# Standard Operating Procedures for Management of Comorbidities

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# Standard Operating Procedures for Management of Comorbidities

## PURPOSE

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| This standard operating procedure (SOP) describes the management of co-morbidities in the endTB clinical trials. |

## SCOPE

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| This SOP applies to the activities at sites monitored by the endTB clinical trials for both the experimental and control arms. The specific co-morbidities covered in this SOP are:   * HIV disease * Diabetes * Cardiovascular disease * Psychiatric disorders including depression * Substance dependence * Seizure disorder * Hepatitis B and C * Renal insufficiency |

## RESPONSIBLE FUNCTIONS

|  |  |
| --- | --- |
| **Function** | **Activities** |
| **Site Principal Investigator (Site PI)** | * Advises the Site Co Investigator (Site CI) on the management of co-morbidities. |
| **Site Principal Investigator (Site PI) and/or delegated Site Co Investigator (Site CI)** | * Oversees that the management of co-morbidities is performed within the standard of medical care. |

## DEFINITIONS and ABBREVIATIONS

**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.

Abbreviations are provided in the text in Section 5 as they are introduced.

## PROCEDURE

### Management of HIV infection

HIV-coinfected patients represent a population with special risks, in particular the risk of interactions and shared toxicities between antiretrovirals and TB drugs. The use of lopinavir and ritonavir (a CYP3A4 inhibitor) was shown to increase the exposure to bedaquiline. The co-administration of these drugs will therefore be contraindicated. In addition, the use of efavirenz (a CYP3A4 inducer) in bedaquiline-containing arms will be disallowed. Table 1 summarizes the antiretroviral drugs that are allowed and disallowed.

**Table 1 – Antiretroviral therapy (ART) allowed and disallowed in the endTB Clinical Trials**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug Class** | **Name** | **Abbreviation** | **Use of ARV with TB drugs** |
| Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) | Efavirenz | EFV | Disallowed in bedaquiline arms |
| Nevirapine | NVP | Allowed |
| Rilpivirine | RPV | Allowed |
| Nucleoside Reverse Transcriptase Inhibitors (NRTIs) | Abacavir | ABC | Allowed |
| Didanosine | ddI | Allowed (avoid because of increased risk of neuropathy) |
| Zalcitabine | ddC | Allowed |
| Emtricitabine | FTC | Allowed |
| Lamivudine | 3TC | Allowed |
| Stavudine | D4T | Allowed (avoid because of increased risk of neuropathy) |
| Tenofovir | TDF | Allowed |
| Zidovudine | AZT | Allowed (avoid with linezolid) |
| Protease Inhibitors (PIs) | Atazanavir + ritonavir | (ATV/r) | Disallowed in bedaquiline arms |
| Darunavir + ritonavir | (DRV/r) |
| Lopinavir/ritonavir | (DRV/r) |
| Integrase strand transfer inhibitors (INSTIs) | Raltegravir  Dolutegravir | RAL  DTG | Allowed |

HIV must be managed closely throughout the MDR-TB treatment. The following is recommended:

* The physician managing the patient’s TB treatment should be in close communication with the physician or clinic that manages the patient’s HIV treatment.
* Antiretroviral therapy (ART) is recommended for all patients with HIV and MDR-TB. The initiation or continuation of ART should be prescribed according to WHO guidelines on the use of antiretroviral (ARV) drugs with the allowed HIV medicines described in this SOP (Table 1). Refer to the SOP ***SP-019-CT*** on ***Concomitant Medications*** for guidance.
  + If an HIV-positive patient is not on ART at the start of MDR-TB therapy, a regimen of allowed medications should be started shortly after start of the MDR-TB study regimen, as per WHO recommendations (see Reference 1, 2, and 3 below).
  + All patients on an ART regimen at the start of MDR-TB therapy should be assessed to evaluate if the regimen is working through a clinical evaluation, CD4 count, and measurement of the viral load (and HIV drug resistance testing, if indicated and available).
    - If the patient is on an ART regimen with allowed medications, continue the regimen.
    - If the patient is on an ART regimen with disallowed medications, evaluate if the patient can be safely changed to an ART regimen with allowed medicines. If this is possible, the patient is eligible for randomization and may have to change his/her antiretroviral treatment regimen after randomization according to the SOP ***SP-019-CT***. If the change is not possible, the patient is considered ineligible for randomization.
    - A recent study (Meintjes et al, see References) found that prophylactic prednisone may reduce the incidence of TB-IRIS in patients on treatment for drug-susceptible tuberculosis who were starting ART and with a CD4 count of 100 cells or fewer per microliter. In the study the incidence of TB-IRIS was 30% lower in participants who received prednisone compared to those who received placebo. Prednisone was started on the same day of ART start at 40 mg daily orally for 2 weeks, followed by 20 mg daily orally for 2 weeks, and then stopped. Currently, no evidence is available on the use of prednisone in patients with rifampin-resistant tuberculosis cases. Rifampin lowers the blood concentrations of corticosteroids and the equivalent dose of prednisone in a regimen that does not include rifampin is therefore unknown. In addition, the use of prednisone is not recommended in patients affected by cryptococcal meningitis and could be contraindicated in the presence of other comorbidities (e.g., diabetes). Given the above, the use of prednisone could be considered on a case-by-case basis for trial patients starting an ART regimen and with a CD4 count of 100 cells or fewer per microliter, after the exclusion of cryptococcal meningitis and in consultation with the CAC. The dose of prednisone could be half of what has been used in the study.
* Changing a patient’s ART regimen because it contains disallowed drugs or because of drug resistance (regimen failure) should be done in consultation with an experienced physician in HIV. The specific protocols of ART design and changes are beyond the scope of this SOP. The Clinical Advisory Committee (CAC) (see SOP ***SP-024-CT*** on ***Modus Operandi and Communication with the Clinical Advisory Committee***) is available for advice with patient management on designing or changing a patient’s ART.
* Provide co-trimoxazole to patients with HIV according to WHO recommendations (see Reference 1 below). Considering that co-trimoxazole has the potential to prolong the QT interval, use caution when administering it together with other QT-prolonging drugs.
* The use of azole antifungals is contraindicated in the patients who are receiving bedaquiline.
* Adverse events are more frequent in HIV infected patients and overlapping toxicities can occur with ART and MDR-TB treatment. The following adjustments should be made to the monitoring schedule:
  + Risk of nephrotoxicity is increased for HIV patients on MDR-TB treatment. Therefore, while on the injectable agent (kanamycin, amikacin, and capreomycin) creatinine and potassium levels should be monitored more often, weekly for the first month, and then at least twice monthly while receiving the injectable agent.
  + Risk of nephrotoxicity may be increased with tenofovir – the same adjustment in creatinine and electrolyte monitoring for all HIV patients should be followed (weekly for the first month and then at least twice monthly while receiving the injectable agent).
  + Risk of myelosuppression is increased with AZT – no change in monitoring schedule, avoid concomitant use with linezolid.
  + Risk of peripheral neuropathy is increased with D4T and ddI – avoid these drugs if possible. No change in monitoring schedule required if they are prescribed.
  + Risk of hepatotoxicity increases with nevirapine, efavirenz, and protease inhibitors – no change in monitoring schedule.
  + ART has been associated with QTc prolongation – no change in monitoring schedule.

### Management of diabetes

Diabetic patients with MDR-TB are at risk for poor treatment outcomes. In addition, the presence of diabetes mellitus may potentiate the adverse effects of TB drugs, especially renal dysfunction, peripheral neuropathy, and dysglycemia. Diabetes must be managed closely throughout the MDR-TB treatment. The following is recommended:

* The physician managing the patient’s TB should be in close communication with the physician or clinic that manages the patient’s diabetes.
* Medicines to control the diabetes (oral hypoglycemic agents and insulin) are not contraindicated during the MDR-TB treatment of drug-resistant TB but may require dose adjustments as the use of ethionamide, prothionamide, linezolid or fluoroquinolones (moxifloxacin, levofloxacin) may make it more difficult to control blood sugar levels.
* Creatinine and potassium levels should be monitored more frequently for diabetic patients on injectable agents (kanamycin, amikacin, and capreomycin), weekly for the first month and then at least twice monthly while receiving the injectable agent.
* Patients receiving fluoroquinolones (moxifloxacin, levofloxacin) and linezolid should be instructed to be vigilant for signs of hypo/hyperglycemia and monitor their blood sugar as indicated by their physician.

### Management of patients with cardiovascular disease

If the patient has diagnosed cardiovascular disease but no cardiac condition that resulted in exclusion of the patient from entering the studies, the patient should be followed under the normal study monitoring schedule. In patients with congestive heart failure, increased frequency of ECQ monitoring is warranted due to the increased risk of developing QT prolongation and severe arrhythmia.

Medicines for the management of cardiovascular disease should be continued if medically indicated. The physician managing the patient’s TB should be in close communication with the physician or clinic that manages the cardiovascular disease. The CAC should be contacted to support in the management of patients with severe cardiovascular disease.

As the same for any patient, if a cardiac arrhythmia, ischemia, infarction or worsening congestive heart failure occurs the patient should receive proper medical care. Study medicines or other medicines that may have contributed to the condition should be considered for suspension (e.g., see SOP ***SP-018-CT*** on ***Management of Specific Adverse Events***, section 5.2.3 on management of QT interval prolongation).

### Management of patients with psychiatric disorders including depression

Because of potential interactions with linezolid, patients that have or develop psychiatric disorders including depression that are on linezolid containing regimens must be managed without the use of:

* Any medicinal product that inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid);
* Tricyclic antidepressants (e.g. amitriptyline);
* Selective serotonin reuptake inhibitors (e.g. fluoxetine, paroxetine);
* Selective serotonin/norepinephrine re-uptake inhibitor (e.g. venlafaxine, duloxetine);
* Other serotoninergic agents.

If management of the patient’s psychiatric condition cannot be managed safely without the inclusion of the above medicines, the linezolid may have to be suspended or suspended with a TB drug replacement. Refer to the SOP ***SP-019-CT*** on ***Concomitant Medications*** for the full list of disallowed drugs and guidance on the management of possible drug interactions.

The physician managing the patient’s TB should be in close communication with the physician or clinic that manages the psychiatric disorder. This is extremely important as many psychiatrists are not aware of the drug-drug interactions with psychiatric medicines and linezolid.

### Management of substance dependence

Patients with substance dependence and on opioid replacement therapy require increased monitoring for potential QT prolongation – with weekly ECGs for 4 weeks and then return to the normal monitoring schedule. Whenever there is an increase in the opioid replacement therapy, weekly ECGs should be done for 4 weeks. Note that because of potential interaction with linezolid, patients receiving this drug should not receive methadone. Refer to the SOP ***SP-019-CT*** on ***Concomitant Medications*** for guidance on the management of possible drug interactions.

### Management of Seizure disorders

Because of potential interactions with bedaquiline and delamanid, patients with seizure disorder must be managed without the use of the following medicines:

* For bedaquiline: phenytoin, carbamazepine, phenobarbital;
* For delamanid: phenytoin, carbamazepine.

Refer to the SOP ***SP-019-CT*** on ***Concomitant Medications*** for guidance on the management of possible drug interactions.

The physician managing the patient’s TB should be in close communication with the physician or clinic that manages the seizure disorder. This is extremely important as many care providers including physicians are not aware of the drug-drug interactions with anti-seizure medicines and the new TB drugs bedaquiline and delamanid.

### Management of hepatitis B and C

The treatment for viral hepatitis B and C is rapidly evolving and includes a number of options of multidrug regimens with a backbone of antivirals. The exact regimen depending on the viral genotype. Some of the anti-hepatitis antiretroviral medicines are inhibitors of CYP3A4 (such as both boceprevir and telaprevir) and others have QT prolongation effect. Therefore, the choice of drugs for the treatment of hepatitis B and C during the treatment of MDR-TB should be evaluated carefully. If treatment of hepatitis B or C is indicated and a hepatitis regimen cannot be designed that does not have significant drug-drug interactions, it is suggested the patient be removed from the study and an individualized MDR-TB regimen and hepatitis antiviral regimen be designed by appropriate experts. It is recommended that all study participants that plan to have a hepatitis antiviral regimen during the study be reviewed by the CAC.

Patients that are hepatitis B- or C-infected with or without significant liver fibrosis may have entered the study without any plans for hepatitis antiviral therapy because many areas have no treatment with hepatitis antivirals available. If treatment of hepatitis B or C becomes available in the time period that a patient is in the study and the treating physician feels hepatitis treatment is indicated, it is suggested to review each case with the CAC. For specific guidance on the management of hepatitis C infection, refer to the SOP ***SP-033-CT*** on ***Management of Hepatitis C****.*

The physician managing the patient’s TB should be in close communication with the physician or clinic that manages the hepatitis, independent of whether the patient will receive hepatitis antiviral therapy or not.

### Management of renal insufficiency

Great care should be taken in the administration of TB drugs in patients with renal insufficiency, and the dose and/or the interval between dosing should be adjusted according to Adjustment of anti-TB drugs in renal insufficiency (See Appendix of SP-018-CT Management of Specific Adverse Events). Note that the dosing with bedaquiline and delamanid has not been well established in severe renal failure and caution is warranted. The dosing in Table 2 is based on the patient’s creatinine clearance, which is an estimate of the glomerular filtration rate or renal function.

## REFERENCES

* World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs and Preventing HIV Infection: Recommendations for a Public Health Approach. Geneva. 2013.
* World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008. World Health Organization. Geneva. (WHO/HTM/TB/2008.402).
* World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. World Health Organization Geneva. 2015 (WHO/HTM/TB/2014.11).
* World Health Organization. WHO Treatment guidelines for drug-resistant tuberculosis – 2016 update. World Health Organization. Geneva.2016. (WHO/HTM/TB/2016.04).
* Meintjes G, et al. Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS. Engl J Med 2018;379:1915-25. DOI: 10.1056/NEJMoa1800762

## SUPPORTING DOCUMENTS

* Adjustment of anti-TB drugs in renal insufficiency (Appendix to SOP SP-018-CT) (endTB Site Study Document)
* SOP SP-018-CT Management of Specific Adverse Events (endTB Site Study Document)
* SOP SP-019-CT Concomitant Medications (endTB Site Study Document)
* SOPSP-024-CT *Modus Operandi* and Communication with the Clinical Advisory Committee (endTB Site Study Document)
* SOP SP-033-CT Management of Hepatitis C (endTB Site Study Document)

## APPENDIX

None