# Standard Operating Procedures for Management of Specific Adverse Events

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| **SOP Number**: SP-018-CT | **Effective Date**: 21-Jun-2023 |
| **Version Number and Date**: 3.2 Date 20-Jun-2023 | |

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# Standard Operating Procedures for Management of Specific Adverse Events

## PURPOSE

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| This standard operating procedure (SOP) is a guideline for the clinical management of the clinical management of specific adverse events during treatment. |

## SCOPE

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| --- |
| This SOP is developed for trained healthcare workers who are managing the treatment of participants of the endTB clinical trials. |

## RESPONSIBLE FUNCTIONS

|  |  |
| --- | --- |
| **Function** | **Activities** |
| **Site Principal Investigator (Site PI)** | * Supports the delegated site Co Investigator in managing the AE and ensure that adverse events are managed and recorded according to the study protocol * Communicates with the Clinical Advisory Committee for difficult or doubtful cases |
| **Site Principal Investigator (Site PI) and/or delegated Site Co Investigator (Site CI)** | * Makes the diagnosis of an adverse event (AE) and assesses its severity and the relation * Grades the AE according to the MSF severity grading scale * Manages the specific AE * Records the AE, its grading, its evolution and outcome in the source documents * Records the possible treatment changes and ancillary treatment in the source documents * Immediately reports (within 24 hours of awareness) any SAE to the pharmacovigilance (PV) unit and local authorities as per requirements (see PV-TB-D22 Safety reporting guideline) |
| **Clinical Advisory Committee (CAC)** | * Provides advice regarding doubtful cases to clinical staff using the SOP for communication with the CAC |

## DEFINITIONS and ABBREVIATIONS

**Acute kidney injury:** Acute kidney injury is characterized by the acute loss of renal function.

**Adverse event (AE):** An AE is any untoward medical occurrence in a patient or clinical investigation subject after administration of an investigational drug. It does not necessarily have a causal relationship with the study treatment.

**Allergic reaction:** A disorder characterized by an adverse local or general response from exposure to an allergen. Worst stage 'anaphylaxis' is characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.

**Arrhythmia:** An arrhythmia is an irregularity in the rate or rhythm of the heartbeat. It means the heart beats too quickly, too slowly, or with an irregular pattern. It is identified by an abnormal ECG, with or without accompanying signs and symptoms.

**Clinical Advisory Committee (CAC):** The CAC is composed of both internal and external clinical experts representing various disciplines and specialties. It serves as an advisory body to endTB site investigators by providing consultation regarding subject eligibility, case management, medical monitoring, and permanent treatment discontinuation.

**Deep venous thrombosis (DVT):** A disorder characterized by acute or chronic thrombus (blood clot) formation in deep veins anywhere in the body.

**Hearing impairment:** Hearing impairment is a disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures.

**Hepatitis:** Hepatitis is characterized by the elevation of liver function tests, with or without accompanying signs and symptoms of hepatic impairment.

**Hypocalcemia:** A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.

**Hypokalemia:** Hypokalemia is defined by blood potassium levels below 3.4 mEq/L, with or without accompanying signs and symptoms.

**Hypomagnesemia**: A disorder characterized by laboratory test results that indicate a low concentration of magnesium in the blood.

**Hypothyroidism**: Hypothyroidism is diagnosed by the presence of signs or symptoms associated with the deficit of thyroid hormones, or by serum level of TSH greater than 10.0 mU/L.

**International normalized ratio (INR):** A measure of blood coagulation potential (specifically, the extrinsic pathway of coagulation) used to titrate dosing of warfarin.

**Myelosuppression:** Myelosuppression is defined by any of the following: anemia, thrombocytopenia, or neutropenia.

**Optic neuritis**: Optic neuritis defines the inflammation of the optic nerve eventually resulting in permanent vision loss.

**Partial thromboplastin time (PTT):** A measure of blood coagulation potential (specifically, the intrinsic pathway of coagulation) used to titrate dosing of heparin IV drip.

**Peripheral neuropathy:** Peripheral neuropathy defines the impairment of the nerves of the peripheral nervous system.

**Pulmonary embolism (PE):** A disorder characterized by embolization of thrombus (blood clot) from the right heart circulation into either or both pulmonary arteries, potentially leading to distal pulmonary infarction, acute hypoxia, right heart failure, arrhythmia, or sudden death.

**QT interval prolongation:** QT interval prolongation is defined by increased values of the corrected QT interval. QT interval is corrected according to the Fridericia formula.

**Severity of AE:** The severity of any AE is classified from Grade 1 (mild) to Grade 4 (life-threatening) according to MSF severity grading scale.

## PROCEDURE

### AE diagnosis and severity assessment

Site PI or Site CI, according to their clinical judgement, test results, and available guidance (see Supporting Documents):

* Establishes the diagnosis of a specific AE;
* Defines the severity of the AE as described in the SOP PV-001-CT Safety data collection and reporting at trial

### Management of the specific AE

Material:

* Source documents (including any AE log/worksheet used at site level)
* MSF severity grading scale
* Case report form
* Reference guidelines

#### Management of peripheral neuropathy

***Suspected anti-TB drugs (from most likely to less likely responsible):* Lzd, H, Cs/Trd, Km, Cm, FQ, Pto/Eto, E**

**Possible other causes: d4T, ddI**

***Site PI or Site CI*** manages this AE according to its severity ***(see SOP SP-002-ET on Brief Peripheral Neuropathy Screening).*** According to the MSF severity grading scale, peripheral neuropathycan lead to two different AEs: paresthesia and neuro-sensory disorders.The clinical management is based on the severity of paresthesia. Neuro-sensory disorders should be declared as AEs but should not be taken into account for the clinical management of the patient.

* **Grade 1:** continue the current treatment and see the patient back in a week. If the AE is resolved, continue the current treatment. If the AE is still present, stop high-dose isoniazid, cycloserine/terizidone, and linezolid, if currently administered. If symptoms improve, consider restarting these drugs. Consider restarting linezolid at a lower dose; the reduced dose of linezolid is defined by balanced randomization for linezolid-containing experimental arms. If cycloserine/terizidone or high-dose isoniazid are not essential to the regimen, consider suspending these drugs.
* **Grade 2:** If currently administered, stop high-dose isoniazid, cycloserine/terizidone, and linezolid.
* For cycloserine/terizidone or high-dose isoniazid: If symptoms resolve, consider restarting high-dose isoniazid, and cycloserine/terizidone. If these drugs are not essential to the regimen, consider suspending them. If they are essential, consider replacing them with a different agent.
* For linezolid: if symptoms resolve or improve (i.e. symptoms return to Grade 1), consider restarting linezolid at lower dose. If moderate discomfort persists, consider permanently stopping linezolid.
* **Grade 3:** If currently administered, stop high-dose isoniazid, cycloserine/terizidone, and linezolid. If symptoms resolve, consider restarting high-dose isoniazid and cycloserine/terizidone. Linezolid should not be restarted. If cycloserine/terizidone or high-dose isoniazid are not essential to the regimen, consider suspending these drugs.
* **Grade 4:** If currently administered, permanently stop high-dose isoniazid, cycloserine/terizidone and linezolid, and add additional anti-TB drugs to reinforce the regimen.

In all patients experiencing peripheral neuropathy:

* provide pyridoxine treatment at 100 to 200 mg/day until symptoms resolve;
* check if the patient receives other drugs that may increase the risk of peripheral neuropathies (e.g. d4T, ddI, or isoniazid) and if it is the case stop the drug(s) if possible;
* provide symptomatic relief if needed: non-steroidal anti-inflammatory drugs, acetaminophen, tricyclic antidepressants, and carbamazepine may be used according to efficacy and drug-drug interactions at the discretion of the clinician;
* All patients taking linezolid should receive at least 50 mg of pyridoxine daily;
* All patients taking isoniazid should receive 50 mg of pyridoxine daily;
* All patients taking cycloserine/terizidone should receive 50 mg of pyridoxine daily for every 250 mg of cycloserine/terizidone;
* All patients taking ethionamide/prothionamide should receive 50 mg of pyridoxine daily.

#### Management of myelosuppression

***Suspected anti-TB drug:* Lzd**

**Possible other causes: AZT, co-trimoxazole**

***Site PI or Site CI*** manages this AE according to its severity:

* **Grade 1 (anemia, neutropenia, leukopenia and/or thrombocytopenia):** Monitor carefully (full blood count [FBC] every week).
* **Grade 2:** 
  + **Anemia, leukopenia and/or thrombocytopenia:** Monitor carefully (FBC every week) and consider reducing the linezolid dose without interruption.
  + **Neutropenia:** Stop linezolid immediately, monitor FBC on a weekly basis. Restart at reduced dose once toxicity has decreased to Grade 1.
  + The dose reduction strategy is defined by balanced randomization for linezolid-containing experimental arms.
* **Grade 3:** 
  + Stop linezolid immediately and any other potential myelosuppressive drugs, monitor FBC twice weekly.
  + In case of anemia, consider erythropoietin (EPO) administration.
  + Restart linezolid at reduced dose once toxicity has decreased to Grade 1.
  + The dose reduction strategy is defined by balanced randomization for linezolid-containing experimental arms.
* **Grade 4:** 
  + Stop linezolid immediately and any other potential myelosuppressive drugs, monitor FBC twice weekly.
  + Consider hospitalization and, in case of anemia erythropoietin (EPO) administration and blood transfusion according to patient’s conditions and the dynamics of the myelosuppression.
  + Restart linezolid at reduced dose once toxicity has decreased to Grade 1 or less.
  + The dose reduction strategy is defined by balanced randomization for linezolid-containing experimental arms.

In all patients experiencing myelosuppression:

* check if the patient receives other drugs that may increase the risk of myelosuppression (e.g. zidovudine and cotrimoxazole) and if this is the case stop the drug(s) if possible; zidovudine can be replaced by tenofovir or abacavir (if HLA\*B5701 negative), and cotrimoxazole by dapsone;
* rule out or treat any other causes of anemia;
* all patients taking linezolid should also be receiving at least 50 mg of pyridoxine daily to prevent peripheral neuropathy.

#### Management of QT interval prolongation and/or arrhythmia

***Suspected anti-TB drugs (from most likely to less likely responsible):* Mfx, Cfz, Bdq, Dlm, Lfx**

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

Also see sections 5.2.8, 5.2.10 and 5.2.11 for QT prolongation related to hypokalemia, hypocalcemia and hypothyroidism, respectively.

**Signs and symptoms of serious arrhythmia:** The definition for a Grade 4 adverse event associated with QT prolongation includes “signs/symptoms” of serious arrhythmia (see ***SOP SP-008-CT*** on ***ECG Reading*** for QT measurement). Listed below are signs and symptoms that are concerning for serious arrhythmia:

* Shock, hypotension, shortness of breath, chest pain, and/or decreased level of consciousness.
* Unexplained sudden syncope without prodrome.
* Recurrent episodes of palpitations associated with lightheadedness or syncope (excluding patients with confirmed sinus tachycardia while symptomatic, as these patients are more likely to have an alternative contributing cause of rapid heart rate).

The presence of any of these signs or symptoms should trigger an ECG and check of electrolytes, in, addition to other diagnostic workup as needed.

***Site PI*** *or* ***Site CI*** manages this AE according to its severity ***(See SOP SP-008-CT*** on ***ECG Reading*** for QT Measurement***)***:

* **Grade 1:** Monitor closely; perform ECG and electrolyte blood tests (potassium, calcium, magnesium, and albumin) at least weekly, repleting electrolytes as needed, until QT interval has returned to less than Grade 1.
* **Grade 2:** Monitor closely; perform ECG and electrolyte blood tests (potassium, calcium, magnesium, and albumin) at least twice weekly, repleting electrolytes as needed, until QT interval has returned to Grade 1 or less.
* **Grade 3 and 4:**
  + Stop the suspected causative drug(s). Hospitalize if necessary.
  + Perform ECG and electrolyte blood tests (potassium, calcium, magnesium, and albumin) at least twice weekly, repleting electrolytes and hospitalizing as needed, until QT interval has returned to Grade 1 or less.
  + If there are non-anti-TB medications which may contribute to prolonging the QT interval, then stop the non-anti-TB QT-prolonging medications.
  + Once the QT interval has returned to Grade 2 or less, critical QT prolonging anti-TB drugs can be added back:
* If the patient was on moxifloxacin, consider using levofloxacin instead.
* If the patient is on bedaquiline, clofazimine, or delamanid, and it is considered critical to the regimen, consider adding the drug back to the patient’s regimen while suspending all other QT prolonging drugs.

In all patients experiencing QT prolongation, electrolyte blood tests (potassium, calcium, magnesium, and albumin) should be measured (see management of hypokalemia, hypocalcemia, hypomagnesemia in sections 5.2.8-10 below) and repeated as necessary. All other drugs (non TB drugs) that are known to prolong the QT should be stopped if feasible.

#### Management of optic neuritis

***Suspected anti-TB drugs (from most likely to less likely responsible):* Lzd, E, Eto/Pto, Cfz, Rifabutin, H**

**Possible other causes: ddI**

***Site PI or Site CI*** manages this AE according to its severity (**see SOP SP-003-CT for acuity visual screening**):

* **Grade 1 to 4:** If currently administered, stop linezolid and/or ethambutol immediately if there are any suspicions of optic neuritis. Do not restart it.

#### Management of hepatitis

***Suspected anti-TB drugs (from most likely to less likely responsible):* Z, H, Bdq, Eto/Pto, PAS, Mfx, Lfx, Amx/Clv, Cfz, Lzd.**

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

***Site PI or Site CI*** manage this AE according to its severity using clinical presentation and liver function tests (AST, ALT and bilirubin):

* **Grade 1:** Continue treatment regimen.
* **Grade 2 :**
  + Without symptoms: continue same treatment with weekly monitoring of liver function test until resolution (return to baseline) or stabilization to Grade 1 or less.
  + With symptoms: discontinue potentially responsible anti-tuberculosis drugs and monitor liver enzymes and INR weekly.
* **Grade 3 and 4:** Stop all drugs, including anti-tuberculosis drugs; measure liver enzymes and INR weekly (or more frequently, if clinically indicated).

In all patients experiencing hepatitis, review the concomitant treatment the patient is receiving and stop any other hepatotoxic non-tuberculosis drug. Systematically look for another cause (viral hepatitis, biliary or hepatic disease, hepatitis flush due to TB IRIS). Request further laboratory tests (alkaline phosphatase) and abdominal ultrasound, especially in patients with increase of bilirubin or AST and systematically in patients with Grade 4 hepatitis.

**Reintroduction of anti-TB drugs:**

* Reintroduce anti-TB drugs once liver enzymes return to baseline or at least lower than 2xULN. Anti-TB drugs should be reintroduced in serial fashion by adding a new medicine every three to four days. The least hepatotoxic drugs should be added first, while monitoring liver function tests after each new exposure.
* Consider suspending the most likely offending drug permanently if it is not essential to the regimen. This is often the case for pyrazinamide if it is less likely to be effective by clinical history. Consider additional anti-TB drugs to reinforce the regimen.

#### Management of hearing impairment

***Suspected anti-TB drugs (from most likely to less likely responsible):* Km, Am, Cm**

***Site PI or Site CI*** manages this AE according to its severity (see **SOP SP-007-ET for audiometry screening**):

* **Grade 1:** 
  + Initiate discussion with patient about risks and benefits of the injectable.
  + Consider decreasing injectable frequency (e.g. three times per week).
  + Consider replacing the injectable with a non-ototoxic TB drug.
  + Perform audiometry every 2 weeks.
* **Grade 2:** 
  + Initiate discussion with patient about risks and benefits of the injectable.
  + Consider decreasing injectable frequency (e.g. three times per week), or replacing injectable agent with a non-ototoxic TB drug.
  + Perform audiometry every week until improvement or stabilization.
* **Grade 3:** 
  + Stop the injectable and replace with a non-ototoxic TB drug.
  + Perform audiometry every week until improvement or stabilization.
* **Grade 4:** 
  + Stop the injectable and replace with a non-ototoxic TB drug.
  + Perform audiometry every week until improvement or stabilization.
  + In cases of complete hearing loss, some clinicians will continue the injectable as the hearing loss is irreversible. Consider suspension of the injectable if some hearing might be still preserved or if it is causing other reversible symptoms such as tinnitus or vestibular disturbances.

In all patients, check that the patient does not receive any concomitant drug that could increase the risk of AE (e.g., furosemide) and stop this drug if possible.

#### Management of acute kidney injury

***Suspected anti-TB drugs (from most likely to less likely responsible):* Km, Am, Cm.**

**Possible other cause: TDF**

***Site PI or Site CI*** manages this AE according to its severity:

* Review the concomitant treatment the patient is receiving and stop any other nephrotoxic non-tuberculosis drugs.
* **Grade 1-3:** If currently administered, stop the injectable, follow creatinine and electrolytes weekly until Grade <2
  + - If Grade decreases to 1 or below within 2 weeks:
      * Consider restarting the injectable at lower frequency if the drug is essential to the regimen (e.g. three times per week); otherwise, consider the permanent suspension of the injectable and the addition of a non-nephrotoxic anti-TB drug to reinforce the regimen.
* Adjust the dose of other renally excreted drugs according to the creatinine clearance (Appendix 1).
  + If Grade remains >1 after 2 weeks of interruption or if nephrotoxicity recurs after re-introduction of the injectable:
  + Consider permanent suspension of the injectable and the addition of a non-nephrotoxic anti-TB drug to reinforce the regimen.
  + Adjust the dose of other renally excreted drugs according to the creatinine clearance (Appendix 1).
* **Grade 4:** 
  + If currently administered, stop the injectable.
  + Follow creatinine and electrolytes weekly until Grade <2.
  + Adjust the dose of other renally excreted drugs according to the creatinine clearance (Appendix 1).
  + Permanently stop the injectable and add a non-nephrotoxic anti-TB drug to reinforce the regimen.

#### Management of hypokalemia

***Suspected anti-TB drugs (from most likely to less likely responsible):* Cm, Km, Am.**

**Possible other cause: TDF**

***Site PI or Site CI*** manages this AE according to its severity:

* **Grade 1 (3.4-3.0 mmol/L):** Continue injectable. Start oral potassium replacement therapy. Check serum magnesium and calcium, and replace if necessary.
* **Grade 2 (2.9-2.5 mmol/L):** Continue injectable. Start aggressive oral potassium replacement therapy. Check serum magnesium and calcium, and replace if necessary.
* **Grade 3 (2.4-2.0 mmol/L):** Consider stopping injectable temporarily. Start intravenous potassium replacement therapy in addition to oral. Check serum magnesium and calcium, and replace if necessary.
* **Grade 4 (<2.0 mmol/L):** Stop injectable temporarily. Start intravenous potassium replacement therapy in addition to oral. Check serum magnesium and calcium, and replace if necessary.

**In all cases of detected hypokalemia (Grade 1-4) obtain an ECG as soon as possible and then weekly until potassium and other electrolytes return to normal.**

***Potassium replacement therapy***

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

*Note:*

1. Potassium chloride controlled release tablets of 600mg = 8mmol/tablet

2. Potassium chloride 10% (100mg/ml) ampoules= 1g per ampoule = 13.4 mmol

3. The normal preparation of a potassium chloride infusion is 40 mmol (3 ampoules) in 1L of NaCl 0.9% infused over 4 hours. Do not exceed an infusion rate of 10 mmol/hour (250 mL/hour).

#### Management of Hypomagnesemia

***Site PI or Site CI*** manages this AE according to its severity:

* **Grade 1 (0.60-0.70 mmol/L):** Start oral magnesium replacement therapy.
* **Grade 2 (0.45-0.59 mmol/L):** Start aggressive oral magnesium replacement therapy.
* **Grade 3 (0.30-0.44 mmol/L) and 4 (<0.30 mmol/L):** Start intravenous magnesium replacement therapy in addition to oral. Replace other electrolytes as necessary.

***Magnesium replacement therapy***

| **Magnesium level (mmol/L)** | **Total daily dose of magnesium oxide, mg (dose of elemental Mg, mEq)** | **Monitoring frequency** |
| --- | --- | --- |
| >0.7.0 or more | None | Monthly |
| 0.60-0.70 | 800-1,200 mg (40-60 mEq) | Monthly |
| 0.45-0.59 | 1600-2,000 mg (80-100 mEq) | One to seven days |
| < 0.45 | 3,000 mg-6,000 mg (150-300 mEq) | Daily |
| *Note:* The dose for replacement therapy expressed in mg is applicable to the use of magnesium oxide only. If other preparations are used, the reference should be the dose of elemental magnesium, expressed in mEq. If available, sustained-release preparations should be used for oral administration to prevent diarrhea. Quantities greater than 2,000 mg (100 mEq) are usually given IV or IM. The normal preparation is magnesium sulfate 2 grams in 100 mL or 4 grams in 250 mL of normal saline. Do not exceed an infusion rate of 150 mg/min (Suggested infusion rates: 2 grams in 100 mL administered over one to two hours, 4 grams in 250 mL administered over two to four hours). | | |

#### Management of hypocalcemia

**Possible anti-TB drug: Km, Am.**

***Site PI or Site CI*** manages this AE according to its severity. Both albumin-corrected or uncorrected levels of Total calcium can be used to guide the clinical management, as follows:

* **All grades:** In the AE log, please indicate in the AE term whether the classification is due to albumin- corrected or uncorrected levels of total calcium.
* **Grade 1 (1.95-2.10 mmol/L):** Start oral calcium replacement therapy. Check serum magnesium and potassium, and replace if necessary. Check and monitor ECG every 2 weeks.
* **Grade 2 (1.75-1.94 mmol/L):** Start oral calcium replacement therapy. Check serum magnesium and potassium, and replace if necessary. Check and monitor ECG every 2 weeks.
* **Grade 3 (1.52-1.74 mmol/L) and 4 (<1.52 mmol/L):** Intravenous calcium replacement. Check serum magnesium and potassium, and replace if necessary Monitor ECG daily. Drugs that prolong the QT interval should be discontinued in patients with evidence of QT interval prolongation. Stop injectable temporarily.

**Calcium replacement therapy**

| **Total calcium level (corrected or uncorrected according to albumin levels)** (mmol/L) | **Dosing** | **Monitoring frequency** |
| --- | --- | --- |
| >2.10 | None | Monthly |
| 1.95-2.10 | 500 mg PO three times a day | 2 weeks |
| 1.75-1.94 | 1000 mg three times PO a day | One to 2 weeks |
| <1.75 | One 10 ml ampoule of 10% calcium gluconate diluted in 100 ml of normal saline 0,9% and infused slowly over 10 minutes. Can be repeated if required. Oral calcium supplements should be given concurrently. | Daily |

*Note:*

1. If albumin dosing has been performed, this formula can be used to correct total values of calcium:  
**Corrected total calcium = 0.8 x (4.0 – measured albumin) + uncorrected total calcium**

2. The half-life of albumin in serum is approximately 20 days. In the setting of hypocalcemia, it is preferable to recheck serum albumin (if possible) to correct the value of total calcium using the formula above if the serum albumin has not been checked in the previous 3-4 weeks.

3. If ionized calcium is being tested, it does not need to be corrected for low albumin and its normal value is 1.11–1.30 mmol/L.

#### Management of hypothyroidism

***Suspected anti-TB drugs:* Eto/Pto, PAS**

***Site PI or Site CI*** manages this AE according to its severity:

* **Grade 1:** Continue anti-tuberculosis drugs.
* **Grade 2-3:** Continue anti- tuberculosis drugs. Start treatment with thyroxine.
* **Grade 4:** Stop all anti-TB drugs. Start treatment with thyroxine. Restart anti-TB drugs when severity decreased to grade 3.

**In all cases of detected hypothyroidism (Grade 1-4) obtain an ECG as soon as possible and if normal continue ECG monitoring as defined in the protocol, if abnormal obtain a cardiac consultation for guidance on management.**

Independent of the presence of clinical signs or symptoms of hypothyroidism, treatment with thyroxine should be considered whenever serum level of TSH greater than 10.0 mU/L is recorded:

* Most adults will require 100 to 150 mcg of levothyroxine daily.
  + Young adults can be started on 75 to 100 mcg daily.
  + Older patients should begin treatment with 50 mcg daily.
* Monitor TSH at least every month and increase dose by 25 to 50 mcg until TSH is in normal range. Adjust dose more slowly in the elderly and patients with cardiac conditions.
* Hypothyroidism is reversible upon discontinuation of ethionamide/prothionamide or PAS. As a result, thyroid hormone replacement may be stopped several months after completion of MDR-TB treatment

#### Management of allergic reaction

***Possible cause: all anti-TB drugs, NNRTI antiretrovirals (ie. efavirenz, nevirapine), cotrimoxazole***

***Site PI or Site CI*** manages this AE according to its severity:

* **Grade 1-2:**

In case of localized and mild skin rash:

* Rule out other possible causes not related to drugs (i.e., scabies, contact dermatitis due to an environmental allergen).
* If no obvious cause, stop all anti-TB drugs.
* Give an antihistamine PO up to 3 to 4 times daily.
* Try to determine which drug caused the reaction

Once the reaction has resolved, anti-TB drugs can be reinstated as a “challenge”– a partial dose – in the following order: H - Z - Eto/Pto – FQ - Cs - E - PAS - Cm and the aminoglycosides – Lzd – Dlm – Cfz – Bdq. Add the most likely culprit last in the challenge. If the most likely culprit drug is not essential, consider not re-introducing it in the challenge. If the rash recurs after resumption of an agent, then its discontinuation may be required and another agent should be substituted.

* **Grade 3-4:**
* Stop all anti-TB drugs
* In the case of anaphylaxis (grade 4), manage with standard emergency protocols, including the use of epinephrine (adrenaline).
* In the event of severe generalized rash, a parenteral corticosteroid (i.e., dexamethasone IM or IV: 2 to 4 mg 4 times daily) may be needed.
* Once the reaction has resolved, try to determine which drug caused the reaction: see re-challenge of anti-TB drugs below.

Any drug resulting in Stevens-Johnson syndrome or grade 3-4 reaction should never be re-introduced.

**Re-challenge of anti-TB drugs:**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug** | **Day 1** | | **Day 2** | **Day 3** |
| H | | 50 mg | Full dose | Full dose |
| Z | | 250 mg | 1000 mg | Full dose |
| Eto/Pto | | 125 mg | 250 mg | 500-750 mg |
| FQ | | 50 mg | 200-250 mg | Full dose |
| Cs | | 125 mg | 250 mg | 500-750 mg |
| E | | 100 mg | 500 mg | Full dose |
| PAS | | 1 gram | 4 grams | 6-8 grams |
| Cm | | 125 mg | 500 mg | Full dose |
| Km | | 125 mg | 500 mg | Full dose |
| Amk | | 125 mg | 500 mg | Full dose |
| Lzd | | 150 mg | 300 mg | Full dose |
| Dlm | | 50 mg once a day | 100 mg once a day | Full dose |
| Cfz | | Full dose | Full dose | Full dose |
| Bdq | | Full dose | Full dose | Full dose |

#### Management of DVT/PE

Please see Appendix 2 for additional information on the clinical manifestation, prevention, and diagnosis of DVT/PE.

**Treatment of DVT/PE:**

* The goal of treatment of DVT is to prevent PE. Patients generally should be hospitalized for treatment of DVT, especially during the first few days after initiating treatment. Prolonged hospitalization is not obligatory if the patient can be monitored carefully as an outpatient.
* Start **enoxaparin (LMWH) and warfarin** at the same time. If partial thromboplastin time (PTT) is available and can be checked quickly and reliably every 6 hours, then a **heparin IV drip** can be used instead of **enoxaparin**. Therapeutic doses of **enoxaparin** or **heparin IV drip** are shown below.

**Therapeutic dosing of intravenous heparin and subcutaneous enoxaparin for the *treatment* of DVT/PE**

|  |  |  |
| --- | --- | --- |
| **Agent** | **Route** | **Dose** |
| Enoxaparin  (low molecular weight heparin, LMWH) | Subcutaneous | 40 mg once daily (For GFR < 30, dose at 30 mg once daily;  Avoid in patients with hepatic impairment) |
| Heparin | Intravenous | Initial dose: 80 units/kg bolus, then start rate at 18 units/kg/hour  (Consider no bolus if at high risk of bleeding)  Subsequent dosing based on PTT q6hours\*:   * PTT <35: 80 units/kg bolus, increase rate by 4 units/kg/hour * PTT 35-59: 40 units/kg bolus, increase rate by 2 units/kg/hour * PTT 60-89: No change, at therapeutic range * PTT 90-100: Decrease infusion rate by 3 units/kg/hour * PTT >100: Hold infusion by 1 hour, decrease infusion rate by 4 units/kg/hour   \* Once PTT has been therapeutic at 60-89 on two consecutive PTT checks 6 hours apart, heparin dosing can be assumed to have reached steady state and the PTT can be checked once daily thereafter. |

* **Enoxaparin** or **heparin IV drip** should be continued until **warfarin** (as measured by the INR) is therapeutic per the schedule below. Adjust **warfarin** according to protocol. There are many similar protocols. If your hospital does not have one, you can use the tables below (adapted from UpToDate).

**Initial therapeutic dosing of oral warfarin for the *treatment* of DVT/PE (Week 1) targeting INR goal 2-3**

|  |  |  |
| --- | --- | --- |
| **Day of therapy** | **INR value** | **Total daily dose (mg)** |
| Day 1 | Not checked | 5 (2.5 for high sensitivity) |
| Day 2 | Not checked | 5 |
| Day 3 | < 1.5  1.5-1.9  2.0-3.0  > 3.0 | 10  5  2.5  0 |
| Day 4 | < 1.5  1.5-1.9  2.0-3.0  > 3.0 | 10  7.5  5  0 |
| Day 5 | < 2.0  2.0-3.0  > 3.0 | 10  5  0 |
| Day 6 | < 1.5  1.5-1.9  2.0-3.0  > 3.0 | 12.5  10  7.5  0 |

**Maintenance therapeutic dosing of oral warfarin for the *treatment* of DVT/PE targeting INR goal 2-3 (after Week 1)\***

|  |  |
| --- | --- |
| **INR value** | **Total daily dose (mg)** |
| ≤ 1.5 | Increase 15% per week |
| 1.51-1.99 | Increase 10% per week |
| 2.0-3.0 | No change |
| 3.01-4.0 | Decrease 10% per week |
| 4.01-4.99 | Hold one dose, restart with dose decreased by 10% per week |
| 5-8.99 | Hold until INR is 2 to 3, restart with dose decreased by 15% per week |

\* For example, a patient taking 35 mg of warfarin per week (5.0 mg daily seven days per week) with an INR of 1.6 would increase the total weekly dose by 10% (increase by 3.5 mg to 38.5 mg per week). The new total weekly dose could be distributed as 5 mg daily on five days of the week and 7 mg on the remaining two days (39 mg per week). Several alternate means of distributing the total weekly dose could also be used (e.g., 5 mg daily on five days of the week, 6 mg on one day, and 7.5 mg on one day [38.5 mg per week]). The INR would be rechecked 1 week after the dose change, per the table below.

**Frequency of INR monitoring for maintenance therapeutic dosing of warfarin**

|  |  |
| --- | --- |
| Every 3-5 days | If dose needed adjustment by 15%, if start/stop interacting medication, change in diet, change in activity level, or other change that could affect INR |
| Every 1 week | If dose needed adjustment by 10% |
| Every 4 weeks | If maintained on same stable dose < 6 months |
| Every 6-8 weeks | If maintained on same stable dose for at least 6 months |

* Total duration of **warfarin** should be at least three months.
* An I-STAT INR cartridge can be used in the outpatient setting to adjust **warfarin** dosing.
* If the patient is discharged to an outpatient clinic that does not have access to INR monitoring, then consider stopping **warfarin** and continuing therapeutic **enoxaparin**.
* Note: Some antibiotics, such as linezolid, levofloxacin, and moxifloxacin have been reported to enhance the anticoagulant effect of **warfarin**. The mechanisms for this interaction are not known. As a result, caution should be used in dosing **warfarin** for patients in the endTB trial, who may require lower typical doses than patients not on antibiotics.

Note: If the INR is supratherapeutic (INR > 5.0) but there is no bleeding, simply withhold warfarin for several days until the INR is within the correct range as per the table above. For INR > 10.0, a small dose of **Vitamin K** (2.5 mg once) may be administered. **Vitamin K** will reverse the INR quickly within 24 hours, and often it will take days to become therapeutic again. If a patient has been reversed and the INR is not rising, and there is no bleeding, consider restarting a **heparin IV drip** or **enoxaparin** until the INR is therapeutic as per the schedule above.

5.2.14 Management of depression and/or anxiety **Suspected anti-TB drugs: Cs**

***Site PI or Site CI*** manages this AE according to its severity:

**Grade 2 or higher (GAD-7 and/or PHQ-9 scale):** Alert counsellors and treatment supporters. Evaluate referral to a psychologist and/or psychiatrist. Repeat GAD-7 and PHQ-9 after four weeks (i.e. Week 4 visit for baseline depression/anxiety): in case of worsening, refer urgently to a psychologist and/or psychiatrist.

If the treatment includes Cs: reassess the risk/benefit balance and consider discontinuing/replacing the drug. Repeat GAD-7 and PHQ-9 monthly: in case of worsening, discontinue permanently Cs.

#### 5.2.15 Management of other adverse events

***Site PI or Site CI*** manages any other AE according to their clinical expertise and to available guidance (see references). The PIH Guide to Medical Management of Multidrug Resistant Tuberculosis, 2nd *edition* (2013) is available in English and Russian with a complete chapter on managing adverse events (the 1st edition, 2003 is available in Spanish).

### Management of complicated AE

**Site PI** will contact the **Clinical Advisory Committee (CAC)** to ask for advice regarding complicated and/or difficult to manage AE. The **CAC** will provide guidance about individual cases.

**Note**: As per ***SOP SP-024-CT*** ***Modus Operandi and Communication with the CAC,*** CAC has to be consulted before any permanent regimen change recommended in this SOP.

### Recording of AEs and AEs management

**Site PI** **or** **Site CI** will record each AE, possible study treatment changes and ancillary treatment, severity grade evolution and outcome in the source documents. The designated site staff will be in charge of capturing data in the case report form.

## REFERENCES

* World Health Organization. Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Geneva, Switzerland: World Health Organization; 2014

<http://apps.who.int/iris/bitstream/handle/10665/130918/9789241548809_eng.pdf;jsessionid=BBB62ABAA8E0E07C7B57DC06011742B2?sequence=1>

* endTB Clinical and Programmatic Guide for Patient Management with New TB Drugs. Version 4.0. January 2018. <http://endtb.org/guide>
* Médecins Sans Fronitères and Partners In Health. Tuberculosis: practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries. 2014 edition.

<http://refbooks.msf.org/msf_docs/en/tuberculosis/tuberculosis_en.pdf>

* Diagnosis and management of hypocalcaemia Mark S Cooper, Neil J L Gittoes.BMJ. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2413335/#!po=61.1111>

## SUPPORTING DOCUMENTS

* MSF severity grading scale (endTB Site Study Document)
* SOP PV-001-CT Safety data collection and reporting at trial sites (endTB Site Study Document)
* SOP SP-002-ET Brief Peripheral Neuropathy Screening (endTB Site Study Document)
* SOP SP-008-CT ECG Reading (endTB Site Study Document)
* SOPSP-024-CT *Modus Operandi* and Communication with the Clinical Advisory Committee (endTB Site Study Document)
* PV-TB-D22 Safety Reporting Guideline (endTB Site Study Document)
* SOP SP-003-ET Visual Acuity Screening (endTB Site Study Document)
* SOP SP-007-ET Audiometry Screening (endTB Site Study Document)

## APPENDIX

|  |  |
| --- | --- |
| **Number** | **Title** |
| A1 | SP-018-CT\_ A1- Adjustment of anti-TB drugs in renal insufficiency |
| A2 | SP-018-CT\_A2- Clinical manifestation, prevention and diagnosis of DVT/PE |