

A Shorter-Course Oral Treatment Regimen for Multidrug-Resistant Tuberculosis in Haiti

Version 1.0

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Abbreviations

AE	Adverse Event
ART	Antiretroviral therapy
Bdq	Bedaquiline
BMI	Body Mass Index
Cfx	Clofazimine
Cs	Cycloserine
DR-TB	Drug-resistant Tuberculosis
DST	Drug Susceptibility Testing
E	Ethambutol
ECG	Electrocardiogram
Eto	Ethionamide
FDA	United States Food and Drug Administration
FQ	Fluoroquinolone
H	Isoniazid
HIV	Human Immunodeficiency Virus
Lfx	Levofloxacin
Lzd	Linezolid
MDR	Multidrug-resistance
MDR-TB	Multidrug-resistant Tuberculosis
MSPP	Ministere de la Sante Publique et de la Population
MTB/RIF	Mycobacterium Tuberculosis/Rifampicin
MWF	Monday-Wednesday-Friday
NIAID	National Institute of Allergy and infectious Diseases
NTP	National Tuberculosis Program
Ofx	Ofloxacin
PNLT	Programme National de Lutte contre la Tuberculose
Pto	Prothionamide
SAE	Serious Adverse Event
TB	Tuberculosis
WHO	World Health Organization
XDR	Extensive Drug Resistance
XDR-TB	Extensively Drug-resistant Tuberculosis
Z	Pyrazinamide

Investigators and roles

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1.0 STUDY OBJECTIVES

The objective of this study is to evaluate treatment outcomes of an oral, 39-week regimen that includes Bdq, Cfz, Lzd, Lfx, and Z under programmatic conditions. All of these drugs are already in use for MDR-TB treatment in Haiti.

Primary Objective: To determine the treatment outcomes for a cohort patients treated with a shorter-course MDR-TB regimen.

Secondary Objectives:

- To determine the proportion of patients with serious adverse events or adverse events of at least Grade 3 in severity, over the 39-week treatment period.
- To evaluate the tolerability of the novel regimen, by reporting the proportion of patients who stop study medication for >14 days during the 39-week treatment period for any reason.
- To determine the proportion of patients with recurrence during 48 weeks after successful treatment with a new shorter MDR-TB regimen.

2.0 INTRODUCTION

2.1 Summary

Haiti's National Tuberculosis Program proposes the implementation of this shorter-course MDR-TB regimen under programmatic conditions in Haiti. Enrollment of 30 MDR-TB patients will take place under the supervision of the National Tuberculosis Program, in collaboration with two non-governmental organizations, Partners In Health/Zanmi Lasante (PIH/ZL) and the Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections (GHESKIO), which have been involved in management of patients with new TB drugs as a part of the endTB Project. Prior the initiation of the novel shorter treatment regimen, each patient will sign an informed consent form. Clinical monitoring and cohort event monitoring will be performed during therapy with the shorter treatment regimen with information collected and recorded as a part of the endTB observational study.

2.2 Background

For many years, MDR-TB patients have been treated with World Health Organization (WHO) recommended conventional treatment regimens which generally include an intensive phase of treatment of 8 months and a total duration of treatment of at least 20 months. These WHO recommendations were based on observational data, including an analysis of 9153 patients treated in observational studies. Of the 9153 patients, 4934 (54%) were judged to have treatment success, 732 (8%) failed or relapsed, 1392 (15%) died, and 2095 (23%) were lost to follow-up.¹

In October 2016, the WHO recommended that in patients with rifampin-resistant (RR-TB) or MDR-TB who were not previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents was excluded or is considered highly unlikely, a shorter MDR-TB regimen may be used instead of the longer conventional regimens (conditional recommendation, very low certainty in the evidence).² The WHO-recommended shorter regimen is composed of high-dose moxifloxacin, clofazimine, pyrazinamide and ethambutol throughout, supplemented by kanamycin, prothionamide, and high-dose isoniazid

in the intensive phase. The treatment duration of the intensive phase is four months (extended to a maximum of six months until sputum smear conversion), and the duration of the continuation phase is five months. This regimen is currently being evaluated in the STREAM randomized controlled trial. A preliminary summary of trial results made public by the researchers in October 2017 indicated almost similar outcomes of the STREAM regimen as compared to the conventional 20-month regimen under trial conditions.

In addition to the shorter MDR-TB regimen recommended by the WHO, there are other shorter regimens that are currently being evaluated in clinical trials. Many of these regimens have theoretical advantages, including the use of new or repurposed drugs such as bedaquiline, delamanid, clofazimine, and linezolid, which have been shown to be effective in clinical trials. Many of these regimens exclude the use of a second-line injectable, which is associated with a high rate of adverse events, is programmatically difficult to administer, and has limited data in support of efficacy. Although these novel shorter regimens are currently undergoing testing in clinical trials, the programmatic use of these regimens, under operational research conditions, can also provide important data to the global TB community about their effectiveness and safety, while expanding access to their potential benefits.

2.3 MDR-TB in Haiti

Haiti has an estimated TB incidence of 188/100,000, and an estimated MDR/RR-TB incidence of 7.1/100,000 (WHO TB Report, 2017). In 2016, the National TB Program reported 15,567 cases of TB, with an estimated case detection rate of 75%. Among TB cases with known HIV status, 15% are co-infected with HIV and TB. Overall treatment success for new and relapse cases registered in 2015 was 80%. Among MDR-RR-TB cases started on treatment in 2014 (n=89), 79% had successful treatment outcomes; among those starting treatment in 2013 (n=82) 82% had successful outcomes.

In 2016, there were an estimated 530 cases of MDR/RR-TB cases, among notified TB patients. An estimated 2.9% of new TB cases and 13% of previously treated cases have MDR-TB. In 2016, 132 patients were diagnosed with laboratory-confirmed MDR-TB, and 131 started MDR-TB treatment; one patient had XDR-TB.

MDR-TB is treated with a mixed model of care (hospitalization during part or all of the intensive phase and ambulatory during maintenance phase). MDR-TB is diagnosed based on molecular and phenotypic methods. Patients with samples that test positive for rifampin resistance based on Xpert MTB/RIF testing receive first and second-line drug susceptibility testing (DST) at GHESKIO. First-line DST is performed using Becton Dickinson Bactec MGIT liquid culture and tested for rifampin, isoniazid, ethambutol, pyrazinamide and streptomycin resistance. Second-line DST is performed using Lowenstein-Jensen agar proportion solid culture and tested for resistance against kanamycin, amikacin, capreomycin, ofloxacin, ethionamide, cycloserine and p-aminosalicylic acid. Table 1 includes the DST patterns for all adult patients treated for MDR-TB at GHESKIO from 2008 to 2017 (n=239).

Table 1: Resistance to Medications in Patients with MDR-TB, GHESKIO, Haiti

Drug	HIV-negative n=191 (%)	HIV-positive n=48 (%)	Total n=239 (%)
Isoniazid ^{LD}	191 (100)	48 (100)	239 (100)
Isoniazid ^{HD}	179 (94)	47 (98)	226 (95)
Ethambutol	146 (76)	37 (77)	183 (77)
Pyrazinamide	110 (58)	25 (52)	135 (57)

Streptomycin	97 (51)	25 (52)	122 (51)
Ethionamide	28 (15)	10 (21)	38 (16)
Cycloserine	0 (0)	0 (0)	0 (0)
P-aminosalicylic acid	3 (2)	1 (2)	4 (2)
Kanamycin*	3 (2)	2 (4)	5 (2)
Capreomycin	0 (0)	0 (0)	0 (0)
Amikacin*	1 (0.5)	0 (0)	1 (0.4)
Ofloxacin	2 (1)	1 (2)	3 (1)

Isoniazid^{LD} = low-dose isoniazid; Isoniazid^{HD} = high-dose isoniazid

Patients with MDR-TB are initially treated with a standard regimen which is then adapted to each patient's individual resistance profile. The standard regimen includes a second-line injectable (generally kanamycin, with capreomycin for HIV-infected patients when available), a late generation quinolone (levofloxacin), ethionamide, cycloserine, and pyrazinamide. The injectable is provided for six months after culture conversion; the other drugs are continued through the 20-24 month treatment period. In 2017, the endTB program began providing Haiti with access to new and repurposed medications (bedaquiline, delamanid, clofazimine, and linezolid). These drugs are now used for patients with resistance to one of the core drugs, toxicity to one of the core drugs, or high risk of poor treatment outcomes, according to WHO guidelines.

2.4 Rationale

The conventional 20-month MDR-TB regimen is associated with frequent adverse reactions, and a low rate of cure, with about 50% of patients worldwide achieving successful outcomes in programmatic settings worldwide. This evidence base in support of the conventional regimen is poor, and based on observational data rather than clinical trials. In addition, the long duration of treatment is burdensome for patients, and results in high rates of attrition in many MDR-TB programs.

For these reasons, there is great interest in substituting the new and repurposed drugs in place of certain conventional MDR-TB drugs, with the goal of improving efficacy, reducing toxicity, shortening treatment duration, and providing oral regimens. The shorter duration of treatment, the lack of an injectable, and the use of drugs with better side effect profiles, all mean that patients are more likely to complete the treatment with one of these new shorter regimens. All four new or repurposed drugs—bedaquiline, delamanid, clofazimine and linezolid—have been shown in clinical trials to be effective when included as part of a multi-drug regimen. Thus, substitution of conventional MDR-TB drugs with these drugs may result in a more effective regimen with fewer poor outcomes.

STREAM Stage 1 is a clinical trial comparing the WHO-recommended shorter regimen (9 months) to the conventional 20-month regimen. Enrollment has been completed, but follow-up of the last patients will end in the beginning of 2018. Preliminary results were presented at the Union Meeting in Guadalajara in October 2017. These showed that the STREAM 1 regimen was almost equivalent to the 20-month regimen in terms of efficacy. 78% of the patients in the STREAM 1 regimen arm experienced a favorable outcome, compared to 81% of the patients in the conventional regimen arm. This did not meet the non-inferiority threshold, but was not significantly inferior either. In addition, adverse events were not significantly different in the two arms.

In addition to the STREAM trial, several other studies are being conducted to evaluate the safety and efficacy of shorter regimens (Table 2). Compared to the current WHO-recommended shorter regimen, all of these regimens are using new or repurposed drugs such as bedaquiline, delamanid, clofazimine, and linezolid administered from 28 to 40 weeks in duration. Bedaquiline and delamanid appear to be well tolerated. Linezolid has well-known toxicities of peripheral neuropathy, bone marrow suppression, and optic neuritis, but it still may be better tolerated than conventional MDR-TB drugs such as prothionamide, cycloserine or the second-line injectables.

Table 2: Regimens Tested in Recently Completed or Ongoing Clinical Trials

Clinical Trial	Regimen	Study Status	All Drugs are Commercially Available?
STREAM 1 regimen B	Cfz, E, Z, Mfx, H, Km (16 weeks); followed by Cfz, E, Z, Mfx (24 weeks)	Enrollment completed	Yes
NiX-TB	Bdq, Pa, Lzd (24-36 weeks)	Enrollment completed	No
MDR END	Dlm, Lzd, Lfx, Z (36-52 weeks)	Enrolling	Yes
STREAM 2 regimen C	Bdq, Cfz, E, Z, Lfx, H, Pto (16 weeks); followed by Bdq, Cfz, E, Z, Lfx (24 weeks)	Enrolling	Yes
STREAM 2 regimen D	Bdq, Cfz, Z, Lfx, H, Km (8 weeks); followed by Bdq, Cfz, Z, Lfx (20 weeks)	Enrolling	Yes
PRACTECAL regimen 1	Bdq, Pa, Lzd (24-36 weeks)	Enrolling	No
PRACTECAL regimen 2	Bdq, Pa, Lzd, Cfz (24-36 weeks)	Enrolling	No
PRACTECAL regimen 3	Bdq, Pa, Lzd, Mfx (24-36 weeks)	Enrolling	No
endTB regimen 1	Bdq, Lzd, Mfx, Z (39 weeks)	Enrolling	Yes
endTB regimen 2	Bdq, Cfz, Lzd, Lfx, Z (39 weeks)	Enrolling	Yes
endTB regimen 3	Bdq, Dlm, Lzd, Lfx, Z (39 weeks)	Enrolling	Yes
endTB regimen 4	Dlm, Cfz, Lzd, Lfx, Z (39 weeks)	Enrolling	Yes
endTB regimen 5	Dlm, Cfz, Mfx, Z (39 weeks)	Enrolling	Yes

*Cfz=clofazimine; E=ethambutol; Z=pyrazinamide; Mfx=moxifloxacin; H=isoniazid; Km=kanamycin; Bdq=bedaquiline; Pa=pretomanid; Lzd=linezolid; Dlm=delamanid; Lfx=levofloxacin; Pto=prothionamide.

Due to the high rates of resistance to first-line TB medications in Haiti (Tables 1 and 3), there is concern about using the WHO recommended shorter-course regimen in Haiti. As illustrated in Table 3, about 50% of MDR-TB patients in Haiti would be left with only two drugs that are likely to be effective in the continuation phase of this regimen. Hence, the WHO-recommended short-course regimen would expose patients to the toxicity of medications that are unlikely to be effective, while potentially including an insufficient number of drugs to provide successful treatment outcomes.

Table 3: Resistance Patterns and Presumed Effective Drugs in the WHO Short-Course Regimen in Haiti

Resistance Patterns	# Effective Drugs Remaining in Proposed Shorter-Course Regimen*		HIV-neg n=191 (%)	HIV-pos n=48 (%)	Total n=239 (%)
	Intensive Phase 4-6 Km-Mfx-Pto-Cfz-Z- H ^{HD} -E	Continuation Phase 5 Mfx-Cfz-Z-E			
Pre-XDR-TB			5 (3)	3 (6)	8 (3)
R + H ^{HD} + E + Z + Km	Mfx-Pto-Cfz	Mfx-Cfz	1 (0.5)	0 (0)	1 (0.4)
R + H ^{HD} + E + Z + Km	Mfx-Pto-Cfz	Mfx-Cfz	1 (0.5)	2 (4)	3 (1)
R + H ^{HD} + Km	Mfx-Pto-Cfz-Z-E	Mfx-Cfz-Z-E	1 (0.5)	0 (0)	1 (0.4)
R + H ^{HD} + E + Z + Ofx	Km-Pto-Cfz	Cfz	0 (0)	1 (2)	1 (0.4)
R + H ^{HD} + Z + Ofx	Km-Pto-Cfz-E	Cfz-E	1 (0.5)	0 (0)	1 (0.4)
R + H ^{HD} + Ofx	Km-Pto-Cfz-Z-E	Cfz-Z-E	1 (0.5)	0 (0)	1 (0.4)
Resistant to Pyrazinamide			107 (56)	22 (46)	129 (54)
R + H ^{HD} + E + Z + Eto	Km-Mfx-Cfz	Mfx-Cfz	16 (9)	3 (6)	19 (8)
R + H ^{HD} + Z + Eto	Km-Mfx-Cfz-E	Mfx-Cfz-E	1 (0.5)	1 (2)	2 (1)
R + H ^{HD} + E + Z	Km-Mfx-Pto-Cfz	Mfx-Cfz	75 (40)	17 (35)	92 (39)
R + H ^{LD} + E + Z	Km-Mfx-Pto-Cfz-H ^{HD}	Mfx-Cfz	4 (2)	0 (0)	4 (2)
R + H ^{HD} + Z	Km-Mfx-Pto-Cfz-E	Mfx-Cfz-E	10 (5)	1 (2)	11 (5)
R + H ^{LD} + Z	Km-Mfx-Pto-Cfz-H ^{HD} -E	Mfx-Cfz-E	1 (0.5)	0 (0)	1 (0.4)
Other Resistance Patterns			79 (41)	23 (48)	102 (43)
R + H ^{HD} + E + Eto	Km-Mfx-Cfz-Z	Mfx-Cfz-Z	9 (5)	4 (8)	13 (5)
R + H ^{HD} + Eto	Km-Mfx-Cfz-Z-E	Mfx-Cfz-Z-E	1 (0.5)	1 (2)	2 (1)
R + H ^{LD} + Eto	Km-Mfx-Cfz-Z- H ^{HD} -E	Mfx-Cfz-Z-E	1 (0.5)	1 (2)	2 (1)
R + H ^{HD} + E	Km-Mfx-Pto-Cfz-Z	Mfx-Cfz-Z	39 (20)	10 (21)	49 (21)
R + H ^{LD} + E	Km-Mfx-Pto-Cfz-Z-H ^{HD}	Mfx-Cfz-Z	1 (0.5)	0 (0)	1 (0.4)
R + H ^{HD}	Km-Mfx-Pto-Cfz-Z-E	Mfx-Cfz-Z-E	23 (12)	7 (15)	30 (13)
R + H ^{LD}	Km-Mfx-Pto-Cfz-Z-H ^{HD} -E	Mfx-Cfz-Z-E	5 (3)	0 (0)	5 (2)

*Pre-XDR=pre-extensively resistant; R=rifampin; H^{LD}=low-dose isoniazid; H^{HD}=high-dose INH; E=ethambutol; Z=pyrazinamide; Km=kanamycin; AMK=amikacin; CM=capreomycin; Ofx=ofloxacin; Mfx=moxifloxacin; Eto=ethionamide; Pto=prothionamide; CS=cycloserine; Cfz=clofazimine; PAS=para-aminosalicylic acid; **Mfx and Pto sensitivity was presumed based on ofloxacin and ethionamide sensitivity testing respectively. Clofazimine sensitivity presumed for all patients.

2.5 Drugs in the Short-Course MDR-TB Regimen

2.5.1 Bedaquiline

2.5.1.1 Bedaquiline Dosing, Indication, and Mechanism of Action

Bedaquiline is a diarylquinoline antimycobacterial drug that inhibits ATP synthase. It is indicated for the treatment of MDR-TB. It is dosed at 400 mg once daily for two weeks, followed by 200 mg three times per week.

2.5.1.2 Bedaquiline Pharmacokinetics and Metabolism

Bedaquiline is primarily metabolized in the liver by cytochrome P450 (CYP)

isoenzyme 3A4 into the M2 metabolite. It is primarily excreted in feces; urinary excretion is negligible. The half-life of bedaquiline is very long – about 5.5 months.

2.5.1.3 Bedaquiline Toxicity

The most common side effects of bedaquiline are gastrointestinal symptoms (nausea, vomiting, abdominal pain, loss of appetite), joint pain, and headache. Less common adverse events include QT prolongation, hyperuricemia, phospholipidosis (the accumulation of phospholipids in the body's tissues), and elevated aminotransferases.

2.5.1.4 Bedaquiline Drug Interactions

Bedaquiline has drug interactions with CYP3A4 inhibitors and inducers. Rifampin reduces bedaquiline levels by about half. Lopinavir/ritonavir is both a substrate and inhibitor of CYP3A4. Levels of bedaquiline may increase in combination with lopinavir/ritonavir, so this combination should be given with caution. Efavirenz is an inducer of CYP3A4, and may reduce bedaquiline levels by about 50%; therefore efavirenz should not be administered in combination with bedaquiline. Other drugs that prolong the QT interval must be given with monitoring for QT prolongation.

2.5.2 Clofazimine

2.5.2.1 Clofazimine Dosing, Indication, and Mechanim of Action

Clofazimine is a riminophenazine that has been used most often in the treatment of leprosy. It has been recently repurposed for use in MDR-TB treatment. The usual dose for MDR-TB is 200 mg daily for two months, followed by 100 mg daily.

2.5.2.2 Clofazimine Pharmacokinetics and Metabolism

Clofazimine distributes primarily into fatty tissues, as well as cells of the mononuclear phagocyte system.

2.5.2.3 Clofazimine Toxicity

Common side effects of clofazimine include an reddish/brown discoloration of the skin, conjunctiva, cornea, and body fluids; this gradually resolves after stopping the drug. Dry skin, pruritis, rash, gastrointestinal symptoms, and photosensitivity are also common side effects. Less commonly, retinopathy, severe abdominal symptoms, bleeding, bowel obstruction, and QT prolongation can occur.

2.5.2.4 Clofazimine Drug Interactions

Clofazimine can prolong the QT interval, so ECG monitoring should be conducted in patients receiving clofazimine in combination with other drugs that prolong the QT interval.

2.5.3 Linezolid

2.5.3.1 Linezolid Dosing, Indication, and Mechanism of Action

Linezolid is an oxazolidinone antibiotic, which inhibits protein synthesis. It is widely used for the treatment of resistant gram positive infections, and more recently has been repurposed for use in the treatment of MDR-TB. The optimal dose in MDR-TB has not yet been defined, but it is generally started at a dose of 600 mg daily. If symptoms develop, the dose and/or frequency is often reduced.

2.5.3.2 Linezolid Pharmacokinetics and Metabolism

Linezolid is well absorbed, with a bioavailability of approximately 100% in healthy volunteers.

2.5.3.3 Linezolid Toxicity

Common side effects with linezolid include gastrointestinal symptoms (nausea, vomiting, and/or diarrhea) and myelosuppression (anemia, neutropenia, and/or thrombocytopenia). Less common side effects include headache, lactic acidosis, elevated transaminases, peripheral neuropathy, and optic neuritis.

2.5.3.4 Linezolid Drug Interactions

Serotonin syndrome may develop with the combination of linezolid and antipsychotic and antidepressant medications that modulate serotonin, causing symptoms such as agitation, confusion, hallucinations, myoclonus, shivering, and tachycardia. Avoid or monitor closely in combination with tricyclic antidepressants.

2.5.4 Levofloxacin

2.5.4.1 Levofloxacin Dosing, Indication, and Mechanism of Action

Lfx is a fluoroquinolone antibiotic currently approved for the treatment of lung, sinus, skin, and urinary tract infections caused by bacteria. Chemically, Lfx, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin, and inhibits DNA gyrase and topoisomerase IV. It is given at a dose of 750-1000mg daily.³

2.5.4.2 Levofloxacin Pharmacokinetics and Metabolism

The T_{max} of Lfx is 1 hour, it is 100% bioavailable when taken orally and it is 30-40% protein bound. The PK/PD parameter that corresponds to maximal bactericidal (or sterilizing activity) for fluoroquinolones in the treatment of TB has not been identified. Evidence from other serious bacterial infections has suggested that the ratio of the area under the concentration-time curve divided by minimum inhibitory concentration (AUC/MIC) ratio correlates with bactericidal efficacy. This parameter is the best predictor of fluoroquinolone activity in the mouse model of TB disease. Lfx is absorbed from the intestine and excreted via the kidney. Dose adjustment is required for patients with significant renal insufficiency (i.e. glomerular filtration rate of <50mL/min).

2.5.4.3 Levofloxacin Toxicity

Lfx is generally well tolerated, but there are a number of well-recognized but uncommon adverse effects, including tendonopathy and tendon rupture, hypersensitivity reactions, hepatotoxicity, central nervous system effects, Clostridium difficile infection (5%), peripheral neuropathy (<1%), prolongation of the QTc interval (<1%), musculoskeletal disorders, blood glucose disturbances (<1%), photosensitivity/phototoxicity and development of drug resistant bacteria.⁴

2.5.4.4 Levofloxacin Drug Interactions

Lfx should be administered at least 3 hours before or 3 hours after antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or didanosine chewable/buffered tablets or the pediatric powder for oral solution. The potential for pharmacokinetic drug interactions

between Lfx and warfarin, theophylline, cyclosporine, digoxin, probenecid, and cimetidine has been evaluated and dose adjustment is not required for concomitant use.

2.5.5 Pyrazinamide

2.5.5.4 Pyrazinamide Dosing, Indication and Mechanism of Action

Pyrazinamide is an analog of nicotinamide and has unique activity against *M. tuberculosis*, allowing the duration of treatment to be decreased from 9 months to 6 months (assuming rifampin is used throughout). The mechanism of action of pyrazinamide is multifactorial.

2.5.5.5 Pyrazinamide Pharmacokinetics and Metabolism

Pyrazinamide is well-absorbed from the gastrointestinal tract and widely distributed into all tissues. Peak serum concentrations are achieved approximately 2-3 hours after a dose. Food and antacids do not significantly affect the absorption of pyrazinamide. The half-life of pyrazinamide is approximately 9-10 hours, and is prolonged in the presence of hepatic insufficiency. Pyrazinamide is metabolized to pyrazinoic acid by the hepatic microsomal enzyme pyrazinamide deamidase. Approximately 40% of a dose is recovered in the urine as pyrazinoic acid and an additional 4% is excreted in the urine as the unchanged parent drug. The remaining drug is thought to be excreted in the bile.

2.5.5.6 Pyrazinamide Toxicity

The most frequent side effects are skin rash, gastrointestinal intolerance, hepatotoxicity (1.3%), arthralgias (1-7%), hyperuricemia due to blockade of urate excretion (up to 66%), and rarely acute gouty arthritis. These side effects are seldom dose-limiting. Asymptomatic elevations in serum uric acid are frequent, usually occur during the first or second month of treatment, and are self-limited and require no specific treatment. Minor arthralgias also may occur during pyrazinamide treatment and can usually be treated with salicylates or non-steroidal inflammatory agents such as indomethacin while continuing the drug. The most common serious side effect of pyrazinamide is hepatotoxicity.

2.5.5.7 Pyrazinamide Drug Interactions

There are no known clinically significant drug-drug interactions involving pyrazinamide.

3.0 DESIGN

Thirty patients with MDR-TB will be treated with an oral regimen including Bdq, Cfz, Lzd, Lfx, and Z for 39 weeks.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

- Ability and willingness to provide informed consent
- Age from 18 to 65 years
- Bacteriologically-confirmed TB with initial laboratory result of resistance to at least rifampicin
- Willing to adhere to the following contraception requirements: Female candidates of reproductive potential who are participating in sexual activity that could lead to pregnancy must agree to use two reliable methods of contraception: a barrier method of contraception (condoms or cervical cap) together with another reliable form of contraceptive (condoms with a spermicidal agent, a diaphragm or cervical cap with spermicide, an IUD, or hormone-based contraceptive) throughout the 39-week MDR-TB treatment period, and for 30 days after stopping study medications.
- Willing to adhere to the follow-up schedule and to study procedures.

4.2 Exclusion Criteria

- DST showing infection with a strain resistant to any of the quinolones
- Previous exposure to second line anti-TB drugs for more than one month
- Pregnant or breastfeeding
- Unable to attend or comply with treatment or follow-up schedule
- Unable to take oral medications
- Unwilling to accept home visits for directly observed treatment
- Allergy to Bdq, Cfz, Lzd, Lfx, or Z
- Participation in any clinical trial
- AST or ALT >5 times the upper limit of normal. *(If this is temporary, the patient can be enrolled once this is corrected.)*
- Severe renal insufficiency (estimated creatinine clearance (CrCl) less than 30 mL/min based on the Cockcroft-Gault equation).
- ECG with QTcF interval of >500 msec
- Presence of co-morbidities, including diabetes, chronic renal insufficiency, advanced cardiac failure, and cardiac arrhythmias.

5.0 STUDY TREATMENT

5.1 Regimen and Duration

Study provided treatment will include:

- Bedaquiline 100 mg tablets
- Clofazimine 100 mg gel capsules
- Linezolid 600 mg tablets
- Levofloxacin 250 mg and 500 mg tablets
- Pyrazinamide 500 mg tablets

Table 4: Dosing Table

Drug*	Weight Band (kg)
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	30-35	36-45	46-55	56-70	>70
Bedaquiline	400 mg QD x 2 weeks followed by 200 mg 3x/week				
Levofloxacin	750 mg		1000 mg		
Linezolid**	600 mg QD for up to 4 months (followed by 300 mg QD or intermittent dosing for 5 months)				
Clofazimine	100 mg				
Pyrazinamide	800 mg	1200 mg	1600 mg	1600 mg	2000 mg

* Dosing is once a day unless otherwise indicated.

** Linezolid dosing will be routinely modified at month 4 or sooner if necessary to reduce toxicity related to linezolid. The modification will entail either decreased (300 mg daily) or intermittent dosing.

The shorter-course MDR-TB regimen will be administered orally, seven days per week, throughout treatment. At least 6 doses per week will be given as directly observed treatment (DOT) by a health care worker, with the option of a self-administered dose once per week. Participants will be treated for 39 weeks.

5.2 Concomitant Medications

Whenever a concomitant medication is initiated or a dose changed, the clinicians must review the package insert to obtain the most current information on drug interactions, contraindications, and precautions.

6.0 CLINICAL AND LABORATORY EVALUATIONS

Evaluation	Screening/ Treatment Start	Treatment Period (Weeks)													Follow-up Post-Treatment			
		W1	W2	W4	W6	W8	W12	W16	W20	W24	W28	W32	W36	W39	W51	W63	W75	W87
Medical History	X																	
Medication History	X																	
Complete Physical Examination	X																	
Targeted Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV Testing	X																	
Pregnancy Testing	X																	
Chemistry Tests	X		X	X		X	X	X	X	X	X	X	X	X				
Liver Function Tests	X			X		X	X	X	X	X	X	X	X	X				
Complete Blood Count	X		X	X		X	X	X	X	X	X	X	X	X				
AFB Smear and Culture	X			X		X	X	X	X	X	X	X	X	X		X		X
Xpert MTB/RIF	X																	
Drug Susceptibility Testing	X																	
Visual Acuity	X			X		X	X	X	X	X	X	X	X	X				
Peripheral Neuropathy Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Chest X-ray	X																	
ECG	X		X	X		X	X	X	X	X	X	X	X	X				

6.1 Inpatient and Ambulatory Treatment

Inpatient treatment is not mandatory, but patients may be hospitalized at the initiation of MDR-TB treatment for a short period of time to ensure that they can tolerate the regimen. It may also be advisable for specific groups and for very ill people, for instance during the initiation of treatment or when adverse events occur during treatment.

Ambulatory treatment from the outset without initial hospitalization is also feasible, since Haiti has a strong DOT program for MDR-TB. DOT will be administered for at least six days per week throughout the whole treatment course, and the shorter regimen will be administered seven days per week. Ambulatory DOT services will either be "facility-based" in which patients visit a health care facility daily for treatment or "community-based" in which a trained treatment supporter visits the patients daily for drug administration (or vice versa), accompanies the patient to follow-up visits and liaises with the clinical staff.

In the case of community-based DOT, a trained independent treatment supporter who is not directly related to the patient must be identified. The treatment supporter has the following responsibilities:

- Strictly administer DOT on a daily basis.
- Ensure the patient attends all scheduled follow-up visits and examinations.
- Monitor adverse events closely and address adverse events in a timely manner by informing clinical staff.
- Update the patient treatment card on a daily basis.
- Initiate patient tracing if the patient fails to return for treatment as per schedule.

6.2 Examinations at Baseline and During Treatment

Each patient should receive appropriate monitoring at baseline, during and after treatment, including clinical evaluation, bacteriological and laboratory testing as described in Section 6.0.

Medical History: The medical history must include all diagnoses within the past 30 days.

Medication History: A medication history must be taken, including start and stop dates. Table 5 includes the medications that must be included in the history.

Table 5: Medications Included in History

Medication Category	Complete History of Time Frame
TB therapy for the current episode	Complete history
Prior TB treatment	Complete history
Antiretroviral therapy (for HIV-infected patients only)	Complete history
Prescription drugs for all chronic diseases, including for treatment and/or prophylaxis of opportunistic infections	Within 30 days prior to start date of the novel MDR-TB regimen

Complete Physical Examination: A complete physical examination will be performed at screening only and is to include, at a minimum, an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; and examination of the lower extremities for edema. The complete physical exam will also include signs and symptoms,

diagnoses, and vital signs (height, weight, temperature, pulse, respiration rate, and blood pressure).

Targeted Physical Examination: At and after entry, a targeted physical examination is to include vital signs (weight, temperature, pulse, respiration rate, and blood pressure) and is to be driven by any previously identified or new signs or symptoms including diagnoses that the participant has experienced since the last visit.

Laboratory Evaluations

- All patients should receive HIV testing as part of study screening.
- All females <50 years of age will be screened for pregnancy as part of study screening, and as needed during treatment.
- Chemistry: Serum creatinine and potassium will be measured at study screening, 2 week visit, and then monthly during treatment.
- Liver function tests (ALT, AST) will be conducted at study screening, and repeated monthly throughout treatment.
- Complete blood count will be conducted at study screening, 2 week visit, and then repeated monthly throughout treatment.
- Sputum smears and cultures should be done at baseline and then monthly until completion of treatment. They should also be repeated at six and 12 months after the completing treatment.
- Xpert MTB-RIF testing will be conducted as part of study screening.
- Drug susceptibility testing to first and second-line MDR-TB medications (including quinolones) will be conducted as part of study screening.
- Visual acuity testing and Ishihara testing should be done at the start of treatment and monthly thereafter for patients receiving linezolid.
- Peripheral neuropathy will be assessed at every visit using the ACTG Brief Peripheral Neuropathy Screen
- A chest x-ray will be done as part of study screening, and repeated if clinically indicated during treatment.
- An ECG will be done as part of study screening, and it will be repeated on a monthly basis throughout treatment.

6.3 Procedures Following Missed Doses

Any days of medication that are missed should be made up by extending the regimen by the number of days missed (up to two consecutive months, after which time the patient will be classified as loss-to-follow-up, and will no longer be eligible to receive the shorter regimen). Reasons for missed doses must be identified and addressed.

6.4 Discontinuation of the Novel Shorter MDR-TB Regimen

The novel shorter MDR-TB regimen will be discontinued in some patients. In such cases, patients will be evaluated by a Central Clinical Committee and switched to an individualized regimen, based on the WHO guidelines for regimen design and the endTB clinical guide v 4.0. The most common situations include:

- Resistance to drugs in the shorter MDR-TB regimen. For patients who submit a sputum sample for culture-based second-line DST at the beginning of treatment, the results may be delayed until after treatment has started. If resistance to drugs in the shorter

MDR-TB regimen is discovered, it may be necessary to modify or discontinue the regimen.

- Pregnancy during treatment. If a patient becomes pregnant during treatment, she will stop the shorter MDR-TB regimen. The Central Clinical Committee will make recommendations on a case-by-case basis in regards to optimal therapy for completion of treatment.
- Intolerable severe toxicity. One or more drugs may need to be suspended permanently due to severe toxicity. In such cases, the Central Clinical Committee will review the medical history carefully to determine how the patient's regimen should be modified.
- Treatment failure. If clinical and bacteriological responses to treatment are poor, a change in the treatment regimen will be considered. The DST should be repeated, whether or not the regimen is changed, in order to inform future management decisions. The Central Clinical Committee will provide recommendations on whether the novel shorter-course regimen should be stopped.

6.5 Post Treatment Follow-up

After completion of treatment, patients will be informed of the risk of recurrent TB and advised to return for clinical assessment on a quarterly basis. Patients will also be advised to return for sputum examinations at 6 and 12 months after completion of treatment. A single sputum specimen for smear and culture will be collected at each follow-up visit.

7.0 REPORTING AND MANAGEMENT OF ADVERSE EVENTS

7.1 Scope for Safety Data Collection and Definitions

A system for pharmacovigilance is already in place in the MDR-TB programs for both GHESKIO and Partners In Health, as part of the endTB program, which provides access to new and repurposed MDR-TB medications. This system will be continued to ensure timely detection and proper transmission of information relating to drug safety, especially adverse events, as part of this protocol.

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

All patients will be monitored and assessed clinically for AEs (including lab abnormalities) at all visits during treatment, as described in Section 6.0. Systematic symptomatic screening and referral for potential AEs is a mandatory part of scheduled and unscheduled visits. In addition, the evolution and outcome of the previously recorded AEs will be systematically assessed.

Laboratory screening for hematologic and biochemical abnormalities and ECG for monitoring of the QT length will be conducted at specific visits during treatment (see Section 6.0) and more frequently as needed. Safety data collection will start at time of first MDR-TB treatment administration. Each AE will followed-up until resolution or stabilization.

Safety data collection in the frame of endTB, and for this protocol as well, will be focused on the following types of adverse events:

- Serious Adverse Events (SAEs), defined as any untoward medical occurrence that, at any dose:

- Results in death
 - Requires hospitalization or prolongation of hospitalization
 - Results in persistent or significant disability/incapacity
 - Is life-threatening (life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction, it does not refer to a reaction that hypothetically might have caused death if more severe)
 - Is a congenital anomaly or a birth defect
 - Is otherwise medically significant. Medical and scientific judgment will be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Suspected transmission of an infectious agent (e.g. pathogenic or non-pathogenic) via drug is always considered an SAE.
- AEs of interest, defined as all AEs regardless of their seriousness, severity or causal relationship to the MDR-TB treatment, pertaining to the following medical conditions.
 - Peripheral neuropathy
 - Myelosuppression (anemia, thrombocytopenia, or neutropenia)
 - Prolonged QT interval
 - Optic nerve disorder (optic neuritis)
 - Hepatitis
 - AEs leading to treatment discontinuation or change in drug dosage, defined as all AEs regardless of their seriousness, severity, or causal relationship to the MDR-TB treatment, leading to a discontinuation of MDR-TB treatment, including permanent and temporary treatment interruption, or changes in drug(s) dosage(s) or drug regimen, as decided by the clinician.
 - Adverse events judged as otherwise clinically significant, defined as all AEs regardless of their seriousness, severity, or causal relationship to the MDR-TB treatment, not pertaining to one of the above-mentioned categories but considered of clinical significance by the treating physician.
 - Pregnancy must be avoided during MDR-TB treatment and effective contraception is recommended. If despite all precautions, a patient is found to be pregnant, the pregnant patient will be referred to receive the local, standard of MDR-TB treatment for pregnant women. All pregnancies will be followed-up until an outcome is known. Infants born from exposed pregnancies will be followed-up until they reach 12 months of age.
 - Medication errors, defined as unintended mistakes in the prescribing, dispensing and administration of a medicine that could cause harm to a patient (e.g. wrong drug prescribed, overdose) will be managed on a case-by-case basis. Hospitalization will be considered as appropriate.

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

7.2 Recording, Medical Assessment and Notification of Adverse Events

Recording and notification of adverse events will occur as follows:

- Immediate transmission (within 24 hours of awareness) of Serious Adverse Events (as defined in section 7.1), drug-exposed pregnancies and medication errors (with or without associated AEs/SAEs) to the pharmacovigilance (PV) unit (PVunit.GVA@geneva.msf.org) as recorded using the *SAE or Pregnancy Report Form*.
- Routine recording of all other AEs (non-serious) using the *AE Form/AE Log*.

Upon recording, all SAEs and AEs should be graded for severity according to the provided Severity Grading Scale of the Division of AIDS of the National Institutes of Health. For those AEs not described in this grading scale, the general definition of clinical severity should apply, as described in Table 6.

Table 6: General Definition of Severity (endTB Program)

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

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

All AEs will additionally be evaluated to determine their causal relationship with MDR TB treatment (including MDR-TB drugs and other drugs as appropriate), using the standard terms as displayed in Table 7. This evaluation will take into account all other possible causal factors (e.g. medical history, risk factors, past drug use, concomitant procedures, TB progression).

Table 7: Causality Categories Definitions (endTB)

Causality Category	Description
Related	<p>There is a reasonable possibility that the AE may be related to the drug(s). Elements in favour of a reasonable causal relationship include:</p> <ul style="list-style-type: none"> • A favourable temporal relationship • A positive dechallenge and/or rechallenge

	<ul style="list-style-type: none"> • A plausible pharmacological/biological mechanism of action (whether proven or potential) • Previous knowledge of similar reaction with the drug(s), • No other evident cause (e.g. previous disease, other drugs) <p>There is insufficient information to evaluate the causal relationship between the AE and the exposure. Conservatively, the AE should be considered related to the drug(s) until a proper assessment is feasible (i.e. upon follow-up).</p>
Not Related	<p>There is no reasonable possibility that the AE is related to the drug(s). This implies that there is a plausible alternative cause for the AE that better explains the occurrence of the AE or that highly confounds the causal relationship between the drug(s) and the AE.</p>

7.3 Clinical Management of Adverse Events of Interest

7.3.1 Peripheral Neuropathy

Possible drugs in the novel regimen to cause peripheral neuropathy: Lzd and Lfx

- Peripheral neuropathy is a common side effect of Lzd, and may also be caused by Lfx.
- Skin punch biopsies, nerve conduction studies or other specialized tests are the gold standard but are not necessary for a diagnosis.
- According to the ACTG Brief Peripheral Neuropathy Screen (BPNS), a patient can be diagnosed with peripheral neuropathy if he/she reports typical symptoms (numbness, tingling, burning, pain) plus decreased vibration sense in the big toes or decreased ankle tendon reflexes.
- When assessing the patient's symptoms with the BPNS (See Step 1 of the BPNS description), assess whether his/her symptom is suggestive of neuropathic pain. Although difficult to define and variable for each individual, neuropathic pain is often described as "burning", "electric", "tingling", and "shooting" in nature. It can vary from a constant pain to intermittent sharp shooting pains. As described, the pain is most often present without associated stimulation, but can be exacerbated by stimuli.

Suggested management strategy:

- Many patients experience improvement when offending drugs are suspended, especially if the symptoms are mild.
- The neuropathy associated with Lzd is common after prolonged use and often extremely painful and irreversible. For this reason, Lzd should be immediately stopped and not reintroduced when symptomatic neuropathy develops (grade 2 or above). If this occurs, the Central Clinical Committee will provide advice regarding alternative TB medications.
- Provide symptomatic relief with non-steroidal anti-inflammatory drugs or acetaminophen. Tricyclic antidepressants have also been used successfully.

7.3.2 Myelosuppression (anemia, thrombocytopenia, or neutropenia)

Possible drug in the novel regimen to cause myelosuppression: Lzd

- Myelosuppression is very common with Lzd
- It is also important to evaluate for other causes of anemia, such as acute blood loss, TB, and iron-deficiency.

Suggested management strategy:

- Stop the causative drug immediately.
- Monitor full blood counts regularly.
- Hospitalize the patient and consider transfusion if the myelosuppression is severe.
- Consider additional anti-TB drugs to reinforce the regimen, in consultation with the Central Clinical Committee.

7.3.3 Prolonged QT Interval

Possible drugs in the novel regimen to cause prolonged QT interval: Cfz, Bdq, Lfx

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

Suggested management strategy:

- Stop all QT prolonging drugs immediately. ART is usually not stopped unless the patient is severely unstable.
- Hospitalize patient for severe QT prolongation
- Check and replete electrolytes.
- Once stable (QT interval below 450 and normal electrolytes), critical QT prolonging anti- TB drugs can be added back, starting with the most critical drugs first, in discussion with the Central Clinical Committee.

Once stable (interval below 450 and normal electrolytes), critical QT prolonging drugs may be added back, starting with the most important drug first.

7.3.4 Optic Neuritis

Possible drugs in the novel regimen to cause optic neuritis: Lzd

- Optic neuritis is inflammation of the optic nerve. The first sign of optic neuritis is usually the loss of red-green color distinction. This is best tested by using the Ishihara test. Other symptoms include central scotomas.
- Optic neuritis that is due to Lzd usually develops after four months of treatment.
- Patients with diabetes are at increased risk for optic neuritis. They should be managed with tight glucose control as a means of prevention. Patients with advanced kidney disease are also at increased risk for optic neuritis.

Suggested management strategy:

- Do not restart the suspected causative drug (Lzd)
- Refer patient to an ophthalmologist for immediate evaluation and management.
- Optic neuritis generally improves following cessation of offending drug, if it can be stopped early enough.
- If Lzd is stopped, discuss alternative TB medications with the Central Clinical Committee.

7.3.4 Hepatotoxicity

Possible drugs in the novel regimen to cause hepatotoxicity: Z, Cfz, Bdq, Lzd.

- Hepatitis is characterized by nausea, vomiting, jaundice, scleral icterus, tea-colored urine, pale stool, and diminished appetite in the setting of elevated liver function tests.
- Mild elevation of liver enzymes, especially at baseline, may be related to TB rather than an adverse effect of treatment.
- Generally hepatotoxicity due to medications resolves upon discontinuation of suspected drug.
- In HIV coinfection, cotrimoxazole can be a cause of hepatotoxicity.

Suggested management strategy:

- If AST or ALT are over 3X the upper limit of normal in the presence of hepatitis symptoms, or 5X the upper limit of normal without symptoms, stop all ant-TB drugs, and discuss management strategy with the Central Clinical Committee.
- Treatment may be re-introduced after ALT and AST have normalized. Anti-TB drugs should be reintroduced in serial fashion by adding a new medicine every 3 to 4 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 Z. Consider additional TB drugs to reinforce the regimen, in discussion with the Central Clinical Committee.

8.0 OUTCOME MEASUREMENTS

There are some patients who can be retrospectively removed from the outcome analysis:

- Patients who are discovered to have second-line drug resistance after starting the shorter regimen. Patients who receive culture-based DST results several months after starting a shorter regimen may be switched to a conventional regimen. These patients should be removed from the outcome analysis. The numbers of such patients and reasons for the removal should be reported.
- Patients who are baseline sputum culture negative or contaminated. Culture conversion and final treatment outcome may be difficult to assess in patients who are truly culture-negative. Cultures up to 90 days before the treatment start date are acceptable to use as the baseline culture. The numbers of such patients and reasons for the removal should be reported.

Outcome analysis is based on "Definitions and Reporting Framework for Tuberculosis" of the WHO⁵:

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

- Treatment failed: Treatment terminated or need for permanent regimen change of ≥ 2 anti-TB drugs because of:
 - lack of conversion
 - bacteriological reversion after conversion to negative
 - evidence of additional acquired resistance to fluoroquinolones
 - adverse drug reaction
 - decision made by clinician to terminate the shorter regimen due to poor response.
- Died: A patient who dies for any reason during the course of treatment.
- Lost to follow-up: A patient whose treatment was interrupted for 2 consecutive months or more. (This category was previously known as defaulted.)
- Not evaluated: A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown, or where the shorter regimen was not available.)
- Treatment success: The sum of cured and treatment completed

The terms conversion and reversion of culture results are defined as follows:

- Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures taken at least 30 days apart are found to be negative. In such case, the specimen collection date of the first negative culture is used as the date of conversion.
- Reversion (to positive): culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures taken at least 30 days apart are found to be positive. For the purpose of defining Treatment failed, reversion is only considered when it occurs in the continuation phase.

Recurrent TB is defined as 1) two consecutive positive cultures or 2) one positive culture with clinical signs and symptoms and radiographic deterioration after cure or completion of treatment. An isolated positive smear or culture without clinical deterioration after treatment completion provides insufficient evidence to define recurrent TB. If genotyping is available, recurrent TB may be further classified as 1) relapse, 2) reinfection, or 3) undetermined.

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

9.0 DATA MANAGEMENT AND PROJECT REPORTING

Patient data will be recorded on standard NTP treatment cards and documents, and standard endTB documents that are already in use in Haiti for the use of new and repurposed MDR-TB medications.⁶ Monitoring indicators are given in Chapter 2 of the *Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis*.⁷

The objectives of project monitoring are:

- To ensure that the rights of human subjects are protected and that the conduct of the operational research is in compliance with the approved protocol.
- To identify constraints in the identification of MDR-TB suspects, sputum examinations, diagnosis of patients with rifampicin resistance, timely enrolment, pre-treatment assessment, initiation of treatment, management of adverse events, monitoring examinations during treatment, DOT services in the community, tracing of late patients, and assessment of outcome of treatment.
- To verify that the reported data are complete, timely and accurate.

Enrolment and progress of patient treatment should be reviewed on a quarterly basis by a committee that is designated for this purpose by the NTP.

Study results will be shared with national health authorities, stakeholders, and the larger scientific community, with the aim to influence and improve MDR-TB treatment within the country and globally.

10.0 HUMAN SUBJECTS PROTECTION

This study will follow the principles of the Declaration of Helsinki. The study protocol will be submitted to and approved by a local ethics review committee, and to ethics committees for all associated institutions, prior to initiation of the operational research. No patient will be enrolled into this study until the investigator has obtained the patient's informed consent.

10.1 Informed Consent

Patients who are eligible for inclusion in the study will be given information about MDR-TB and the novel shorter MDR-TB regimen. Patients will be provided with information in Haitian Creole that is understandable to them. The patients will be assured that their decision to participate in the study or not will not affect the quality of care they will receive. Once the patient agrees to participate in the pilot project, the patient will be asked to sign the consent form (or give a thumb print in the presence of a witness if illiterate).

All patients who are not eligible for the observational study, or refuse to be enrolled, or withdraw after enrollment, will be managed by a MDR-TB treatment regimen according to national guidelines.

11.0 References

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