a standardized regimen has been used. 5. Permanently withdraw any drug confirmed to be the cause of a serious drug reaction, and counsel the patient on avoidance of the drug in future.	1. History of previous drug allergies should be carefully reviewed and noted on the treatment card. 2. A flushing reaction to Z is usually mild and resolves with time; it can be managed with antihistamines. 3. Hot flushes, itching and palpitations can be caused by isoniazid and tyramine-containing foods (e.g. cheese and red wine) – counsel the patient on avoidance of these foods. 4. Although rarely reported, patients (particularly adolescents) receiving MDR/RR-TB treatment regimens containing novel and repurposed agents sometimes experience a non-serious acneiform papular rash. Topical benzoyl peroxide may be helpful, but this rash eventually resolves without intervention. 5. Any drugs can cause urticaria (hives). Reintroduce each drug one at a time to identify the causative agent. Desensitization can be attempted if necessary. 6. Some antihistamines (e.g. diphenhydramine) are associated with QT prolongation; this risk must be balanced with the benefits for the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required, in that setting. 7. Do not consider rechallenging any drugs that resulted in anaphylaxis or Stevens-Johnson syndrome.

AE	Suspected agent	Suggested management strategies	Comments
Alopecia	H, Eto/Pto	1. Reassure the patient that hair loss related to TB medications usually resolves following completion of treatment. 2. It may be helpful to educate the patient on other causes of hair loss because these could also be investigated and addressed.	1. Alopecia occurs more commonly after prolonged exposure (>18 months) to TB medications. 2. Other possible causes of hair loss include childbirth, stressful life events, use of abrasive hair products, polycystic ovary syndrome, psoriasis, thyroid disease, mineral deficiencies, hereditary hair loss and ageing.
Arthritis and arthralgia	Z, Bdq, Lfx Mfx, H	1. Initiate therapy with NSAID (indomethacin or ibuprofen) for symptomatic relief. 2. Rule out other causes of arthralgia (e.g. trauma or injury). 3. If possible, decrease the dose of the suspected agent (probably Z) to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. 4. In severe cases with no improvement of symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required – this may necessitate a change in regimen if a standardized regimen is used.	1. Symptoms of drug-induced arthralgia often diminish over time, even without intervention. 2. If a joint is acutely swollen, red and warm, consider aspiration for diagnosis of gout, infection, autoimmune diseases and other causes. 3. Uric acid levels may be elevated in patients on Z. There is little evidence to support the addition of allopurinol, although it may be helpful if gout is confirmed.
Candidiasis	Lfx, Mfx Mpm, Imp/cln, Lzd	1. Common types of yeast infection are usually easily treated with topical antifungal agents or a short course of oral systemic medications. 2. Presentation among immunosuppressed individuals can be severe and may require treatment with more potent agents. Patients presenting with severe symptoms should be retested for HIV.	1. The most common types of yeast infection associated with antibacterial treatment include vulvovaginal and penile candidiasis, oral thrush and cutaneous candidiasis. 2. Other common risk factors include pregnancy and uncontrolled diabetes.

AE	Suspected agent	Suggested management strategies	Comments
CNS toxicity (dizziness, insomnia and headaches)	Lfx, Mfx, Dlm, Am, Trd/Cs, Mpm Bdq, Eto/Pto, H, Pa	1. Consider other causes of CNS symptoms (e.g. arrhythmias, H-2 receptor antagonists, local anaesthetics, cancer, recreational substance use, stress, hyperventilation) and manage appropriately. 2. Rule out more serious causes of headaches, including raised intracranial pressure, pre-eclampsia, meningitis and other CNS infections – investigate thoroughly in patients coinfected with HIV. 3. Manage drug-related headaches with analgesic agents (ibuprofen, paracetamol) and encourage good hydration. Consider low-dose TCAs for refractory headaches. 4. Administer medications at a different time of day (e.g. before sleeping or early morning) to reduce the impact of specific CNS symptoms on daily activities. 5. For other CNS symptoms, consider decreasing the dose of the suspected agent to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. Also consider starting the drug at a low dose and gradually building up to the full dose over 2 weeks. 6. In severe cases with no improvement of symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required – this may necessitate a change in regimen if a standardized regimen is used.	1. Symptoms of QT prolongation can include dizziness and syncope; closer ECG monitoring may be indicated. 2. Drug-related headaches and dizziness are often self-limiting and ease over time. 3. Pyridoxine (vitamin B6) can help to prevent neurotoxicity during exposure to Trd/Cs and H. 4. High doses of TCAs are associated with QT prolongation; this risk must be balanced with the benefits for the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required, in that setting. 5. Fullness in the ears and intermittent ringing are early symptoms of vestibular toxicity and symptoms generally do not improve on withholding medications; in such cases, patients must be counselled to report these symptoms early and the injectable agent should be withdrawn. 6. Dlm has been associated with insomnia and sleep disturbance due to nightmares – this may become intolerable and require drug withdrawal, particularly in children.

AE	Suspected agent	Suggested management strategies	Comments
Depression, suicidal ideation	Trd/Cs, Dlm Lfx, Mfx	1. Acknowledge and assess psychological and socioeconomic circumstances, emotional issues and level of control of other chronic conditions. Refer to available services for counselling and social support. 2. Screen for substance use and other mental illness using validated screening tools and refer to relevant services for intervention and support. 3. In cases where depressive symptoms are impacting adherence to treatment and other activities of daily living, antidepressant therapy may be indicated. SSRIs and TCAs may be considered but drug–drug interactions are common. 4. If possible, decrease the dose of the suspected agent (e.g. Cs) to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. 5. In severe cases with no improvement of symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required – this may necessitate a change in regimen if a standardized regimen is used. 6. Always screen for symptoms and signs of suicidal ideation in patients with depressive symptoms – if indicated, withdraw all suspected agents and hospitalize the patient with 24-hour surveillance until stable.	1. Although depressive symptoms may be expected upon diagnosis of MDR/RR-TB, and some TB medications may be associated with psychiatric AEs, do not underestimate the contribution of underlying psychological, emotional and socioeconomic conditions and chronic illness as contributing factors to depression. Some patients may require medical intervention for depression even beyond completion of treatment for MDR/RR-TB and they should be referred or followed up appropriately. 2. History of previous depressive illness is not a contraindication to the use of these agents listed but this might increase the likelihood of depression developing during MDR/RR-TB treatment. If a patient has significant depressive symptoms at the start of treatment, avoid the use of Cs and Dlm, if possible. 3. SSRIs and TCAs are associated with QT prolongation; this risk must be balanced with the benefits for the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required, in that setting.

AE	Suspected agent	Suggested management strategies	Comments
Diarrhoea and/or flatulence or bloating	PAS Eto/Pto, Mpm, Amx/Clv, Lzd, Lfx, Mfx, Pa, S	1. Counsel patients that some degree of loose stools and flatulence is inevitable with these medications, but that these symptoms are likely to improve over time without having to withhold medication. 2. Encourage sufficient fluid intake. 3. Administer PAS only once daily if tolerated. 4. Treat persistent uncomplicated diarrhoea (no blood in stool and no fever) with loperamide. 5. If diarrhoea is severe, check serum electrolytes and dehydration status and manage accordingly. In children with acute diarrhoea, supplement zinc (20 mg per day) for 10–14 days to improve water and electrolyte absorption. 6. In severe cases with no improvement of symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required.	1. Fever and diarrhoea or blood in stools suggest causes other than simple side-effects of TB medications: • Pseudomembranous colitis related to broad-spectrum antibiotics (including FQs) is serious and can be life threatening. Warning signs include fever, bloody diarrhoea, intense abdominal pain and increased white blood cells. • Parasites and common waterborne pathogens should be investigated and treated. • Consider lactose intolerance. 2. Loperamide must not be used in children aged below 2 years.
Electrolyte disturbances	Am S	1. Consider other causes of electrolyte imbalance (e.g. vomiting, diarrhoea, burns, diabetes and use of insulin, cardiac failure and use of diuretics) and manage accordingly. 2. Assess renal function and check other electrolytes (i.e. potassium, magnesium, calcium and phosphate) if possible. 3. Rehydrate and replace electrolytes as needed – if unable to check magnesium levels, consider magnesium supplementation in cases of refractory hypokalaemia. 4. Amiloride or spironolactone may help to reduce potassium and magnesium wasting. 5. Patients with severe hypokalaemia (<2.5 mmol/L) should be hospitalized for IV electrolyte replacement and cardiac monitoring.	1. Clinical symptoms (e.g. muscle weakness and cramps, dizziness, nausea and impaired concentration) may not be evident until the potassium level is <3 mmol/L. 2. Hypokalaemia, hypomagnesaemia and hypocalcaemia can prolong the QT interval; closer ECG monitoring is warranted until levels are corrected. 3. Oral potassium replacements may cause nausea and vomiting, and oral magnesium may cause diarrhoea.

AE	Suspected agent	Suggested management strategies	Comments
Gastritis and abdominal pain	Eto/Pto, PAS, Cfz Lfx, Mfx, H, E, Z, Mpm, Dlm, Amx/clv	1. Abdominal pain may be associated with SAEs such as pancreatitis, lactic acidosis and hepatitis (see relevant sections). If these conditions are suspected, the most likely causative agent or agents should be withheld while awaiting further investigations and appropriate management. 2. If symptoms are consistent with gastritis (e.g. epigastric burning or discomfort, sour taste in mouth associated with reflux) initiate medical therapy with the use of H2 blockers (e.g. ranitidine) or proton-pump inhibitors (omeprazole). Avoid the use of antacids if possible because they reduce absorption of FQs, and to a lesser extent H and E. 3. If possible, decrease the dose of the suspected agent to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. 4. In severe cases with no improvement of symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required – this may necessitate a change in regimen if Cfz or an FQ is withdrawn.	1. Consider other causes of gastritis, such as NSAIDs or *Helicobacter pylori* infection, and manage accordingly. 2. Gastritis must be acknowledged and managed appropriately to provide relief to patients and facilitate adherence to TB treatment. 3. Proton-pump inhibitors can induce hypomagnesaemia and lead to QT prolongation; this risk must be balanced with the benefits for the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required, in that setting. 4. If antacids must be used, time their administration to avoid interference with TB medications (e.g. take antacid 2 hours before or 3 hours after TB medications). 5. Gastritis is common in pregnancy, but pregnant patients with persistent or severe abdominal pain must be investigated for other non-drug-related causes. 6. Severe abdominal distress has been reported with the use of Cfz and the drug should be withdrawn if it is considered to be the most likely cause.
Gynaecomastia	Eto/Pto, H	1. Consider other causes (e.g. obesity, older age, puberty in boys, recreational substances and other drugs) and educate the patient on possible causes. 2. Reassure the patient that changes in breast tissue that are related to TB medications are temporary and that the tissue will return to normal following completion of treatment.	1. Other drugs that can cause gynaecomastia include spironolactone, cimetidine, ketoconazole, risperidone, omeprazole and efavirenz.

AE	Suspected agent	Suggested management strategies	Comments
Hepatitis	Z, H, Pa, Bdq Eto/Pto, Trd/Cs, PAS	1. Stop all drugs if liver enzymes are >5 times the upper limit of the normal range (regardless of symptoms), or if they are >3 times the upper limit along with symptoms and signs of drug-induced liver injury. Wait for liver enzymes to return to <3 times the upper limit of normal. 2. Investigate and treat other potential causes of hepatitis (e.g. viral hepatitis, alcohol induced hepatitis and other hepatotoxic drugs). 3. Reintroduce three of the least hepatotoxic TB drugs first: for example, Lzd, Dlm and an FQ. All three drugs can be started together to provide a backbone regimen. 4. Then introduce potentially hepatotoxic drugs one by one, every 5–7 days, while monitoring liver enzymes to identify the responsible drug. 5. If the most likely causative agent is not essential in the treatment regimen, do not reintroduce it. 6. Depending on the most likely causative agent, withdrawal of the drug may necessitate a change in treatment regimen.	1. Symptoms and signs of liver injury include nausea, vomiting, fatigue, malaise, pruritus, fever, right upper quadrant pain, tender liver and jaundice. 2. Hepatocellular drug-induced liver injury with jaundice (and raised total bilirubin levels) indicates a serious reaction (Hy's law) and presents a high risk for acute liver failure. 3. Viral serology should be carried out to investigate for hepatitis A, B and C. 4. History of previous drug-related hepatitis may suggest a likely causative agent or agents – counsel the patient and document in their file that these drugs must be avoided in future treatment. 5. Patients with alcohol or substance use problems may benefit from additional psychosocial intervention and adherence support. 6. Do not rechallenge with Z following a drug-induced liver injury.

AE	Suspected agent	Suggested management strategies	Comments
Hypothyroidism	Eto/Pto, PAS	1. Exclude other causes (e.g. lithium, amiodarone, previous radioiodine therapy, pregnancy-associated thyroid dysfunction and Hashimoto's disease). 2. Consider thyroxine supplementation if TSH is raised >5 IU/mL and free T4 is decreased or the patient has symptoms of clinical hypothyroidism. 3. If TSH is >10 IU/mL, start levothyroxine at 50 mcg daily (start at a lower dose in older patients and those with significant cardiovascular disease). 4. Monitor TSH monthly and increase the dose by 12.5–25 mcg until TSH normalizes. 5. Continue levothyroxine supplementation for the duration of exposure to the causative agent.	1. Symptoms of hypothyroidism include fatigue, drowsiness, cold intolerance, dry skin, coarse hair, constipation, depression and inability to concentrate. These can be difficult to distinguish from TB symptoms and drug side-effects; hence, routine TSH monitoring is recommended in patients receiving PAS or Eto/Pto. 2. Hypothyroidism can lead to QT interval prolongation; these patients may require closer ECG monitoring depending on their exposure to QT-prolonging drugs. 3. The combination of PAS and Eto/Pto increases the likelihood of hypothyroidism, but it is completely reversible upon discontinuation of these drugs.
Lactic acidosis	Lzd, H	1. Suspect lactic acidosis in patients presenting in shock or acutely ill while on treatment with Lzd or H. 2. Check electrolytes and measure serum lactate if the anion gap is >12 mmol/L or if there are other reasons to suspect lactic acidosis. 3. Withhold Lzd and H, and do not rechallenge if lactic acidosis occurs.	1. Clinical signs of lactic acidosis may include severe hypotension, altered mental state, tachypnoea and oliguria. 2. The calculated anion gap = sodium – (chloride + bicarbonate).
Metallic taste	Eto/Pto H, Lfx, Mfx	1. Consider other causes (e.g. pregnancy, upper respiratory infections, underlying medical conditions and other drugs) and educate the patient on possible reasons for the change in their taste. 2. Sucking hard candy or chewing gum can be helpful. 3. Reassure the patient that changes in taste that are related to TB medications will return to normal following completion of treatment.	1. Other drugs leading to metallic taste include metformin, lithium and phenytoin. 2. Underlying conditions that can cause metallic taste include diabetes, zinc deficiency and Crohn's disease.

AE	Suspected agent	Suggested management strategies	Comments
Myelosuppression	Lzd Mpm, H, Pa	1. Do not initiate or continue Lzd when serum haemoglobin <8 g/dL, neutrophils <0.75 x 10^9/L or platelets <50 x 10^9/L. Referral for hospitalization and blood transfusion may be required in these cases. 2. Investigate other causes of anaemia (e.g. TB and other chronic diseases, nutritional deficiencies, pregnancy and blood loss), neutropoenia (HIV and other viral infections, leukaemia and lymphoma) or thrombocytopenia (pregnancy, other drugs and autoimmune disorders), and manage appropriately. 3. Lzd may be introduced at the full dose if the haematological parameters improve with blood transfusion at the start of treatment. 4. Lzd-induced myelosuppression tends to recur with ongoing exposure to Lzd following blood transfusion; Lzd should not be continued long term in these cases. 5. Do not drop the Lzd dose to subtherapeutic levels in response to this AE; rather, withdraw Lzd and substitute with another effective drug – this may necessitate a change in treatment regimen.	1. Lzd-induced myelosuppression usually affects red blood cells, but sometimes it affects only neutrophils or platelets in isolation. 2. In rare cases, Mpm and H can cause haemolytic anaemia. 3. Effective TB treatment, including with Lzd, usually leads to improvement of anaemia that is due to chronic disease; initial blood transfusion at the start of treatment may improve haematological parameters enough to allow Lzd to be initiated within an effective regimen. 4. Blood transfusions might also facilitate completion of the recommended duration of Lzd, to avoid substituting with other medications or changing treatment regimens. 5. There have been some case studies reporting that pyridoxine (daily dose of 50 mg in adults) may protect against Lzd-induced anaemia, but the evidence is equivocal. 6. Iron supplements are unlikely to be useful in the acute management of Lzd-induced anaemia. 7. Unless indicated for severe confirmed iron deficiency anaemia, iron supplementation can be delayed until later in TB treatment, when the pill burden and side-effects of ferrous compounds can be better tolerated.

AE	Suspected agent	Suggested management strategies	Comments
Nausea and vomiting	Eto/Pto, PAS, Amx/Clv, Bdq Lfx, Mfx, Mpm, H, E, Z, Cfz, Dlm, imp/cln, Pa, Lzd, S	1. Assess for danger signs (e.g. dehydration, electrolyte disturbances and hepatitis). Initiate rehydration therapy if indicated and correct electrolyte disturbances. Check haemoglobin and treat for bleeding ulcers in cases of haematemesis. 2. Exclude and manage other causes of new onset nausea and vomiting (e.g. hepatitis, pancreatitis, raised intracranial pressure, pregnancy or pre-eclampsia, and gastroenteritis). 3. Counsel the patient that these symptoms are common and usually worse at the start of treatment, and that they often improve over time without having to withhold medication. 4. Encourage the patient to try different ways of taking their medication in relation to food and the timing of their usual daily activities: • Take Eto/Pto or PAS at a different time of day (e.g. just before going to sleep). • Eat a light snack before or after taking medication or try different foods. • Take Eto/Pto or PAS 2 hours after other TB medications. 5. Consider antiemetic(s) if nausea and vomiting persists: • Metoclopramide – administer 30 minutes before TB medications. • Ondansetron (or promethazine) – administer 30 minutes before TB medications and again 8 hours later; can be used on its own or with metoclopramide. 6. If possible, decrease the dose of the suspected agent to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen.	1. Nausea is common in the early weeks of TB treatment; it usually abates with time, although some patients need adjunctive therapy. 2. Ongoing information, education and peer support may help patients to anticipate and cope with common symptoms. 3. Absorption of TB medications is often affected by the type and timing of food intake; however, the "ideal" administration of TB medications with or without food may have to be altered if not tolerated by the patient. 4. Monitor renal function and replace electrolytes and fluids, as necessary, in cases of severe persistent vomiting. 5. Consider temporarily withholding the most likely causative agent and reintroduce it gradually by slowly increasing the dose over 2 weeks. 6. Ondansetron is a serotonin 5-HT3 receptor antagonist and has strong antiemetic properties. Different antiemetics, even from the same class, may be worth trying for some patients. 7. Ondansetron can prolong the QT interval; this risk must be balanced with the benefits for the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required, in that setting. 8. Patients with "anticipatory nausea and vomiting" may benefit from a small dose of an anxiolytic (diazepam) 30 minutes before taking medications. 9. Antihistamines may be useful for nausea associated with CNS or vestibular toxicity.

AE	Suspected agent	Suggested management strategies	Comments
		7. For non-remitting symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required – this may necessitate a change in regimen if a standardized regimen is used.	
Nephrotoxicity (renal toxicity)	Am	1. Investigate and manage other causes of renal toxicity (e.g. NSAIDs, diabetes, other medications, dehydration, congestive cardiac failure and urinary obstruction). 2. Discontinue the injectable agent and replace it with another effective TB medication if required. 3. Adjust doses of renally excreted TB medications according to creatinine clearance. 4. Monitor creatinine and electrolyte levels every 1–2 weeks until normal or stabilized.	1. A history of diabetes or renal disease is not a contraindication to using Am; however, patients with these comorbidities may be at increased risk of renal failure following exposure to this injectable agent; renal impairment may be permanent. 2. Renal dosing is recommended for selected TB medications in patients with creatinine clearance <30 mL/min.
Optic neuritis	Lzd, E	1. Withhold Lzd and E immediately in patients experiencing symptoms of optic neuritis. 2. Consider other causes of optic neuritis (e.g. autoimmune conditions, exposure to toxic substances such as methanol, and other bacterial or viral infections) and refer to an ophthalmologist. 3. Check blood sugar and diabetic control. 4. Do not reintroduce E. 5. Only consider reintroducing Lzd if other MDR/RR-TB treatment options are severely limited and optic neuritis has been definitively ruled out.	1. Symptoms of optic neuritis include ocular pain, loss of vision and flashing lights; symptoms are often unilateral. 2. All patients receiving Lzd and E must be counselled at the start of therapy to recognize the early symptoms of this potentially sight-threatening AE and seek medical assistance urgently. 3. Drug-induced optic neuritis is usually reversible with early cessation of the offending agent.

AE	Suspected agent	Suggested management strategies	Comments
Ototoxicity (hearing loss, tinnitus and vertigo)	Am S	1. Withdraw the injectable agent if there is new or worsening tinnitus, dizziness, fullness in the ears or evidence of hearing loss; replace with another effective agent. 2. Check renal function because nephrotoxicity is also an AE associated with injectable agents, and a reduced creatinine clearance may lead to increased exposure to ototoxic medications, with exacerbation of symptoms. 3. Vestibular symptoms (e.g. dizziness and nausea) may improve with antihistamines such as meclizine or dimenhydrinate.	1. Audiology screening, to detect early changes and high-frequency hearing loss, is essential for patients requiring treatment with this injectable agent. 2. Aspirin and loop diuretics are also ototoxic and may exacerbate the effects of aminoglycosides.

AE	Suspected agent	Suggested management strategies	Comments
Peripheral neuropathy	Lzd, H, Trd/Cs Lfx, Mfx, Am	1. Manage baseline risk factors – correct and prevent vitamin or nutritional deficiencies, obtain better diabetic control and educate the patient on possible causes of peripheral neuropathy. 2. Pyridoxine doses of 50 mg in adults (25 mg in children) should be administered for peripheral neuropathy prophylaxis; however, pyridoxine doses must not be increased beyond 100 mg in adults because, paradoxically, this may contribute to worsening peripheral neuropathy symptoms. 3. Neuropathic pain relief may be achieved with NSAIDs or paracetamol (acetaminophen), TCAs, pregabalin, gabapentin or carbamazepine. 4. Discontinue high-dose H if not considered essential in the regimen. 5. If possible, decrease the dose of the suspected agent (e.g. Trd/Cs) to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. 6. For worsening or non-remitting symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required – this may necessitate a change in regimen if a standardized regimen is used.	1. Risk of peripheral neuropathy is increased in malnutrition, diabetes, heavy alcohol use, HIV, pregnancy and co-administration of multiple suspected drugs; these conditions are not contraindications for the agents listed. 2. H inhibits the metabolic action of vitamin B6 and Trd/Cs increases its renal excretion; therefore, pyridoxine supplementation can protect against drug-induced vitamin B6 deficiency, which leads to peripheral neuropathy; pyridoxine does not appear to protect against Lzd-induced peripheral neuropathy. 3. Peripheral neuropathy can manifest in various ways and can be difficult to assess properly, especially in young children – ask about crying at night, pulling at feet, kicking off bed covers, weakness, clumsiness and changes in gait or balance. 4. Note that TCAs are associated with QT prolongation; this risk must be balanced with the benefits for the patient, taking into account the patient's exposure to other QT-prolonging drugs and the feasibility of closer ECG monitoring, if required, in that setting. 5. Carbamazepine is a strong CYP3A4 inducer and should not be used with Bdq (the drug–drug interaction is likely to lead to subtherapeutic Bdq levels). 6. Many patients report improvement in symptoms when the offending agent is withheld; however, drug-induced peripheral neuropathy is common after prolonged drug exposure and may become irreversible (particularly with Lzd); good communication and joint decision-making with the patient is crucial when considering ongoing treatment with the suspected agent or agents.

AE	Suspected agent	Suggested management strategies	Comments
Psychotic symptoms (hallucinations and delusions)	Dlm, Trd/Cs, H Lfx, Mfx	1. Consider other causes of psychotic symptoms (e.g. fever, CNS infections, head injury or trauma, emotional abuse, food or sleep deprivation, heavy metal poisoning, recreational substance use, and psychological and neurological conditions) and manage appropriately. 2. In severe cases – particularly if the patient is a potential risk to themselves or others – initiate antipsychotic therapy (e.g. haloperidol) and refer for hospitalization. 3. Check renal function because this may lead to reduced excretion and increased exposure to toxic drugs – amended dosing of TB medications may be required. 4. Increase pyridoxine to maximum daily dose (100 mg per day in adults) if Trd/Cs or H are used. 5. If possible, decrease the dose of the suspected agent (e.g. Trd/Cs or H) to the lower end of the weight-based dosing band, provided this is not likely to compromise the efficacy of the drug or TB regimen. 6. In severe cases with no improvement of symptoms, withdraw the suspected agent or agents, and substitute with another effective drug if required.	1. Prior history of psychotic symptoms or psychiatric disease is not a contraindication to the drugs listed but may increase the likelihood of psychotic symptoms developing during treatment with these drugs. 2. Drug-induced psychotic symptoms are generally reversible upon withdrawal of the offending agent. 3. Renal dosing is recommended for selected TB medications in patients with creatinine clearance <30 mL/min. 4. Some patients who experience psychosis can tolerate these drugs along with an antipsychotic agent throughout MDR/RR-TB treatment, but this should only be considered if treatment options are limited and in consultation with a psychiatrist. 5. Haloperidol is known to prolong the QT interval; hence, closer ECG monitoring is recommended, particularly if the patient is receiving multiple other QT-prolonging TB medications.

AE	Suspected agent	Suggested management strategies	Comments
QT prolongation	Cfz, Bdq, Mfx, Dlm Pa, Lfx	1. Obtain a thorough drug history. 2. Ask about history of cardiac symptoms: chest pain, palpitations, dizziness or syncope. 3. Repeat the ECG when the patient is relaxed and at rest. 4. Manually calculate the QTcF interval by taking an average reading from multiple ECGs done at least 1 minute apart (if available). 5. Measure serum electrolytes (potassium, magnesium and calcium) and TSH, and correct if necessary. 6. In children under 20 kg, consider reducing the dose of Cfz. 7. For QTcF >460 ms, withhold non-essential QT-prolonging concomitant medications (e.g. antihistamines) and use more frequent ECG monitoring. 8. For QTcF >480 ms, monitor ECGs more closely and withhold one or more QT-prolonging TB medications if the patient complains of cardiac symptoms. 9. For QTcF >500 ms, withhold all QT-prolonging medications and monitor ECG closely – refer for hospitalization if the patient has cardiac symptoms. 10. QT-prolonging drugs that are essential to the TB regimen may be rechallenged sequentially, with close ECG monitoring, once QTcF improves to <500 ms. 11. Withdraw the most likely QT-prolonging agent in cases of recurrent or persistent severe QT interval prolongation – this may necessitate a change in treatment regimen.	1. The QT interval is a physiological parameter that fluctuates throughout the day and is affected by emotional state, hunger, anxiety, exercise, endocrine and metabolic disturbances, and exogenous substances. 2. A normal QT interval is usually considered as QTcF <450 ms but there is some borderline variation, which can also vary by gender; the corrected QT interval is considered prolonged if it is >450 ms in males and >470 ms in females. 3. Cfz exposure is relatively high in young children at recommended doses; reduction in dose may reduce the risk of QT prolongation while maintaining drug efficacy in this population. 4. Many drugs have the potential to prolong the QT interval.[a] 5. Risk is increased with multiple QT-prolonging drugs and additional risk factors (electrolyte and thyroid disturbances). 6. Patients with prolonged QTc are at risk of developing cardiac arrhythmias such as TdP, which can lead to sudden death – this risk increases substantially with QTcF >500 ms.

AE	Suspected agent	Suggested management strategies	Comments
Seizures	H, Trd/Cs Mpm, Lfx, Mfx, Lzd, Imp/cln	1. Consider other causes of seizures (e.g. fever, CNS infections, recreational drug use, hypo/hyperglycaemia, head injury and epilepsy) and manage appropriately. 2. Check blood sugar and serum electrolytes, and correct as needed. 3. Check renal function because this may lead to reduced excretion and increased exposure to toxic drugs – amended drug dosing may be required. 4. Increase pyridoxine to maximum daily dose (100 mg per day in adults) if Trd/Cs or H are used. 5. Anti-convulsant therapy (e.g. sodium valproate) may be necessary to control seizures. 6. Withhold all suspected agents until seizures have stabilized and then reintroduce TB medications one at a time. Do not reintroduce H.	1. Seizures are a common complication of tuberculous meningitis. 2. Renal dosing is recommended for selected TB medications in patients with creatinine clearance <30 mL/min. 3. Prior history of seizures is not a contraindication to the drugs listed, provided the patient's seizures are under control or the patient is receiving anti-convulsant therapy (or both); however, such patients may still be at increased risk of developing seizures during MDR/RR-TB treatment and these agents should only be used if therapeutic options are severely limited. 4. Phenytoin and carbamazepine are strong CYP3A4 inducers and should not be used with Bdq (the interaction is likely to lead to subtherapeutic drug levels).
Skin and sclerae hyperpigmentation	Cfz	1. Some degree of skin hyperpigmentation is inevitable with prolonged use of Cfz, and patients should be informed of this at the start of treatment. 2. Occasionally, patients experience staining of the whites of their eyes; this may be mistaken for conjunctivitis. 3. Some patients may also complain of skin rashes and dry, itchy skin – this can be managed conservatively with moisturizing lotions and other topical agents. 4. Reassure the patient that drug-induced skin and sclerae changes will return to normal following completion of treatment.	1. This AE can be distressing and stigmatizing for some patients (particularly adolescents) and they may require extra psychological counselling and peer support. 2. This effect is likely to be exacerbated by prolonged sun exposure.

AE	Suspected agent	Suggested management strategies	Comments
Tendonitis or tendon rupture	Lfx, Mfx	1. Mild to moderate tendonitis or partial tendon tears may be managed conservatively with rest, ice, compression, elevation, immobilization of the affected joint or tendon, and therapy with NSAIDs. 2. Patients with complete tendon rupture should be referred for surgical assessment and physiotherapy-led rehabilitation. 3. Unless MDR/RR-TB treatment options for the individual are severely limited, ongoing treatment with FQs should be avoided in patients with tendinopathy.	1. Prolonged exposure to FQ (beyond 1 week) increases the risk of tendonitis and tendon rupture. 2. Tendon rupture associated with FQ use is more common among diabetic patients and people aged over 30 years; men are at higher risk than women. 3. Patients who participate in sports that involve running, jumping or sudden movements should be counselled about the higher risk of tendon rupture while taking FQs. 4. Exposure to corticosteroids, both systemic and with local application, also contribute to tendon weakening and increase the risk of tendon rupture.

AE: adverse event; CNS: central nervous system; ECG: electrocardiogram; FQ: fluoroquinolone; HIV: human immunodeficiency virus; IU: international units; IV: intravenous; MDR/RR-TB: multidrug-resistant or rifampicin-resistant TB; NSAID: non-steroidal anti-inflammatory drug; QTcF: corrected QT interval per Fridericia's formula; SAE: serious adverse event; SSRI: selective serotonin reuptake inhibitor; TB: tuberculosis; TCA: tricyclic antidepressant; TdP: torsades de pointes; TSH: thyroid stimulating hormone.

Drugs: Am: amikacin; Amx: amoxicillin; Bdq: bedaquiline; Cfz: clofazimine; Clv: clavulanic acid; Cs: cycloserine; Dlm: delamanid; E: ethambutol; Eto: ethionamide; H: isoniazid; Lfx: levofloxacin; Lzd: linezolid; Mfx: moxifloxacin; Mpm: meropenem; Pa: pretomanid; PAS: *p*-aminosalicylic acid; Pto: prothionamide; Trd: terizidone; Z: pyrazinamide.

[a] For a list of drugs, see https://crediblemeds.org/.

Ancillary medications

Clinical management of people receiving treatment for MDR/RR-TB often requires the use of ancillary medications to prevent, lessen or eliminate the AEs associated with TB medications. NTPs may choose to make ancillary medications available for health care providers to prescribe to patients free of charge, to reduce the burden of catastrophic costs on patients and their households. Table A2.3 presents a list of commonly used ancillary medications and their indications for use; this list may be adapted by countries according to best practices in those settings.

Table A2.3. Commonly used ancillary medications

Indication	Drug	Notes
Anaemia	Folate, vitamin B12, ferrous compounds and anthelmintics (mebendazole and albendazole)	Deworming medicines may assist in reducing anaemia, particularly in children
Bronchospasm	Inhaled beta-2 receptor agonists (e.g. albuterol/ salbutamol), inhaled corticosteroids (e.g. beclomethasone), oral steroids (e.g. prednisone and prednisolone) and injectable steroids (e.g. dexamethasone and methylprednisolone)	Spacers are useful to ensure adequate administration of inhaled medications in children and some adults
Candidiasis (oral, genital, cutaneous)	Topical miconazole, nystatin suspension (mouthwash), clotrimazole lozenges, oral fluconazole; nystatin, miconazole or clotrimazole creams and suppositories	Azole antifungal drugs inhibit the CYP3A4 pathway and increase exposure to bedaquiline; co-administration should be limited to <2 weeks. Fluconazole is a less potent inhibitor and could be used for longer than 2 weeks with closer monitoring for AEs associated with bedaquiline
Cutaneous reactions, itching	Hydrocortisone cream, calamine and caladryl lotions, antihistamines, oral prednisone, sunscreen, moisturizing lotions and topical benzoyl peroxide	Some antihistamines are associated with QT prolongation
Depression	SSRI (e.g. fluoxetine and sertraline) and TCA (e.g. amitriptyline)	Risk of serotonin syndrome with SSRIs and linezolid; TCAs are associated with QT prolongation
Diarrhoea	Loperamide, zinc supplements	Do not use loperamide in children aged <2 years
Electrolyte wasting	Potassium, magnesium and calcium replacement therapy (oral and intravenous formulations), vitamin D supplements, amiloride, spironolactone	Oral potassium and magnesium cause nausea, vomiting and diarrhoea; vitamin D assists the absorption of calcium

Indication	Drug	Notes
Gastritis	H2 blockers (e.g. ranitidine, cimetidine), proton-pump inhibitors (e.g. omeprazole, lansoprazole), antacids	Proton-pump inhibitors are associated with QT prolongation; antacids reduce absorption of fluoroquinolones
Hypothyroidism	Levothyroxine	Monitor TSH monthly and adjust dose until stable in normal range
Insomnia	Sedating antidepressants (e.g. low-dose amitriptyline), antihistamines (e.g. dimenhydrinate), melatonin	TCAs are associated with QT prolongation
Nausea and vomiting	Metoclopramide, ondansetron, dimenhydrinate, prochlorperazine, promethazine and benzodiazepines (e.g. diazepam and lorazepam)	Some antihistamines are associated with QT prolongation
Pain (musculoskeletal, arthralgia, headaches)	Paracetamol/acetaminophen, NSAIDs (e.g. indomethacin, ibuprofen), codeine	–
Peripheral neuropathy	NSAIDs, paracetamol/ acetaminophen, amitriptyline, pregabalin, gabapentin and carbamazepine	TCAs are associated with QT prolongation; carbamazepine induces metabolism of bedaquiline
Prophylaxis of neuropathic complications of isoniazid and terizidone/ cycloserine	Pyridoxine (vitamin B6)	Usual dose 50 mg daily for adults, 25 mg daily for children aged ≥5 years, 12.5 mg daily for children aged <5 years. Do not exceed double these doses daily because paradoxically this may worsen symptoms
Psychosis	Haloperidol and risperidone	Haloperidol and risperidone may prolong the QT interval
Systemic hypersensitivity reactions	Antihistamines (e.g. diphenhydramine, chlorpheniramine and dimenhydrinate) and corticosteroids (e.g. prednisone, prednisolone and dexamethasone)	Some antihistamines (e.g. diphenhydramine) are associated with QT prolongation
Vestibular symptoms	Antihistamines (e.g. meclizine, dimenhydrinate and promethazine)	Some antihistamines are associated with QT prolongation

AE: adverse event; NSAID: non-steroidal anti-inflammatory drug; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; TSH: thyroid stimulating hormone.

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Web Annex 3. Active TB drug-safety monitoring and management for treatment of drug-resistant TB

A3.1 Background

Pharmacovigilance is defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem". It is a fundamental public health surveillance activity designed to inform the management of patient safety measures in health care. Pharmacovigilance is a facet of programme monitoring, and is similar to the way many countries operate routine surveillance of tuberculosis (TB) drug resistance based on diagnostic testing.

Patients can be better served if monitoring of drug safety is implemented in tandem with management of adverse events (AEs) and adverse drug reactions (ADRs). Many of the second-line anti-TB drugs are more likely to cause toxic reactions in patients than first-line drugs, making pharmacovigilance more important in programmatic management of drug-resistant TB (PMDT). By recording the occurrence of ADRs for patients on treatment, many programmes are already collecting basic data inherent to pharmacovigilance. However, the collection of such data and the measurement of indicators on pharmacovigilance are not part of the standard parameters used in the monitoring of TB patients on treatment. Consequently, in most programmes, the nature and frequency of harm caused by the drugs themselves are poorly profiled, and they can only be inferred indirectly, from interruption or failure of treatment. As programmes start to incorporate newly released drugs into treatment regimens, WHO recommends that capacity to undertake pharmacovigilance also be improved, because this is fundamental in ensuring the safety of patients and the updating of patient safety standards, drug-safety profiles and TB treatment guidelines.

In November 2014, a WHO workshop with broad representation from stakeholders and experts was held in Viet Nam, to define methods for active surveillance of drug-safety concerns in TB programmes *(1)*. To improve understanding and arrive at a broad consensus on ways to address patient safety, the WHO Global TB Programme (WHO/GTB) convened a consultation meeting in Geneva, Switzerland, for key technical partners on 28–29 July 2015. The technical partners discussed essential requirements for the implementation of active pharmacovigilance and proper management of AEs and ADRs, which is one of the conditions included in the WHO interim policies on the use of new anti-TB medicines or novel multidrug-resistant TB (MDR-TB) regimens. The consensus reached during this meeting and in subsequent discussions is presented in the framework for the implementation of active TB drug-safety monitoring and management (aDSM) *(2)*. The framework outlines the agreed essential requirements for aDSM in patients on treatment for drug-resistant TB (DR-TB), and proposes key terms that were adapted to the specific context of TB drug-safety monitoring. This section provides advice on implementing the WHO policy on aDSM for the treatment of MDR-TB. TB practitioners,

health officials, planners, public health teams, drug regulatory authorities and others should become familiar with other publications relating to the subject *(3, 4)*.

A3.2 Definitions used in aDSM[2]

Active TB drug-safety monitoring and management (aDSM) is the active and systematic clinical and laboratory assessment of patients on treatment with new anti-TB drugs, novel MDR-TB regimens or extensively drug-resistant TB (XDR-TB) regimens to detect, manage and report suspected or confirmed drug toxicities. Although all detected AEs need to be managed, the core package of aDSM requires the reporting of serious AEs (SAEs) only. MDR-TB and XDR-TB treatment sites with additional resources may also monitor other AEs that are of clinical significance or of special interest to the programme, as part of comprehensive aDSM.

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

Adverse event (AE) is any untoward medical occurrence that may present in a TB patient during treatment with a pharmaceutical product, but does not necessarily have a causal relationship with this treatment.

Serious adverse event (SAE) is an AE that leads to death or a life-threatening experience, hospitalization or prolongation of hospitalization, persistent or significant disability, or a congenital anomaly. The definition includes SAEs that do not immediately result in one of these outcomes but may require an intervention to prevent it from happening. SAEs may require a drastic intervention, such as termination of the drug suspected of having caused the event.

Adverse event of special interest is an AE documented to have occurred during clinical trials and for which the monitoring programme is specifically sensitized to report, regardless of its seriousness, severity or causal relationship to the TB treatment. The centres that offer intermediate and advanced packages of aDSM will include all AEs of special interest in their reporting.

Adverse event of clinical significance is an AE that is serious, is of special interest, leads to a discontinuation or change in the treatment, or is otherwise judged as being clinically significant by the clinician. The centres that offer the advanced package of aDSM will include all AEs of clinical significance in their reporting.

Adverse event leading to treatment discontinuation or change in drug dosage is an event that leads a clinician to stop, interrupt temporarily or change the dosage of one or more drugs, regardless of its seriousness, severity or causal relationship to the TB treatment.

Causal relationship is a relationship between an exposure (A) and an event (B) in which A precedes and causes B. This may refer to the causal association between an exposure to a TB medicine and the occurrence of an adverse reaction.

Causality assessment is the evaluation of the likelihood that a TB medicine was the causative agent of an observed adverse reaction.

Drug-safety profile is a description of the benefits, risks and toxicity of a given TB drug or regimen, specifying any known or likely safety concerns, contraindications, cautions, preventive measures and other features that the user should be aware of to protect the health of a TB patient.

Sentinel sites are centres that, in addition to the core package of aDSM, also undertake intermediate or advanced levels of drug-safety monitoring.

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[2] The definitions of some terms have been modified from those in general usage, to fit better in the context of national TB programmes (NTPs).

Signal is reported information on a possible causal relationship between an AE and a TB medicine, the relationship being unknown or incompletely documented previously or representing a new aspect of a known association. It covers information arising from one or multiple sources that is judged to be of sufficient likelihood to justify verification *(5)*.

A3.3 What to monitor for aDSM

WHO recommends aDSM for all MDR/RR-TB patients treated with new medicines (e.g. bedaquiline, delamanid or pretomanid), repurposed medicines (e.g. linezolid, clofazimine) or novel regimens (e.g. 6-month BPaLM/BPaL regimen, 9-month all-oral regimen or other regimens that include multiple new and repurposed drugs). The appropriate and timely management of all AEs and ADRs is an integral component of aDSM and patient care.

A priority for monitoring is the detection of SAEs that lead to hospitalization or prolongation of hospitalization, a persistent significant disability, a congenital anomaly, a life-threatening condition or death. It is necessary to report SAEs as per the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline definition *(6)*. All deaths are to be reported and as much relevant information as possible on the cause of death should be consistently collected. This may require recovering information from vital registration coding. Reporting of AEs and other events (e.g. pregnancy and lactation exposure) may be required, primarily based on what is known about the safety profile of the new agent and also for other possible harms that have not yet been described.

All reasonable measures are thus needed to ensure that patient safety is monitored alongside the effectiveness of treatment. In this situation, spontaneous reporting is not expected to represent an appropriate level of care, and active and cohort-based drug-safety monitoring approaches are considered necessary to improve early and systematic detection, and management of harms. It is also important to collect safety data accurately, to ensure that any AE is properly investigated and no hasty conclusions about the causative medicine are drawn. A cohort approach is essential to avoid bias in the selection of patients or in the measurement of events; it is also the best way to infer the potential association of an event with the given exposure, and it provides denominators and baseline data for analysis. Many TB practitioners are unfamiliar with the concept of "cohort event monitoring" and other conventional terminology of pharmacovigilance, making it difficult for them to follow recent recommendations for introduction of a drug-safety monitoring component in PMDT programmes. The aDSM approach therefore outlines the agreed "essential requirements for active drug-safety monitoring and management in patients on treatment for drug-resistant TB". It proposes key terms that have been adapted to the specific context of active TB drug-safety monitoring. This adaptation should help the TB community to speak a common language while implementing the required drug-safety activities.

The recording and reporting of aDSM primarily target SAEs as a core requirement. PMDT sites with additional resources may also monitor other AEs that are of clinical significance or of special interest to the PMDT programme as part of an extended aDSM approach.

aDSM is important when patients are treated with a medicine for which the drug-safety profile is not yet complete. This does not depend on the number of patients enrolled. Monitoring needs to be closely associated with early action to prevent and manage any serious consequences to the individual patient. A national programme should also strive to capture data in the private sector and through public–private partnerships.

aDSM is intended to pick up not only known reactions associated with a drug but also any unexpected effect of treatment (some of these may actually be beneficial to the patient). For aDSM, a non-severe event may be the early manifestation of a more consequential process (e.g. a dose-dependent effect).

Where it is feasible for the programme, such events should be captured on data collection forms. To reduce the workload, entering of this information into the aDSM database should be optional.

A3.4 Objectives of aDSM

The overall objectives of aDSM are to reduce risks from drug-related harms in patients on second-line treatment for DR-TB and to generate standardized aDSM data to inform future policy updates on the use of such medicines. To achieve these objectives, the aDSM includes four essential activities:

- Patients targeted for aDSM should undergo active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs.
- All AEs detected should be managed in a timely manner, to deliver the best possible patient care (as described in Web Annex 2).
- Standardized data should be systematically collected and reported for any SAE detected:[3] these data will eventually be used to characterize the types of SAEs, assess the safety of treatment and inform future policy on the use of these medicines.
- Improving the evidence base for global policy on new and repurposed medicines.

For the evidence base to improve, AE data collected by national authorities need to be shared to permit global monitoring and data pooling. This approach is also useful to detect previously unrecognized or poorly documented AEs. A global database for active TB drug-safety monitoring and management has been launched by WHO and the Special Programme for Research and Training in Tropical Diseases (TDR). The aDSM website provides details on how countries can submit data. Close coordination of aDSM activities with the main pharmacovigilance structures at the country level is essential to avoid overlap and duplication. Any future recommendation of WHO on off-label use of new anti-TB medicines (e.g. delamanid or bedaquiline) for more than 6 months will depend on the availability of good-quality safety data – proper implementation of aDSM is paramount for such data.

A3.5 Levels of monitoring in aDSM

There are three levels of monitoring in aDSM:

- core package – which requires monitoring for and reporting of all SAEs;
- intermediate package – which includes SAEs as well as AEs of special interest; and
- advanced package – which includes all AEs of clinical significance.

All PMDT sites treating eligible patients with new anti-TB drugs or novel MDR-TB regimens, or treating patients for XDR-TB, require the core package. These treatment centres should, as a minimum, also take part in spontaneous reporting of ADRs, as required by local regulations. Expansion of aDSM should be implemented in a phased approach as and when resources permit.

All SAEs detected should be reported to the national authority responsible for pharmacovigilance according to individual country requirements (including time limits for reporting) and should be regularly assessed for causality.

A3.6 Implementing aDSM

The implementation of aDSM will require the following eight essential steps:

1. Create a national coordinating mechanism for aDSM.
2. Develop a plan for aDSM.
3. Define management and supervisory roles and responsibilities.

[3] Countries and stakeholders may also monitor other AEs of special interest or clinical significance (see next section).

4. Create standard materials for data collection.
5. Train staff on the collection of data.
6. Define schedules and routes for data collection and reporting.
7. Consolidate aDSM data electronically.
8. Develop (or use existing) capacity for signal detection and causality assessment.

Ideally, all eight steps should be in place before patients are enrolled on treatment with new drugs, novel MDR-TB regimens or XDR-TB treatment. Where this is not feasible, Step 4 (Create standard materials for data collection) and Step 5 (Train staff on the collection of data) are considered essential ahead of any patient enrolment.

A fully functional aDSM is not required at the time of ordering drugs or starting patients on treatment. However, certain key elements need to be in place so that essential safety data are collected for all patients as soon as they are started on a new drug or new regimen. The capacity for aDSM can then be built over the following months.

The aDSM plan would clearly define the activities and standard operating procedures (SOPs), including the plan for data collection, reporting of indicators, analysis and communication. The final document would be incorporated within the national TB or PMDT guidelines. Local or international experts in drug safety as well as the national pharmacovigilance centre (if functional) should be engaged.

Some of the data collection tools for aDSM are separate from those used for routine PMDT monitoring; nevertheless, the process could be integrated with other cohort-based monitoring for bacteriological response and outcomes that have been a standard feature of the PMDT component of TB control programmes for several years (see Section 2 of the guidelines and the corresponding annexes). WHO is working closely with partners towards further integration of aDSM within routine PMDT monitoring.

In the core package of aDSM, clinical and laboratory test records at baseline and during regular reviews (e.g. monthly intervals) would be integrated with an expanded version of the programmatic MDR-TB (second-line TB) treatment card.

Before enrolling any patients, staff at the different levels of health services would be informed and trained on the use of new anti-TB drugs or novel regimens (including instruction on the completion of aDSM forms). This activity should be completed ahead of any patient enrolment, to ensure timely identification of AEs that need to be managed, and proper and complete collection of information.

All AEs detected during routine clinical patient care should lead to an appropriate and timely management response to limit potential harms to the patient. In terms of monitoring, the minimum requirement for aDSM is that all SAEs be registered and reported, regardless of their severity or whether they were caused by any of the medicines to which the patient was exposed.

Some centres with sufficient resources may be designated as "sentinel sites" and undertake monitoring additional to that required by the core package of aDSM (e.g. the reporting of AEs of special interest or AEs of clinical significance, as described above). In many countries, the law mandates the reporting of ADRs to the national pharmacovigilance centre. In all public and private health services, TB practitioners should comply with the national legal requirements for such reporting.

A standard form (in paper or electronic format) will need to be developed to alert the programme when any SAE occurs; the content of the form should be similar to that used by the national pharmacovigilance centre for spontaneous reporting. The creation of an electronic database – or preferably the adaptation of an existing TB patient database to accommodate the additional data fields required – is an important step in aDSM implementation. It will ensure the standardization and safekeeping of data. If data are collected on paper forms, these need to be entered regularly into the electronic database. The management of data in electronic format is indispensable for facilitating data sharing and data analysis, and for generating indicators.

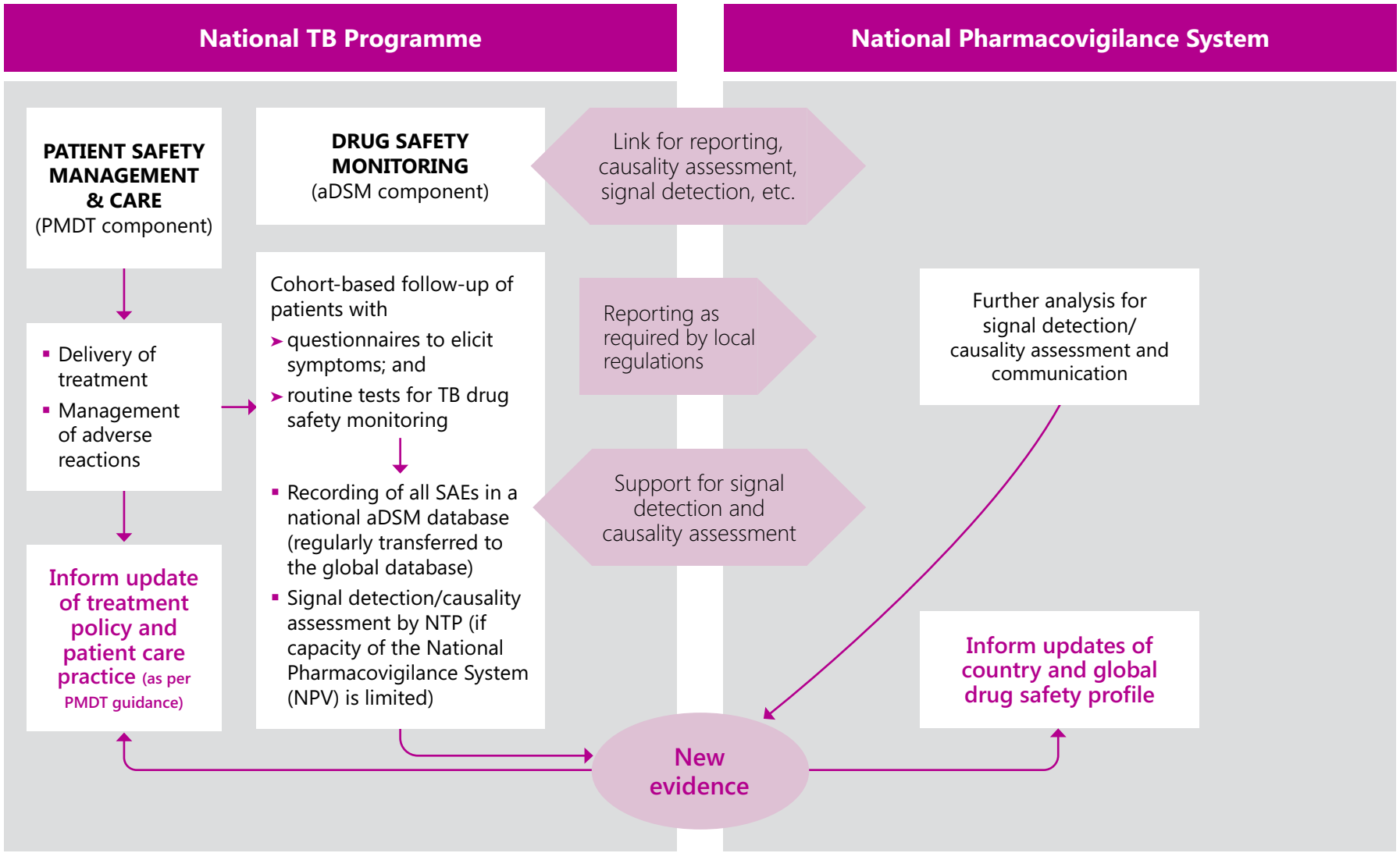
Measures would be taken to avoid duplication of work by revising existing databases, ensuring interoperability of data management systems, consulting with local pharmacovigilance authorities and granting access rights to users for different data as needed (Fig. A3.1). The roles and responsibilities for data management and analysis would be specified in the aDSM plan, to avoid the creation of parallel systems of ADR reporting and to make use of the best possible expertise on drug safety in the country.

Fig. A3.1 outlines the main lead responsibilities for the different components of aDSM; it could be useful in assigning complementary functions and associated funding needs. This construct is subject to adjustment based on local circumstances; for example, if the national pharmacovigilance centre has limited capacity for running an aDSM project in the country, it may be agreed that the national TB programme (NTP) or a technical agency will lead certain functions. Technical agencies could, for instance, catalyse the establishment of a committee or the protocol, organize training or provide technical assistance. Donors could have a role in supporting grant proposals for pharmacovigilance and facilitating the process for accessing the resources at country level.

In addition to the identification of signals and causality assessment, indicators will be useful for assessing the coverage of aDSM activities and summarizing the overall AE experience of monitored patients. For these purposes, Table A3.1 presents the indicators and Table A3.2 a "drug-safety profile" *(1)*. The essential laboratory tests and examinations that need to be conducted will be determined by the programme protocol.

Development of a schedule for screening of AEs and for laboratory, clinical and radiological testing is also recommended. Both the list of data elements and the frequency of testing would be validated and customized based on local needs before they are integrated in the programme's aDSM protocol.

Fig. A3.1. Generic model of aDSM within drug-safety structures at the national level



aDSM: active TB drug-safety monitoring and management; NPV: national pharmacovigilance centre; NTP: national TB programme; PMDT: programmatic management of drug-resistant TB; SAE: serious adverse event; TB: tuberculosis.

Source: WHO (2014) *(7)*.

A3.7 Roles, responsibilities and support for the implementation of aDSM

Responsibility for the coordination of aDSM at the national level should be assigned to an existing TB expert body, such as the MDR-TB committee (or consilium) or the technical working group on new drugs. These committees should primarily have scientific and clinical expertise for MDR-TB care and drug-safety monitoring, but could also include expertise important for coordination and advocacy (e.g. funding, communication and patient representation). Until such a group is tasked with this role, the NTP needs to assign someone to coordinate the necessary aDSM activities and ensure that the key steps mentioned above are in place before patient enrolment.

The ultimate purpose of systematic data collection within aDSM is to enable causality assessment for SAEs, determine the frequency (rates) of SAEs and detect signals. Physicians skilled in MDR-TB management already attempt to assess relationships between drugs and ADRs and take appropriate clinical action. However, formal causality assessment is a separate process that requires involvement of other experts. In several countries, the capacity of national pharmacovigilance centres to conduct formal causality assessment is limited, but where such capacity exists it should be used.

NTP staff need to acquire the skills to undertake essential activities related to aDSM. This is a long-term goal but needs to be started as part of the plan to introduce new anti-TB drugs and novel MDR-TB regimens. To carry out such capacity-building, the NTP should seek local or international expertise in causality assessment; WHO is also working with partners to accelerate these efforts.

The implementation of aDSM at the NTP level will be greatly facilitated by familiarity with the concept of cohort-based follow-up of patients, which is the foundation for the monitoring and evaluation of TB and MDR-TB treatment programmes. The testing schedules used in these projects have largely followed those generally recommended when second-line TB drugs are used.

Experience from observational studies of shorter regimens for MDR-TB has shown that active drug-safety monitoring can be implemented within programmes if dedicated funding is provided. Most of the additional resources are needed to undertake clinical testing (e.g. electrocardiography and audiometry) and laboratory analyses, and to collect drug-safety data.

Once the right skills have been acquired and links have been established with appropriate experts in drug safety, it is envisaged that causality assessment and signal detection could be organized within the PMDT programme, with appropriate capacity-building and support from drug-safety experts (if such capacity is missing at the national pharmacovigilance system). More work is needed to quantify the costs of aDSM, and these will eventually be reflected in the tools that will be provided to help users with budgeting.

Clinicians treating patients with second-line anti-TB drugs are usually familiar with clinical monitoring for AEs; however, this knowledge may not be available to many other health care workers within the programme. The monitoring component of aDSM is also likely to be novel to many health care workers. WHO/GTB and technical partners will be supporting NTPs to build such capacity and to integrate aDSM into routine PMDT monitoring.

Table A3.1. Programmatic indicators for aDSM

Class	Importance	Indicator number and name	Calculation	Stratification	Expressed as	Data sources	Level	Period of assessment	Notes
Coverage (process)	Essential	1) Target MDR/RR-TB patients included in cohort event monitoring	Numerator: Number of TB cases started on target treatment included in aDSM during the period of assessment Denominator: Number of TB cases started on target treatment during the period of assessment and eligible for aDSM	None	Absolute numbers, proportion	Numerator: aDSM register Denominator: Second-line TB treatment register	National; NTP and NPV	3 months	To be computed during the period of recruitment but not in the post-treatment observation phase
Completeness (process)	Optional	2) Time to stopping target drug	The difference in days between the date of start of treatment with a target drug and the date of stopping the target drug; the calculation is done for each member of the cohort	Reason for stopping	Number of patients included in the calculation; median interval and IQR in days	aDSM register	National; NTP and NPV	12 months	Stratify by reason for stopping (e.g. success, died, treatment failed, loss to follow-up, exclusion criterion developing after start of treatment such as pregnancy)
SAE	Essential (but stratification optional)	3) MDR/ RR-TB patients included in aDSM with any SAE	Numerator: Number of TB cases included in aDSM during the period of assessment with one or more SAEs Denominator: Number of TB cases included in aDSM during the period of assessment	By organ group; by outcome	Absolute numbers, proportion	Numerator: aDSM register Denominator: aDSM register	NTP and NPV	3 months	To be computed during the period of patient recruitment and during the post-treatment observation phase Indicate outcome (deaths, hospitalizations or disability)

Class	Importance	Indicator number and name	Calculation	Stratification	Expressed as	Data sources	Level	Period of assessment	Notes
ADRs associated with target treatment	Optional	4) Frequency of ADRs associated with target treatment	Numerator: Number of ADRs attributed to target treatment among patients on aDSM Denominator: Number of TB cases included in aDSM during the period of assessment	By organ group; by seriousness or severity	Absolute numbers, proportion	aDSM register	NTP and NPV	3 months	To be computed during the period of patient recruitment and during the post-treatment observation phase Only to be reported after causality assessment (e.g. dechallenge and rechallenge) suggests target treatment as the causative agent (certain, probable or possible) The same patient may have several ADRs (therefore, the unit of measurement is the ADR and not the number of patients)
ADRs associated with target treatment	Optional	5) Time to development of ADRs associated with target treatment	The difference in days between the date of start of the target treatment and the date of the first detected onset of the ADR attributed to it	By organ group	Number of ADRs included in the calculation; median interval and IQR in days	aDSM register	aDSM centre	6 months	To be computed during the period of patient recruitment and during the post-treatment observation phase The calculation is done for each reaction attributed to the target treatment; the same patient may have several ADRs computed (the unit of measurement is the ADR and not the number of patient); if a particular ADR recurs in the same patient during the aDSM it is not calculated again Only to be reported after causality assessment (e.g. dechallenge and rechallenge) suggests target treatment as the causative agent (certain, probable or possible)

ADR: adverse drug reaction; aDSM: active TB drug-safety monitoring and management; IQR: interquartile range; MDR/RR-TB: multidrug-resistant or rifampicin-resistant TB; NPV: national pharmacovigilance centre; NTP: national TB programme; SAE: serious adverse event; TB: tuberculosis.

Adapted from WHO (2014) *(7)*.

Table A3.2. Elements for a summary profile of drug safety or toxicity

Dimension	Additional notes
The benefit: toxicity profile of the baseline MDR-TB regimen	The MDR-TB regimen, which constitutes the most widely used standard of care, is described in terms of its effectiveness and associated harms; this dimension of the profile uses information originating from the published literature; trials (unpublished or published); observational studies and cohorts (including nested case–controls); prospective aDSM data; and other pharmacovigilance findings based on spontaneous reporting
Safety concerns associated with a specific drug or regimen	The characteristics (organ class), risk, severity, drug–drug interactions and other safety concerns are summarized from the literature as well as local data (including aDSM)
Quantifying risk and benefit	As far as possible, the safety concerns are also expressed in terms of risk (e.g. per 100 or 1000 exposures and as relative risk); the effectiveness is generally expressed in terms of % successful outcome or cure
Risk factors	These include host-related predispositions to harms, such as comorbidities, severity of TB disease, drug–drug interactions or subpopulations (e.g. age group and sex); these could form the basis of contraindications or caution in use of the regimen or drug
Signal detection	The procedure followed for relationship and causality assessments and detection of signals in the cohort is explained, and any departures from agreed methodologies are described; signal detection is attempted both at country and supranational levels; any preliminary signals are discussed with the regulators and manufacturer before widespread communication
Preventive measures	Advice on avoidance of harm or toxicity, precautions and contraindications

aDSM: active TB drug-safety monitoring and management; MDR-TB: multidrug-resistant TB; TB: tuberculosis.

Adapted from the *Draft framework for the harmonized and standardized summarization of both added benefit and risk associated with an intervention (7).*

Appendix 1. List of contributors to the development of the aDSM framework

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Appendix 2. Adverse events of clinical significance or special interest for aDSM

See Section A3.2 (Definitions used in aDSM) for the definitions of types of adverse events (AEs) mentioned in this appendix. AEs of clinical significance or special interest for active TB drug-safety monitoring and management (aDSM) are as follows:[4]

1) All serious adverse events (SAEs).

2) All AEs of special interest (suggested list):[5]

- peripheral neuropathy (paraesthesia);
- psychiatric disorders and central nervous system toxicity (e.g. depression, psychosis, suicidal intention and seizures);
- optic nerve disorder (optic neuritis) or retinopathy;
- ototoxicity (hearing impairment and hearing loss);
- myelosuppression (manifested as anaemia, thrombocytopenia, neutropenia or leukopenia);
- prolonged QT interval (Fridericia correction; see *(7)*);
- lactic acidosis;
- hepatitis (defined as increases in alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥5× the upper limit of normal [ULN], or increases in ALT or AST ≥3× ULN with clinical manifestations, or increases in ALT or AST ≥3× ULN with concomitant increase in bilirubin ≥1.5× ULN);
- hypothyroidism;
- hypokalaemia;
- pancreatitis;
- phospholipidosis; and
- acute kidney injury (acute renal failure).

3) AEs leading to treatment discontinuation or change in drug dosage.

4) AEs not listed above but judged as otherwise clinically significant by the clinician.

[4] List adapted from *Pharmacovigilance guideline for endTB projects outside interventional clinical trial, version 0.7 (8).*

[5] The list shown here is provisional; it may be modified according to the composition of the regimen or the patient cohort.

Appendix 3. Alert for serious adverse events to the TB programme *(Example)*

Confidential – to be sent even when there is suspicion of a serious adverse event (SAE).

Is this report a new event?	Yes	No	Give date when previous SAE form was sent: (DD/MMM/YYYY)

1. Patient details

Surname _____ First name _____

Sex	Male	Female	Date of birth	☐☐ DD	☐☐☐ MMM	☐☐☐☐ YYYY

Age in years if DOB unknown

Pregnancy	No	Yes

ID number _____ Phone no. _____

Address _____

_____

_____

2. Suspected and concomitant medicine(s)

Name (generic name)	Total daily dose	Date started	Date stopped	Continues
				❑
				❑
				❑
				❑
				❑

3. Details of SAE

Date event started		Date event stopped	
Description of event			
Why is the event considered serious?	❑ Death ❑ Life-threatening event (specify……) ❑ Hospitalization or prolongation of hospitalization ❑ Persistent or significant disability (specify……) ❑ Congenital anomaly ❑ Other (specify……)		

4. Action taken

- ❑ Medicine withdrawn
- ❑ Dose increased
- ❑ Dose reduced
- ❑ Dose not changed
- ❑ Unknown

5. Outcome of SAE

- ❑ Recovered / resolved
- ❑ Recovering / resolving
- ❑ Recovered with sequelae
- ❑ Not recovered / not resolved
- ❑ Died
- ❑ Unknown

6. Reporter

Name		Position			
Facility or clinic address					
Email		Phone no.			
Signature		Date sent	☐☐ DD	☐☐☐ MMM	☐☐☐☐ YYYY

Explanatory note – to be adapted according to the local situation:

- This form is intended for the core package of active tuberculosis (TB) drug-safety monitoring and management (aDSM). For more details, please refer to other documents on aDSM. The spontaneous reporting form in use by the national pharmacovigilance authorities may be adapted for the purposes of alerting the TB programme of SAEs and avoiding parallel reporting structures.
- The completed form can be sent electronically, via email or fax to <address> and the responsible authority alerted by phone.
- The report should be sent within <number> hours after it is detected, even when there is a suspicion of seriousness.
- The report should be sent even when not all details are available and the association with any particular medicine is uncertain. The essential details are the identifiers of the patient and the reporter; the name of the suspected medicine(s); and basic details on the SAE.
- If the report relates to a previously notified event, indicate this under Section 3 of the form; if more than one SAE occurs in the same individual, send separate forms for each event.
- All health care professionals are encouraged to report; patients and relatives may also report.
- Upon receipt of the information, the responsible authority will review the information and contact the reporter or the facility (or both) for more details. All information, including the identity of the patient and reporter, must be handled in strict confidence. Apart from action to protect public health, anonymized statistics from these reports will be used to improve drug safety.
- When reporting, use the format DD/MMM/YYYY to report dates. Under "Description of event" in Section 3 of the form, provide a single diagnosis and include anatomical location if applicable. If the diagnosis is unknown, describe the clinical picture.

References for Web Annex 3

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8 Pharmacovigilance guideline for endTB Projects outside Interventional Clinical Trial. version 0.7. UNITAID, Partners in Health, Médecins sans Frontières, Interactive Research & Development; 2015.

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