
# Research Protocol - Effectiveness and safety of a simplified short regimen for Multidrug Resistant Tuberculosis treatment in Manzini Region, Swaziland

# Effectiveness and safety of a simplified short regimen for Multidrug Resistant Tuberculosis treatment in Manzini Region, Swaziland.

**MSF – Operational Center Amsterdam**

**Research Protocol**
April 2013

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## *LIST OF ABBREVIATIONS*

| | |
|---|---|
| AIDS | Acquired Immune Deficiency Syndrome |
| ALT | Alanine aminotransferase |
| Am | Amikacin |
| ART | Antiretroviral Therapy |
| BMI | Body Mass Index |
| Cfz | Clofazimine |
| Cm | Capreomycin |
| CRT | Clinical research team |
| DST | Drug Sensitivity Test |
| DR TB | Drug resistant tuberculosis |
| E | Ethambutol |
| ECG | Electrocardiogram |
| FLD | First line drugs |
| Gfx | Gatifloxacin |
| H | Isoniazid |
| Hb | Hemoglobin |
| HIV | Human Immunodeficiency Virus |
| IPT | Isoniazid Preventive Therapy |
| IUATLD | International Union Against Tuberculosis and Lung Diseases |
| Km | Kanamycin |
| Mfx | Moxifloxacin |
| MSF | Médecins Sans Frontières/Doctors without Borders |
| MDR TB | Multidrug resistant TB |
| MTB | Mycobacterium tuberculosis |
| MoH | Ministry of Health |
| MGIT | Mycobacteria Growth Indicator Tube |
| MIC | Minimum Inhibitory Concentration |
| NRL | National Reference Laboratory |
| OI | Opportunistic Infections |
| OCA | Operational Center Amsterdam |
| QTc | QT interval corrected per heart rate |
| Pto | Prothionamide |
| SLD | Second line drugs |
| TdP | Torsade de Points |
| TB | Tuberculosis |
| TSH | Thyroid stimulating hormone |
| VL | Viral load |
| WBC | White blood cells |
| WHO | World Health Organization |
| XDR TB | Extremely drug resistant tuberculosis |
| Z | Pyrazinamide |

## *SUMMARY*

Multidrug resistant tuberculosis (MDR TB) is a growing problem and few people have access to adequate diagnosis and treatment. The current recommended treatment regimen for MDR TB has a minimum of 20 months duration. Evidence from Bangladesh in 2010 showed that a 9-month short-course regimen could achieve a relapse free-cure rate of 88%. Several countries in West Africa started implementing similar regimens with similar outcomes. Evidence of effectiveness of this shortened regimen amongst HIV co-infected population is still limited. We propose an observational study to evaluate the effectiveness of a shortened course MDR TB regimen in the high HIV prevalence and high MDR TB prevalence setting of Manzini Region, Swaziland.

A prospective observational study has been designed. All patients with presumptive MDR TB indentified with rapid Xpert® MTB/RIF assay and later on culture confirmed MDR TB will be included in the study. The study regimen is composed of an intensive phase of at least 4 months duration of Pyrazinamide (Z) + Ethambutol (E) + Isoniazid (H) + Moxifloxacin (Mfx) + Kanamycin (or amikacin) (Km/Am) + Prothionamide (Pto) + Clofazimine (Cfz) and a continuation phase of oral drugs Z-E-Mfx-Pto-Cfz. Patients will be followed up until the end of treatment and during 12 months after treatment completion in order to evaluate the rate of relapse.

The primary outcome measure is the success rate and safety at the end of treatment, and relapse and re-infection rates during 12 months of follow up after completion of treatment in HIV co-infected patients. Secondary outcome measures include rate of adverse events, interim outcomes with sputum smear microscopy and culture conversion rates at 6 months and time to conversion, risk factors for non favorable outcomes, proportion of H-related mutations and evaluation of correlation between smear microscopy with culture to assess the safety of simplified monitoring with smear microscopy.

Data will be recorded in patient's clinical files and electronic databases and analyzed with *Stata 11.0.*

This study is a result of ongoing collaboration of MSF with the MoH in Swaziland; results will be shared with the national health authorities and the rest of the scientific community and aim to influence and improve treatment and care of patients with MDR TB.

## *INTRODUCTION*

MDR TB is a growing problem and few people have access to adequate diagnosis and treatment. The current recommended treatment regimen for MDR TB is lengthy with a minimum of 20 months duration, poorly tolerated and costly (WHO, 2011). As a result, implementation of MDR TB management in TB programs worldwide shows modest results.

In 2010, evidence was published from a cohort of MDR TB patients in Bangladesh treated with a 9-month short-course regimen, achieving a relapse-free cure rate of 88% (Van Deun, 2010). Following the Bangladesh experience, several countries in West Africa are piloting the implementation of similar regimens reporting similar impressive outcomes from the first cohorts. MSF is currently using the 9-month regimen in the Democratic Republic of Congo, South Sudan and Central African Republic.

HIV-related immunodeficiency is a risk factor for poor outcomes in MDR TB patients (Quy, 2006; Wells, 2007). A small number of HIV co-infected patients in West African countries have had equivalent outcomes to non HIV co-infected MDR TB patients when treated with the 9-month regimen (non published data, MDR TB meeting Yaounde, 2012). However, experience in using this regimen for HIV/MDR TB co-infected patients is limited and relapse in this group of patients is not yet sufficiently documented.

Children have characteristically paucibacillary tuberculosis and thus they may require shorter duration and fewer drugs than adults to treat MDR TB infection and they could benefit from this regimen; however evidence of MDR TB treatment in children is scarce. We aim to include children in this study.

Two of the drugs (Mfx and Cfz) included in this regimen have potential cardio toxicity with increased duration of QTc in ECG (that could potentially lead to ventricular arrhythmia). The AE with this combination of drugs has not been well evaluated, therefore we include this evaluation as an objective in this study.

We are aware of the quick development of new anti-TB drugs on the market, and MSF is intending to invest in trials looking closer at new drugs to find a new regimen that can change the way we treat TB and MDR TB. However, we believe that this shorter regimen might be of immediate benefit for the patients that are in need of treatment today. Therefore, we propose an observational study to evaluate the effectiveness and safety of this short-course MDR TB regimen in the high HIV prevalence and high MDR TB prevalence setting of Manzini Region, Swaziland.

## *CONTEXT*

Swaziland is a small landlocked country of 1.1 million people bordering South Africa and Mozambique. Swaziland is experiencing a dual epidemic of HIV and TB; the prevalence of HIV among adults aged 15-45 years is 31% (CDC, 2012) and TB incidence is estimated to be 1,287/100,000/year (WHO, 2010). In addition, MDR TB cases have been rising rapidly over the last decade. In 2009, the proportion of MDR TB among newly diagnosed TB cases was 7.7 % and 33.8 % among previously treated cases (Sanchez-Padilla, 2012).

As a result of the dual epidemic, MSF established operations in the Shiselweni region of Swaziland (Operational Center Geneva) in 2007 and in the Manzini region (Operational Center Amsterdam) in 2010. The MSF OCA project is focused on provision of comprehensive health care with integrated HIV and TB/MDR TB components in Manzini region, including support to MoH in the third largest TB hospital in the country (Mankayane Hospital) and a primary health center (Matsapha Comprehensive Health Care Center).

Due to the complexity of care, long treatment duration and budget constraints, the majority of patients at risk for MDR TB in Swaziland still remain untested, and those diagnosed often do not start treatment. In 2010, the country reported a 66% TB case detection rate and of the total TB case notifications, only 6% of the patients were investigated for MDR TB (WHO country profile, 2011). Of the confirmed cases with MDR TB, according to the National TB Reference Laboratory, only 50% were initiated on MDR TB treatment (unpublished national monitoring data). It is estimated that in Swaziland, there are more than 2,000 incident MDR TB cases yearly, in 2010 only 344 patients initiated treatment for MDR TB (WHO country profile, 2011). In order to provide access to effective treatment for all TB patients, there is a need to investigate simplified, shorter and better tolerated regimens for MDR TB treatment.

## *LITERATURE REVIEW*

### Methodology of the literature search

Literature available was reviewed to summarize the most relevant references about short MDR TB treatment regimens with or without HIV co-infection in resource-limited settings. All types of studies, participants and interventions have been considered in this review. Scientific databases searched include PubMed and MeSH. We also gathered unpublished evidence from conferences and expert meetings.

### Literature

MDR TB treatment outcomes are mostly documented from long regimens for more than 20 months and most often in low HIV prevalence settings and non HIV co-infected populations.

Treatment success rates of MDR TB programs involving a 20+ month treatment regimen are 62-64% (Orenstein, 2009; Johnston, 2009). Treatment regimens are designed based on low quality evidence, mostly from single arm retrospective cohort reports, expert opinion and anecdotal experience (WHO guidelines for the programmatic management of DR TB, 2011 update). Outcome results come largely from low HIV prevalence settings where outcomes in HIV co-infected patients are poorly documented. However, there is some data on MDR TB treatment outcomes in HIV co-infected patients, success rates reported vary from 17% in New York (Munsiff, 2006), 40% in South Africa (Farley, 2011) or 48% in India (Isaakidis, 2011). Culture conversion rate as an interim indicator of treatment success during MDR TB treatment is also scarcely reported in MDR TB and HIV co-infected patients and it varies from 52% at 4 months in 71 patients cohort (Isaakidis, 2011) to 85% at 6 months in a small cohort of 36 patients (Brust, 2011). At the moment none of these outcomes is yet a reflection of optimum MDR TB programs.

WHO cites that the current recommendation for the duration of MDR TB regimens is based on low quality evidence and it concedes that a shorter regimen would be preferable, but due to a lack of evidence for an optimal alternative, no short-course therapies have yet been endorsed. Cost of drugs is an additional limiting factor for a major scale up of MDR TB programs. The drugs alone for the 20+ month regimen cost approximately 4,000 Euros. In Swaziland, the cost of a full 24 month course of treatment, which includes temperature sensitive PAS, is 4,150 Euros.

A standardized short-course treatment regimen for MDR TB including Kanamycin (Km), Gatifloxacin (Gfx), Clofazimine (Cfz), Prothionamide (Pto), Pyrazinamide (Z), Ethambutol (E) and Isoniazid (H) for 4 months (intensive phase) and 5 months of E, Z, Gfx, Cfz (continuation phase) has demonstrated effectiveness in a prospectively followed cohort of patients in Bangladesh. This 9-month regimen, costing approximately 200 Euros, including Gfx, Cfz and high dose H established a relapse-free cure rate of 87.9% (95% CI, 82.7-91.6) among 206 patients (Van Deun et al 2010) and a culture conversion rate of 85% at 2 months of treatment. Updated data in this cohort of patients enrolled until 09/2010 show a cure, relapse-free rate of 85% among 493 patients (IUATLD conference Lille, 2011). In addition, adverse events recorded are significantly less frequent and less serious than those that have been reported for the 20-month WHO regimen (Shin, 2007).

Three West African countries (Benin, Cameroon and Niger) have implemented the same or a very similar regimen; unpublished evidence so far has shown excellent treatment outcomes. Cameroon is implementing a 12-month course Gfx-based treatment with Pto for the entire

treatment duration. This cohort has a 20% HIV co-infection rate with cure rate amongst the HIV co-infected cohort of 87% and no short term relapse. Benin has similar successful outcomes from implementation of a 9-month MDR TB treatment regimen where Gfx is replaced by Moxifloxacin (Mfx) as a 4$^{th}$ generation quinolone and Pto during the entire regimen. Gfx was replaced by Mfx due to the problems and availability of Gfx and concerns about its safety. In this cohort also 18.5% of the cohort was co-infected with HIV. According to personal communication with The International Union Against Tuberculosis and Lung Diseases (IUATLD), Benin and Niger are reducing treatment length to 9 months due to significant findings of its efficacy. Other countries like Central African Republic are looking into piloting this regimen. None of these countries have reported any major tolerance problems or adverse events in their study populations. However, those cohorts are still very small and the overall number of HIV co-infected patients is less than 50 patients. As a result of the above evidence, the 9-month MDR TB regimen has been formally recommended by the IUATLD for confirmed MDR TB cases (Ait-Khaled N, 2010).

## *HYPOTHESIS*

A standardized short-course MDR TB treatment regimen (of 9-12 months) is effective and safe in a high HIV prevalence population.

## *RESEARCH OBJECTIVES*

### Main objective

To describe outcomes at end of treatment and relapse rate at 1 year and safety following treatment completion of a short course (9-12 month) MDR TB treatment in HIV co-infected patients in programmatic conditions in Manzini region, Swaziland.

### Secondary objectives

1. To describe sputum smear microscopy and culture conversion rates at 6 months and time to sputum conversion in both: HIV/MDR TB co-infected patients and MDR TB/HIV negative patients.
2. To describe outcomes at end of treatment and relapse after 1 year of treatment completion of MDR TB treatment in HIV negative patients.
3. To describe the adverse events of the treatment regimen in both: HIV/MDR TB co-infected patients and MDR TB/HIV negative patients.
4. To evaluate risk factors for unfavorable outcomes (death, lost-to-follow up and failure) and relapse as a combined cohort.
5. To describe proportion of *inhA* and *katG* mutations for H and correlation with DST for high dose at MIC 1.0 mg/ml amongst MDR TB cases and examine whether genetic mutations for H are risk factors for favorable or unfavorable outcomes (including description of outcomes

per baseline level of resistance to H), to increase understanding of the role of high dose H in the regimen.

6. To describe the proportion of relapse and re-infection amongst the patients developing TB at 1 year after treatment completion by genotyping.
7. To describe the correlation of smear microscopy with culture to assess the safety of a simplified monitoring with smear microscopy for MDR TB treatment.
8. To describe the rate of resistance amplification amongst patients with outcome failure.

## *PATIENTS AND METHODOLOGY*

### 1. Study design

We aim to conduct a *prospective observational cohort study* in two sites.

### 2. Study sites

The two study sites will be Matsapha Comprehensive Health Care Center and Mankayane Hospital TB Unit. Matsapha Health Care Center is a primary health center offering general out-patient department care, ante-natal, HIV and TB care and Mankayane hospital is the third largest TB hospital in the country where MSF is supporting the MoH on the integration and decentralization of MDR TB care in their ongoing HIV and TB care. All access to diagnosis and treatment is for free in both health units.

### 3. Partnership/study coordination

The study will be conducted in a partnership between the Ministry of Health of Swaziland and Médecins Sans Frontières/Doctors without Borders (MSF) – Operational Center Amsterdam (OCA). The National Tuberculosis working group representing the MoH will also approve and follow up the implementation and analysis of the study together with MSF study coordination. The National TB Program is actively collaborating in the study.

A study team, known as the Clinical Research Team (CRT) will consist of members of the caregiver team in each site. Each CRT will consist of 1 medical doctor, 1 nurse and 1 counselor led and guided by a study coordinator, the national MDR TB program focal point from MoH will be part of the CRT. The study coordinator will be responsible for the implementation of the study procedures in both clinical sites. The study team will assure correct implementation and follow-up of the study procedures and will discuss study developments and all complex cases with the reference persons (HIV/TB adviser) at the head office level (MSF OCA).

## 4. Study participants and sample size

The study population will constitute all consecutive presumptive MDR TB patients (adults and children) identified by screening with Xpert® MTB/RIF or with MGIT-culture/first line drugs DST (in case of initial Xpert® MTB/RIF negative) and children suspected of MDR TB diagnosis who are close contacts of a confirmed MDR TB patient at the two participating study sites. Participants will fulfill the inclusion/exclusion criteria outlined below as eligible for taking the short MDR treatment regimen and fill an informed consent form.

Patient Inclusion criteria:

- New presumptively diagnosed MDR TB patients (adults and children) with Xpert® MTB/RIF or confirmed from MGIT culture/DST if initial Xpert® MTB/RIF negative;
- Children (<14 yo) suspected of MDR TB without bacteriological confirmation but documented as a close contact of a MDR TB confirmed patient;
  AND
- Informed consent to participate in the study signed by the patient or the responsible caretaker for patients <16 years old (as per national legislation).

Of note, patients with a history of prior treatment with second line anti-TB drugs will be included. Of them, patients who are severely ill will initiate empirical treatment regimen and patients who are clinically stable will wait for bacteriological confirmation (with MGIT culture and DST) of MDR TB (this aims to prevent further amplification of resistance by further exposure to partial treatments with second line drugs in the eventuality of these cases having any SLD resistance).

Patients with documentation of resistance to Ofx (but not to Mfx, and not to Am/Km) will be included in the regimen.

Exclusion criteria at baseline:

- Baseline contraindications to any medications of the study regimen medications, where benefits of the regimen do not outweigh the risks as judged by treating physician;
- Severe renal insufficiency with Creatinine clearance of <30 ml/min at baseline (calculated with Cockcroft-Gault formula);
- Patient with probable or proven involvement of meninges and bones will be excluded from the study because of the different complexity of their management;
- Patients with documented XDR TB (additional resistance to SLD Kanamycin/Amikacin AND Ofloxacin/Moxifloxacin);
- Resistance to Km/Am and Cm.

- Resistance to Mfx.
- Patients with prior documented ECG abnormality such as confirmed prolongation of QTc interval.

Of note, pregnancy and breastfeeding are not exclusion criteria. Consideration to treatment initiation after the first trimester (12 weeks of pregnancy) as it is done with the standard 20+ month regimen and comprehensive information and counseling of risks and benefits will be offered to pregnant women. We decide to include pregnant women because the alternative is a longer regimen with similar toxicity risks and similar safety class drugs and with limited evidence of safety as well.

Withdrawal from study and analysis:

All patients included on the 9-12 month regimen and thereafter found to be either:

- Non MDR TB or
- XDR TB with resistance to Km/Am and Ofx/Mfx with MGIT culture and FLD/SLD-DST or
- Showing resistance to all Km/Am and Cm.
- Showing resistance to Mfx.

In case of resistance only to Am/Km the regimen will be adjusted with the use of Cm at the same dose as Km and this adjustment of regimen will not be considered as change of regimen and therefore will not be cause of withdrawal.

Withdrawal from study but included in intention to treat analysis:

- Withdrawal of consent to participate in the study.
- SAE necessitating change of regimen including prolongation of QTc after treatment initiation.
- Transfer out patients to centers where short regimen cannot be provided.

Patients that withdraw from the study will be offered adjusted treatment regimen according to DST pattern and following international WHO recommendations.

Sample size

The calculation of sample size is based on the expected rate of favorable treatment response of documented TB (defined as cured and absence of relapse at 1 year after treatment completion). The success rate with the current treatment (20+ months) is on average 60% regardless of HIV status (MSF- OCG Swaziland cohort reports overall success rates of 61% from program reporting in 2011). Cohorts of HIV co-infected patients show lower rates of success below 50% (Farley, 2011; Isaakidis, 2011). We hypothesized that a favorable response rate

above 75% for intention-to-treat patients would show that the shortened regimen results in good patient outcomes.

We expect a study withdrawal rate (study withdrawal as defined above) by the end of the follow-up period of 15%.

Patients will be included regardless of HIV status; however, as the main objective is to describe effectiveness in HIV positive populations, the sample size will be powered to inclusion of HIV co-infected patients. Cohort sample size with 95% confidence interval for different expected response rates and power:

| Treatment response | Power | Alpha | HIV+ Cohort size | + withdraw rate (15%) |
|---|---|---|---|---|
| 0.7 | 0.80 | 0.05 | 172 | 198 |
| 0.7 | 0.90 | 0.05 | 233 | 268 |
| 0.7 | 0.95 | 0.05 | 291 | 335 |
| 0.75 | 0.80 | 0.05 | 71 | 82 |
| 0.75 | 0.90 | 0.05 | 97 | 112 |
| 0.75 | 0.95 | 0.05 | 122 | 140 |
| 0.8 | 0.80 | 0.05 | 36 | 42 |
| 0.8 | 0.90 | 0.05 | 50 | 58 |
| 0.8 | 0.95 | 0.05 | 64 | 74 |

As we have included the relapse rate (confirmed by genotyping) in the primary objective, we also calculate a sample size for the number of HIV positive patients needed to be followed for 12 months after treatment completion. For that, we expect a relapse rate of 3% with an error rate of 0.06, alpha level of 0.05 and power 0.80; the estimated sample size of patients who successfully completed 9-12 months of treatment would need to be of 92 patients. Assuming 10% of loss to follow up after treatment we estimate a required sample size of 102 HIV positive patients completing treatment.

Taking all that into account, we propose and initial sample size including at least 120 HIV/MDR TB patients assuming a withdrawl rate of 15% for an estimated favorable response rate of 75%.

Currently, the average number of MDR TB/HIV positive patients identified with Xpert® MTB/RIF is 10 per month in both sites (considering an 80% HIV/TB co-infection rate). Based on that, the estimated period for recruitment will be for a minimum of 10 months (from March 2013) with patients enrolled consecutively.

## 5. Study endpoints

**Primary**

- Rate of success (cure and treatment completion) at the end of short course MDR TB treatment.
- Rate of relapse at 12 months after treatment completion.
- Rate of "QTc prolongation" event.

**Secondary**

- Rates of cure and success per groups of MTB resistance patterns (specifically Ofx resistance).
- Rates of sputum conversion and time to sputum conversion.
- Occurrence, type and severity of treatment-related side effects.
- Treatment interruptions and modifications of treatment.
- Unfavorable outcomes (default, death, failure) while on treatment.
- Risks factors for unfavorable outcome (death, default, failure).
- Rate of *inhA* and *katG* mutations in MDR TB samples and rates of correlation with DST for high dose isoniazid.
- Rate of re-infection.
- Rate of correlation smear microscopy/culture during treatment monitoring.
- Rate of resistance amplification amongst patients with outcome failure.

**Interim analysis**

The program will be routinely monitored producing quarterly results on sputum culture conversion rates and outcomes and severe adverse events. We define a minimum acceptable level of culture conversion below which we will consider study interruption based on the current rate of culture conversion in Swaziland which is 40% for overall cohort at 6 months. Sputum culture conversion rate of HIV co-infected patients at 3 and 6 months after commencement of treatment for the first cohort of 50 patients (compared to historical cohort data from Swaziland programme of time to culture conversion) will offer interim analysis with acceptable 95% confidence intervals.

For extra-pulmonary TB patients who require bacteriological proof of MTB in follow up examinations where it is not possible to obtain those patients will be excluded for the analysis of endpoints.

## 6. Case Definitions

### a) Diagnosis of MDR TB

Diagnosis of MDR TB will be done after sputum (or extra-pulmonary) sample screening with Xpert® MTB/RIF when obtaining result MTB+/Rif+, or with positive MGIT culture/DST of Xpert® MTB/RIF negative patients with clinical suspicion of TB. All patients suspected of TB will be

referred for screening with Xpert MTB/RIF®; one sample will be tested per patient. If a suspected patient is Xpert® MTB/RIF negative, the diagnosis investigation will follow the national algorithm for TB diagnosis (see Annex 1). All identified Xpert® MTB/RIFMTB+/Rif+ patients will be further evaluated and sputum samples will be referred for confirmation with gold standard conventional liquid culture (MGIT) and first line and second line DST. Culture and DST will be considered gold standard for confirmation or exclusion of MDR TB diagnosis.

Rifampicin resistance in Xpert® MTB/RIF will be used as a proxy for MDR TB diagnosis. After Xpert® MTB/RIF testing and presumptive diagnosis, patients will start empirical MDR TB regimen (short regimen with R added to the second line drugs regimen) while awaiting confirmation from conventional culture and DST. Patients with confirmation of MDR TB from culture/DST will continue treatment with second line TB drugs and R will be withdrawn from the regimen (see treatment protocol in Annex 1).

For suspected extra-pulmonary TB patients, extra-pulmonary tissue samples will be analyzed with Xpert® MTB/RIF assay, smear microscopy and MGIT-culture, including FL-DST. Presumptive (based on Xpert MTB+/RIF+) or microbiologically proven (by MGIT culture and FL-DST) extra-pulmonary MDR TB will be included in the study in the same way as pulmonary MDR TB. Bacteriological follow up of extra-pulmonary manifestations will not be done routinely, but the patients will be followed up on clinical grounds. For analysis of endpoints which require bacteriological proof of MTB in follow up examinations those patients will be excluded.

Diagnosis in children will be made according to the following criteria (Annex 1):
1. Bacteriological confirmation from 2 sputum (or extra-pulmonary) samples screened with Xpert® MTB/RIF and obtaining result: MTB+/Rif+ or with positive MGIT culture/DST of Xpert® MTB/RIF negative patients with clinical suspicion of TB. Sputum samples will be obtained by spontaneous expectoration or sputum induction.
2. Children with clinically suspected TB who are contacts of MDR TB bacteriological confirmed patients.

Patients will be classified based on WHO criteria according to:
1. History of previous TB drugs use as new or previously treated patients with first or second line drugs.
2. Previously treated patients will be classified according to previous treatment outcome as relapse, treatment after default, treatment after failure of category 1, treatment after failure of category 2, transfer in or other.
3. Localization of the TB: pulmonary or extra-pulmonary.

### b) Diagnosis of HIV infection

HIV infection will be diagnosed according to the current national protocol in Swaziland. A patient is considered to be HIV positive if 2 different HIV rapid diagnostic tests (Determine® and Unigold®) are found positive.

## 7. Treatment options

### a) Treatment of MDR TB

The MDR TB regimen prescribed will be:

**Intensive phase:**

Pyrazinamide (Z) + Ethambutol (E) + Isoniazid (H) + Moxifloxacin (Mfx) + Kanamycin (or amikacin) (Km/Am) + Prothionamide (Pto) + Clofazimine (Cfz) for at least 4 months and until one negative culture documented with a maximum of 8 months duration.

**Continuation phase:**

Continuation phase of Pyrazinamide (Z) + Ethambutol (E) + Moxifloxacin (Mfx) + Prothionamide (Pto) + Clofazimine (Cfz) for fixed 5 months duration.

The regimen and dosage follows the regimen used in Bangladesh with no modifications, with the exception of including Pto during the entire duration of treatment as implemented in west African countries, and the replacement of Gfx with Mfx as 4$^{th}$ generation quinolones. We will not use Gfx as it is not broadly available in the market due to concerns about its safety. Documentation of dosages (adult and pediatric) is detailed in the clinical protocol (Annex 1). The dose of H is prescribed as in the regimen used in Bangladesh is a higher dose than conventional use. Pyridoxine will be added to the regimen for prophylaxis of peripheral neuropathy with the use of high dose of H in HIV co-infected patients as described in the clinical protocol.

All patients will initiate this regimen and response will be monitored with monthly smear microscopy and culture. From the experience with this regimen in other settings, patients show earlier culture conversion. However, as cohorts of HIV patients who have received this regimen are still small and HIV positive patients have shown delays in culture conversion, we aim for a short intensive phase of 4 months as in the regimen used in Bangladesh, but with the possibility to offer a prolonged intensive phase to a maximum of 8 months (intensive phase duration equivalent to the current standard WHO recommendations (2011) with the 20+ months regimen). Switch from intensive phase to continuation phase will require one negative culture; continuation phase will start at the moment of documentation of negative culture. The regimen used in Bangladesh based the switch to continuation phase on smear conversion. However, as our cohort will be mostly of HIV co-infected patients and currently 60% of patients with Xpert

MTB+ present smear microscopy negative, we opt for a switch based on at least one documented culture negative until further confirmation of correlation between smear microscopy and culture for monitoring purposes. In case a patient is unable to produce a sputum sample for monitoring due to good clinical evolution, switch to continuation phase will be done at 4 months after treatment initiation. In case a patient is persistently culture positive at 6 months (see below outcomes definition) or has 2 consecutive positive culture after becoming culture negative at the 6$^{th}$ month of prolonged intensive phase of the treatment, the patient will be given the outcome of failure (see below outcomes definitions) and the patient will stop the study regimen. In case of one isolated positive culture, if the patient shows clinical good evolution, the patient will continue the regimen awaiting results of a second culture to assess results. Patients with the outcome of failure will be counseled and offered continuation of treatment with regimen adjusted based on repeat DST, previous drug treatment history, national guidelines and study team and TB/HIV adviser recommendations. Provision of drugs for treatment of those patients will also be assured. Outcomes of these patients will be documented.

In case of resistance to Ofx, patients will still be included in the treatment regimen and outcomes in this subgroup of patients will be documented. In case of confirmed resistance to Am/Km, patients will be started (or switched if ETR already initiated) to Cm and will continue a shortened regimen; outcomes will also be documented for this subgroup of patients. Switch to Cm will not be considered a change of regimen.

Patients with confirmation of XDR TB (documented resistance to Am/Km and Ofx) will be withdrawn from the short regimen and removed from the study to initiate a more adequate regimen adjusted to the resistance pattern observed.

**b) Treatment of HIV/AIDS**

All HIV/MDR TB co-infected patients who are ART naïve will be started on first line ART following national and international HIV care and ART recommendations. All included HIV co-infected patients not yet on ART will start ART as soon as possible, between 2 weeks and 2 months after tolerating TB treatment. ART preferred first option will avoid the use of Tenofovir due to the increased risk of renal toxicity in co-administration with aminoglycosides.

Patients already on ART at the moment of MDR TB diagnosis will be thoroughly investigated for ART failure with HIV RNA VL and ART failure diagnosis algorithm following international and national recommendations. A second HIV RNA VL will be repeated after 3 months (after adherence counseling and effective MDR TB treatment initiation) and if ART failure confirmed patients will be initiated on second line ART.

HIV treatment and prevention/treatment of other opportunistic infections will be provided and recorded in the database following national and international recommendations.

ART initiation delay, ART interruption and ART outcomes will be recorded during the study period and taken into account for the analysis as this can influence TB treatment outcomes. ART response will be evaluated with HIV viral load at the end of the TB treatment period and at the end of observation period.

## 8. Monitoring of safety

The main objective includes investigation of safety associated with the use of Mfx and Cfz, which can have potential added cardio toxicity (increased QTc), and one of the secondary objectives is to assess the adverse events associated with the use of the proposed regimen and in combination with antiretroviral drugs in programmatic conditions in an African setting with high HIV prevalence. Therefore, ECG at baseline, at 2 weeks and 1 month after treatment initiation will be added to the complementary examinations and in addition, throughout the study period, all possible adverse events will be scrutinized by a systematic and standardized screening of clinical and/or laboratory data at each visit. The type, severity and possible relationship of side effects will be assessed according to the DAIDS grading score (Annex 2) adapted for the agents used in the current study.

The following **definitions will be use for adverse events and reactions**:
Adverse event (AE): any medical occurrence in a subject to whom a medical product has been administered including occurrences which are not necessarily caused by or related to that product. 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 (investigational) agent, whether or not related to the medicinal (investigational) agent.
Adverse reaction (AR): any unintended response to a medical product which is related to any dose administered to the subject.
Serious Adverse Event (SAE) and Serious Adverse Reaction (SAR): any event or reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization or results in persistent or significant disability or incapacity.

The decision to postpone, modify or to interrupt/discontinue the regimen will be left at the discretion of the clinical team following the patient in discussion with advisors. Some safety rules will be pre-established and standardized in the protocol of MDR TB short regimen management (Annex 1). According to expected toxicities suggestions for alternative management will be provided based on the current evidence and recommendations from the

WHO “Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008”. Any alteration in the scheduled regimen will be thoroughly registered and justified in the patients’ file and database.

Contraception will be systematically offered to the female participants during the treatment period, and a pregnancy test will be performed systematically before starting MDR TB treatment and at each treatment visit if there is uncertainty about consistency of correct contraceptive use. The need to pursue (or to stop) the treatment in case of pregnancy will be evaluated by the clinical team and advisors on an individual basis, according to the benefit/risk balance at that moment. Women who reject hormonal contraception are not excluded from the study.

## 9. Assessment of treatment effectiveness

We will use adjusted international WHO definitions to classify the type of response to TB treatment (see below). An assessment will be performed at the end of the treatment period, and a final assessment will take place at the end of the follow-up (12 months after completion of the treatment).

**Sputum conversion** will be defined as two consecutive sets of negative smears and cultures, from samples collected at least 30 days apart. The date of the collection of the first set of negative cultures and smears will be used as the date of conversion. In case of discordant results between smear and culture, culture will be considered the gold standard and reference test.
Both bacteriological techniques (microscopy and culture) will be monitored and documented throughout the treatment.

The TB treatment outcome at the end of the treatment period is defined as follows (adjusted outcomes definition for MDR TB programs WHO 2008, emergency update of guidelines for the programmatic management of drug resistant tuberculosis):

**Cure**: An MDR TB patient who has completed the treatment according to programme protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart.
If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.

**Treatment complete:** An MDR TB patient who has completed treatment according to programme protocol but does not meet the definition for cure because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final months of treatment) or otherwise, completion of treatment with documented bacteriological conversion persisting through the end of treatment, but fewer than five negative cultures. Treatment completion will only be an outcome for patients that are not able to produce sputum; in case of patients where the lack of bacteriological results is due to other reasons the outcome will be registered as "other" in order to avoid misclassification.

**Treatment outcome "other":** An MDR TB patient who has completed treatment according to programme protocol but does not meet the definition for cure because of lack of bacteriological results due to programmatic reasons (reasons other than the lack of patient's ability to produce sputum) such as culture contamination or no timely referral of sample by the clinician, the outcome will be registered as "other" in order to avoid misclassification. In case of contamination of the culture tube, new sputum samples for culture will be collected and culture tubes de-contaminated and re-inoculated following standard laboratory procedures.

**Death:** An MDR TB patient who dies for any reason during the course of MDR TB treatment and is not already classified as a treatment failure prior to death. Assumed causes of death will be recorded.

**Failure:** Treatment will be considered failed when there is absence of bacteriological response that will be defined as follows:

- Patient fails to show culture negative by the end of month 6 of a prolonged intensive phase.
- Culture positive during the continuation phase: two cultures positive during the continuation phase or one culture positive during the last 3 months of treatment.
- Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early because of poor clinical or radiological response or adverse events where the team decides the regimen is failing and treatment is changed. These latter failures can be indicated separately in order to do sub-analysis.

All failures with documented culture positive will have DST and investigation of resistance to document the rate of resistance amplification.

**Default:** An MDR TB patient whose treatment was interrupted for two or more consecutive months for any reason without medical approval and not meeting the criteria for failure.

**Transfer out:** An MDR TB patient who has been transferred to another reporting and recording unit and for whom the treatment outcome is unknown. Patients that require a transfer out will be informed that it is very unlikely that they can continue the same regimen and they will have to change to standard MDR TB regimen. In case that the treatment can be provided in the receiving center and the outcome documented, this will be recorded.

Outcome will be considered as favorable in case of cure or treatment completion. All other outcomes at the end of treatment (default, death, failure) will be considered as unfavorable.

At the end of the study follow up period the final outcome will be assessed and defined as:

**Relapse-free:** An MDR TB patient who meets the criteria of cured or completed short course of treatment and remains asymptomatic at the end of the follow up period (one year after treatment completion).

**Relapse:** An MDR TB patient who meets the criteria of cured or completed short course of treatment and at any time during the follow up period (first year after treatment completion) is subsequently diagnosed with at least one sample of bacteriologically positive MDR TB by culture and DST of the same strain found in initial diagnosis, proven by molecular techniques (*Mycobacterium tuberculosis* DNA fingerprinting).

**Re-infection:** recurrent disease as defined for a relapse, with a strain showing a molecular pattern different from the initial isolate.

The outcome of the HIV/AIDS disease at the end of the study period will be assessed by a combination of clinical findings (HIV infection stabilized/clinically controlled) and laboratory data (CD4 cell count and HIV RNA VL).

## 10. Study procedure and patient flow

The study protocol will be explained to all physicians and nurses in both facilities (Matsapha and Mankayane). They will confirm the clinical diagnosis of patients and together with the study coordinator will decide on patients' eligibility for inclusion in the study. Informed consent will be obtained at that moment.

The patient flow is described in the clinical protocol (Annex 1).

**Baseline visit at MDR TB diagnosis**

At baseline, the clinical history and physical examination will be evaluated and described in detail. Other baseline clinical data will consist of date of HIV diagnosis, HIV WHO staging, co-morbidities, Karnofsky score and ongoing therapies. A chest X-ray and ECG will be performed at baseline.
Laboratory examinations will include Xpert® MTB/RIF, sputum smear, sputum culture/DST and TB genotyping and in addition basic parameters (full blood count, liver transaminases, electrolytes, TSH, glucose and kidney function), as well as HIV parameters (CD4 cell count baseline for all and HIV RNA viral load in patients that have been at least 6 months on ART) and hepatitis B and C tests. Pregnancy testing will be performed systematically, and contraception will be offered to female patients during the whole treatment period.

**Daily Observed Therapy (DOT)**

Treatment will be administered and observed daily either at the clinical site, or at the home of the patient. All patients with severe clinical conditions will be hospitalized, and DOT will continue in that setting. Data on adherence and pill intake will be recorded. A team of nurse and counselor will assure daily observed therapy seven days per week. Treatment will be assured either by health care worker in direct observation, or by a treatment supporter as is currently the protocol for MDR TB management in Swaziland. Treatment supporters will not be part of the patient's family household and will receive a modest incentive for their time and effort; this is standard procedure in Swaziland implemented by the MoH.

**Follow up visit during treatment**

Patients will do clinical follow up at 2 weeks after MDR TB treatment initiation and then every 4 weeks (monthly) until treatment completion. At each visit, clinical assessment with evaluation of side effects including ECG monitoring and a set of laboratory tests will be performed according to schedule and clinical protocol (see table below and Annex 1). Evolution will be assessed by the doctor and/or nurse with a specific data collection form (drug-o-gram or treatment card) to assess treatment response and complications.

Any relevant clinical event (adverse events or reactions) and any required additional diagnostic testing and/or therapy will be recorded. In case of unexpected events, study participants will be advised where and to whom to present in emergency and they will have an emergency phone number to call.

Transport costs for to clinical visits will be reimbursed to the patient as it is currently done in the program.

**Follow-up after treatment completion/outcome visits**

All patients completing 9-12 months treatment will be followed up until 12 months after treatment completion. A follow-up visit will be planned every 3 months (or at any time earlier in case of re-occurrence of symptoms) for clinical assessment and a final visit will take place at month 12 post-completion to assess the final outcome (relapse).

Transport costs due to clinical visits will be reimbursed to the patient.

The examinations during the study visits are summarized in the following table:

| | **Baseline visit** *1st visit* | **Follow-up during treatment** | | | | | | **After finalizing MDR TB treatment Follow-up/outcome visits** | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | *Every 3 months after treatment completion* | *12 months after treatment completion* |
| | | 2weeks | 1M | 2M | 3M | 4M-end IP | CP | | |
| **Clinical assessment** | | | | | | | | | |
| Anamnesis<br>Physical examination (weight) | x | x | | | | | | x | x |
| Evaluation side effects | | At every clinical consultation | | | | | | x | x |
| Outcome assessment | | At end of treatment | | | | | | | x |
| **Laboratory** | | | | | | | | | |
| TB genotyping | x | | | | | | | In case of relapse | In case of relapse |
| Xpert® MTB/Rif | x | | | | | | | In case of relapse | In case of relapse |
| Smear | x | | x | x | x | Monthly | Monthly | In case of relapse | In case of relapse |
| Culture | x | | x | x | x | Monthly | Monthly | In case of relapse | In case of relapse |
| DST (1st and 2nd line) | x | | | | | Every 2 months | Every 2 months | In case of relapse | In case of relapse |
| Full Blood Count | x | | x | x | x | End IP | End CP | If clinically indicated | |
| Creatinine* | x | x | x | x | x | Monthly until stop of injectable | | | |
| ALT | x | | x | x | x | x | 3-monthly | | |
| Glucose | x | Monthly if elevated at baseline | | | | | | | |
| TSH | x | Perform once at 6 months and if patient has symptoms/signs suggestive of hypothyroidsm | | | | | | | |
| HepBs Antigen | x | Repeat only if indicated | | | | | | | |
| Hep C Antibodies | x | | | | | | | | |
| Pregnancy test | x | | | | | | | | |
| HIV | x | If negative, offer to repeat every 3 months | | | | | | | |
| If HIV+, CD4 | x | At 12 months after ART initiation, and then every 6 months | | | | | | | x |
| If HIV+, RNA VL** | x | At the end of MDR TB treatment completion | | | | | | | x |
| **Other complementary exams** | | | | | | | | | |
| ECG (QTc interval) | x | x | x | If develops syncope or dizziness | | | | | |
| Chest X-ray | x | Repeat only if clinically indicated | | | | | | | x |
| Hearing test (clinical and audiometry) | x | Monthly clinical assessment and audiometry to repeat if indicated | | | | | | | |

*for patients with higher risk of renal insufficiency the monitoring of Creatinine may need to be more frequent. This includes diabetes, elderly and baseline renal dysfunction and in case of co-treatment with TDF.

**if on ART for at least 6 months at MDR TB treatment initiation.

**Informed consent procedure**

All patients at the moment of diagnosis and prior to treatment initiation will be offered the informed consent with thorough explanation on the study and their invitation to participate in the study.

### 11. Laboratory tests and ECG

Hematology, biochemistry, CD4 and Xpert® MTB/RIF assay will be performed with the current available techniques at each site. TSH will be performed by Lancet laboratories (South Africa).
HIV-RNA VL testing will be performed by MSF OCG, Nhlangano, Swaziland.
MGIT Culture and DST for first line drugs will be performed at National Reference Laboratory (NRL) in Mbabane. Smear examination is also performed at the NRL prior to culture.
DST for second line drugs (including Mfx and Cfz) and *pncA* sequencing for PZA resistance will be performed at the tuberculosis supranational reference laboratory of the Institute of Tropical Medicine in Antwerp, Belgium.
Molecular fingerprinting of *Mycobacterium tuberculosis* will be performed at MRC Centre for Molecular and Cellular Biology, Department of Biomedical Sciences, Stellenbosch University, SA.

At the moment of diagnosis the positive primary culture will be stored at the Swaziland NRL and if a suspected relapse/re-infection occurs, a sputum sample will be tested with molecular genotyping in order to diagnose relapse/re-infection. A material transfer agreement will be signed will all laboratories to ensure that samples are destroyed at the end of the study.

ECG

Both moxifloxacin and clofazimine may potentially prolong the QT interval as measured on an electrocardiogram. Prolonged QT interval in the presence of some drugs has been associated with torsade de pointes, which is a life threatening arrhythmia. However, a direct link between QT prolongation and torsade de pointe arrhythmia has not been established, and prolonged QT can occur without increased risk of arrhythmia (Giorgi, 2010).

While the death rates in the cohort studies of the short course regimen that have been reported are low, it is not known whether this will be the case in other populations. In Swaziland, the combination of clofazimine and moxifloxacin has been used in drug regimens for the treatment of XDR TB and some patients failing MDR TB treatment. Anecdotally there has not been cases of sudden death that could be due to arrhythmia, however there has not been specific monitoring with ECG and it is possible that if cases did occur they would have been missed. As there is no universal threshold for identifying drug-induced QTc prolongation, and given the experience of combining these 2 drugs together already (with a higher dose of clofazimine), the thresholds chosen for QTc will be when the QTc exceeds >60ms compared

with the baseline ECG QTc or when the QTc prolongs beyond 500 ms, as these are thresholds that have been associated with the highest risk (Fenichel, 2004). 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.

As safety of this regimen is part of the main objective, a baseline ECG, an ECG at two weeks and at 1 month will be performed. The ECG machine will be located in both health centers and this complementary examination will be part of the routine monitoring of patients after treatment initiation. Patients with an extension of the QT interval from baseline of greater than 60 ms or a QTc of greater than 500 ms will have treatment withheld and will be discussed with the study coordinator and TB/HIV adviser. Reversible causes such as low potassium and magnesium will be checked for and corrected and a decision about stopping treatment or continuing with weekly ECG monitoring will be made based on whether the QTc persists above the thresholds despite correction of reversible factors.

### 12. Variables

The following variables will be collected and monitored (see Annex 3 data collection forms). The follow-up treatment card (or drug-o-gram) is the standard monitoring tool for the follow-up of patients on MDR TB treatment. These variables will allow monitoring the treatment response, safety and risk factors for unsatisfactory response:

- Demographic variables: age, gender.
- Physical examination: weight, height, BMI, hearing test (clinical and audiometry).
- TB: Date of diagnosis, date of treatment initiation, localization, dates of laboratory tests, TB classification according to treatment history, adherence, previous IPT, MDR TB regimen drugs.
- HIV status and date of HIV diagnosis, cotrimoxazole and other prophylactic treatments, ART, type of ART, ART starting date, adherence, and ART outcome.
- Co-morbidities including diabetes mellitus and opportunistic infections.
- Karnofsky score.
- Clinical diagnosis/complications.
- Chest X-ray abnormalities.
- ECG: QTc interval.
- Laboratory: TB smear, Xpert® MTB/RIF, MGIT culture, DST, TB molecular fingerprint, total cell count, Hb, CD4 cell count, HIV RNA VL, ALT, Creatinine, pregnancy test, TSH, glucose, Hepatitis Bs Antigen, Hepatitis C antibodies.
- Side effects: hematologic, peripheral neuropathy, optic neuropathy, gastrointestinal effects, fever, dermatologic events, renal, hepatic, auditive, thyroid.

- TB Outcomes: culture conversion, cure, completion, death, failure, defaulter, transfer out and relapse/re-infection.
- Documented cause of death.

**13. Data collection**

Data collection forms will be used (see Annex 3). Data will be collected at baseline and at each study visit. Data from these forms will be entered into the MSF MDR TB database (Koch'6) that is already in use in the project. HIV-related data is not foreseen to be collected in Koch'6, it will be exported and cross matched from a separate database that will collect all the HIV-related data during the study. Data will be exported from both sources and merged into a single dataset in Stata for statistical analysis.

**14. Statistical Analysis**

Statistical analysis will be done in *Stata 11.0* statistical package. During the analysis, withdrawal from study (as described above) will be handled in 2 ways: an intention-to-treat analysis where patients who are withdrawn from the study will be considered as treatment failures and a per-protocol analysis where withdrawn patients are excluded from the analysis.

The following statistical analyses will be done:

1. Analysis of rates of treatment outcomes.
2. Rates of relapse from same TB strain.
3. Survival analysis for mortality and relapse to obtain Kaplan-Meier survival graphs for mortality and time to relapse.
4. Analysis of rates of QTc interval prolongation.

For the secondary objectives the following analyses will be done:

1. Patients' baseline characteristics.
2. Rates of sputum conversion and survival analysis for time to culture conversion.
3. Rates and severity of side effects.
4. Univariate analysis to assess risk factors for unfavorable response and confounding factors will be investigated and adjusted in a multifactorial model (Cox proportional hazards model). Hazards Ratio will be investigated for each risk factor with a 95% confidence interval and a level of significance of 0.05.
5. Proportion of *inhA* and *katG* mutations amongst MDR TB patients and proportion of DST resistance to Isoniazid 1.0 mg/ml.
6. Rates of re-infection.
7. Rates of correlation between smear microscopy and culture on samples at same moment of collection.

## *ETHICAL ISSUES*

### 1. Ethical Committee

The study will be conducted following approval of both ethical committees of Médecins sans Frontières and the National Ethical Review Board of Swaziland.

### 2. Consent forms

A written informed consent form in English and the local language (*siSwati* or *isiSwazi)* will be given, explained and read to the patients prior to the enrolment in the study (Annex 5). Only patients from whom a signed (or fingerprint for those not able to write their name) informed consent has been obtained will be included in the study. For children <16 years old, informed consent will be obtained from the legal guardian. The information will include the aim of the study, data collection procedures, potential benefits and risks, and assurance of confidentiality. The consent process will make clear that it is the individual's decision to participate in the study or not, and this will not affect the quality of their care. Similarly they will be free to withdraw from the study at any time. Patients refusing participation in the study or use of data for the study will also be eligible for a shortened regimen of MDR TB.

### 3. Expected risks and advantages

The study regimen uses first and second line MDR TB drugs which are recommended for use in HIV positive patients. These drugs are well known to cause side effects, some of which may be severe. However, the best evidence we have is that the side effects are fewer with the study regimen than with the longer WHO recommended regimen. There is a risk of interaction of the TB drugs with ARVs; this risk applies to both the standard regimen and the study regimen and is judged to not be worse with the study regimen; we expect a lower rate due to the shorter duration of treatment. There is a risk of amplification of resistance if the regimen is not effective and in those cases treatment duration will have to be extended after adjustment of regimen if needed, and withdrawal from the study; however, this might not be a significant risk compared with the current treatment regimen that carries high toxicity and long duration. There is a risk that this shorter regimen is not as efficacious in HIV positive patients as the current 20+ month regimen; however results in predominantly HIV negative patients are considerably better both in cure rates and in relapse-free rates. In any case, the outcomes of the current regimen are already very modest with high defaulter rates and high risk of relapse.

Study participants will be required to undergo additional tests such as ECG, genotyping, viral load monitoring, and more frequent sputum samples in order to participate in the study. The results of these additional tests will be communicated to the patient and their physician and used to guide their treatment. Additional visits are required in order to determine relapse-free

survival time, however these visits will be integrated into routine HIV follow up in case of HIV co-infected patients; in case of HIV negative patients, additional follow up visits will have to be scheduled after treatment completion. Overall the number of visits will be decreased compared to routine 20+ month treatment due to the shorter treatment course.

The main advantage of participating in the study is that the individual patient may have MDR TB treated with a shorter and better tolerated regimen. The improved tolerability and shorter treatment time are presumed to lead to decreased defaulter rates, which are a main cause of poor treatment success with the current regimen despite best efforts of the program to improve adherence.

Patient participation is a contribution to scientific knowledge and literature about shorter MDR TB regimens in high prevalence HIV settings. Participation will help to improve the future of treatment and care for affected patients in Swaziland where the length of treatment, toxicity and cost of the current regimen do not allow for scale up of treatment in order to meet the overwhelming needs. The early engagement of the NTP at the concept stage, will help ensure that the MoH will review the results with a view to changing national protocol when the results are positive. MSF is committed to use the results to advocate both in and outside Swaziland to improve MDR regimens.

**4. Confidentiality**

All staff working at each clinical site will be trained in the importance of patient confidentiality. Patient names will be recorded in the clinical forms for the purpose of the clinical follow up. Patients will be identified by a unique ID number from the outset of the study and this ID number will be used for all study databases and reports.

**5. Community Involvement**

The rationale for the study will be presented to community members through patient groups and dissemination of results to media. Final dissemination of results will be shared with study participants and patients with HIV/TB.

## *BUDGET*

The available funding of the project will cover the costs related to the implementation of the proposed study protocol and additional to the ongoing budget for the program. The expected additional expenses related to the study that differ from the ongoing program implementation are detailed in the table below. During the study period, MSF OCA will provide all the required resources (diagnostic tests, TB drugs and additional human resources) which will be required in addition to the ongoing services.

| Nº | Type of expense | Quantity | Cost | Total USD |
|---|---|---|---|---|
| 1 | Second line drugs | 140 | 1000 USD per treatment | 140,000 |
| 3 | NICD, Stellenbosch fees | 1 | 500 USD | 500 |
| 4 | MTB genotype | 10 | 7 USD per test | 70 |
| 5 | HIV RNA viral load | | free | |
| 6 | Presentation study results to health authorities | | 3000 USD | 3000 |
| | **Expected total budget/site** | | | 143,770 USD |

## *TIMELINE*

- May 2012 – July 2012: development of the study protocol.
- July 2012: submission to ethical committees (MSF and Swaziland).
- March 2013: patient inclusion starts.
- December 2013: completion of patient inclusion.
- November 2014: treatment completion outcomes.
- December 2014: analysis of treatment completion outcomes.
- January 2015: dissemination of treatment completion results.
- November 2015: end of 12 months follow up after treatment completion of last patient included.
- December 2015: data analysis.
- Early 2016: Results shared with stakeholders in Swaziland.


## *ACKNOWLEDGEMENTS*

The researchers would like to thank the team in the MSF Swaziland mission and the Health Authorities of Swaziland for the collaboration and future contribution to the study. Special thanks to the team of TB/HIV advisors Philipp du Cros, Marcio Silveira da Fonseca and programs implementer Bern-Thomas Nyang'wa for the valuable contributions to this protocol.


## *DISSEMINATION OF STUDY RESULTS*

The preliminary results of this research will be presented as soon as possible in Swaziland and be used to discuss with key stakeholders how to further improve MDR TB treatment and management. The preliminary and final results of the research will be presented, shared and discussed with the MSF international TB working group. We also aim to publish the results in a peer-reviewed journal, preferably open access, to allow the widest possible access and benefit to health practitioners internationally.

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## *ANNEXES*

**Annex 1. MDRTB short course treatment protocol**

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**Annex 2. Adverse events classification and grading DAIDS**

**DIVISION OF AIDS (DAIDS) TABLE FOR GRADING THE SEVERITY OF ADULT ADVERSE EVENTS**
**PUBLISH DATE: DECEMBER, 2004**

*The below tables have been extracted from the 'DAIDS adverse event grading table'. We attempted to retain only those adverse events that, according to the literature, can be expected with the regimens in use in this study and taking into account as well the diagnostic means available in the study sites. However, whenever another clinical event is suspected to be an adverse event of the therapeutic regimen the patient is taking, clinicians can refer to the complete grading table.*

**General Instructions for use**

Estimating Severity Grade

If the need arises to grade a clinical adverse event that is not identified in the DAIDS adverse events grading table, use the category "Estimating Severity Grade". For adverse events that are not listed in the table but will be collected systematically for a study/trial, protocol teams are highly encouraged to define study specific severity scales within the protocol or an appendix to the protocol. This is particularly important for laboratory values because the "Estimating Severity Grade" category only applies to clinical symptoms.

Determining Severity Grade

If the severity of an adverse event could fall under either one of two grades (e.g., the severity of an adverse event could be either Grade 2 or Grade 3), select the higher of the two grades for the adverse event.

Definitions

- Basic Self-care functions: Activities such as bathing, dressing, toileting, transfer/movement, continence and feeding.
- Usual Social & Functional activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

| **CLINICAL** | | | | |
|---|---|---|---|---|
| ***PARAMETER*** | **GRADE 1 MILD** | **GRADE 2 MODERATE** | **GRADE 3 SEVERE** | **GRADE 4 POTENTIALLY LIFE-THREATENING** |
| **ESTIMATING SEVERITY GRADE** | | | | |
| *Clinical adverse event NOT identified elsewhere in this DAIDS adverse events grading* | Symptoms causing no or minimal interference with usual social & functional activities | Symptoms causing greater than minimal interference with usual social & functional activities | Symptoms causing inability to perform usual social & functional activities | Symptoms causing inability to perform basic self-care functions OR Medical or operative |

| CLINICAL | | | | |
|---|---|---|---|---|
| ***PARAMETER*** | **GRADE 1 MILD** | **GRADE 2 MODERATE** | **GRADE 3 SEVERE** | **GRADE 4 POTENTIALLY LIFE-THREATENING** |
| *table* | | | | intervention indicated to prevent permanent impairment, persistent disability, or death |
| **SYSTEMIC** | | | | |
| *Acute systemic allergic reaction* | Localized urticaria (wheals) with no medical intervention indicated | Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated | Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm | Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema |
| *Chills* | Symptoms causing no or minimal interference with usual social and functional activities | Symptoms causing greater than minimal interference with usual social and functional activities | Symptoms causing inability to perform usual social and functional activities | NA |
| *Fatigue, malaise* | Symptoms causing no or minimal interference with usual social and functional activities | Symptoms causing greater than minimal interference with usual social and functional activities | Symptoms causing inability to perform usual social and functional activities | Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions |
| *Fever (non-axillary)* | 37.7 – 38.6 °C | 38.7 – 39.3 °C | 39.4 – 40.5 °C | > 40.5 °C |
| *Pain (indicated body site)*<br>*Do not use for pain due to injection (see injection site reactions)*<br>*See also Headache, Arthralgia and Myalgia* | Pain causing no or minimal interference with usual social and functional activities | Pain causing greater than minimal interference with usual social and functional activities | Pain causing inability to perform usual social and functional activities | Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated |
| *Unintentional weight loss* | NA | 5-9% loss in body weight from baseline | 10-19% loss in body weight from baseline | ≥ 20% loss in body weight from baseline OR aggressive intervention indicated (e.g. tube feeding or total parenteral nutrition) |
| **INFECTION** | | | | |
| *Infection (any other than HIV infection)* | Localized, no systemic antimicrobial | Systemic antimicrobial treatment indicated | Systemic antimicrobial treatment indicated | Life-threatening consequences (e.g. septic shock) |

| CLINICAL | | | | |
|---|---|---|---|---|
| ***PARAMETER*** | **GRADE 1 MILD** | **GRADE 2 MODERATE** | **GRADE 3 SEVERE** | **GRADE 4 POTENTIALLY LIFE-THREATENING** |
| | treatment indicated AND symptoms causing no or minimal interference with usual social and functional activities | OR symptoms causing greater than minimal interference with usual social and functional activities | AND symptoms causing inability to perform usual social and functional activities OR operative intervention (other than simple incision and drainage) indicated | |
| **INJECTION SITE REACTIONS** | | | | |
| *Injection site pain (pain without touching)*<br>*Or*<br>*Tenderness (pain when area is touched)* | Pain/tenderness causing no or minimal limitation of use of limb | Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social and functional activities | Pain/tenderness causing inability to perform usual social and functional activities | Pain/tenderness causing inability to perform basic self-care function OR hospitalization (other than emergency room visit) indicated for management of pain/tenderness |
| *Localized injection site reaction* | Erythema OR induration of 5 X 5 cm - 9 x 9 cm (or 25 $cm^2$ - 81 $cm^2$) | Erythema OR induration OR edema > 9 cm any diameter (or > 81 $cm^2$) | Ulceration OR Secondary infection OR Phlebilis OR Sterile abscess OR Drainage | Necrosis (involving dermis and deeper tissue) |
| *Pruritis associated with injection*<br><br>*See also Skin: Pruritis (itching – no skin lesions)* | Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment | Itching beyond the injection site but not generalized OR itching localized to injection site ≥ 48 hours treatment | Generalized itching causing inability to perform usual social and functional activities | NA |
| **SKIN –DERMATOLOGICAL** | | | | |
| *Cutaneous reaction – rash* | Localized macular rash | Diffuse macular, maculopapular, or morbilliform rash OR Target lesions | Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR superficial ulcerations of mucous membrane limited to one site | Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis |
| *Pruritis (itching – no skin lesions)* | Itching causing no or minimal interference | Itching causing greater than minimal | Itching causing inability to perform | NA |

| CLINICAL | | | | |
|---|---|---|---|---|
| ***PARAMETER*** | **GRADE 1 MILD** | **GRADE 2 MODERATE** | **GRADE 3 SEVERE** | **GRADE 4 POTENTIALLY LIFE-THREATENING** |
| *See also Injection site reactions: Pruritis associated with injection* | with usual social and functional activities | interference with usual social and functional activities | usual social and functional activities | |
| **GASTROINTESTINAL** | | | | |
| *Anorexia* | Loss of appetite without decreased oral intake | Loss of appetite associated with decreased oral intake without significant weight loss | Loss of appetite associated with significant weight loss | Life-threatening consequences OR Aggressive intervention indicated (eg. Tube feeding or total parenteral nutrition) |
| *Constipation* | NA | Persistent constipation requiring regular use of dietary modifications, laxatives or enemas | Obstipation with manual evacuation indicated | Life-threatening consequences (eg. Obstruction) |
| *Diarrhea* | Transient or intermittent episodes of unformed stools OR increase of ≤ 3 stools over baseline per 24-hour period | Persistent episodes of unformed to watery stools OR Increase of 4-6 stools over baseline per 24-hour period | Bloody diarrhea OR increase of ≥ 7 stools per 24 hour period OR IV fluid replacement indicated | Life-threatening consequences (eg. Hypotensive shock) |
| *Dysphagia/Odynophagia* | Symptomatic but able to eat usual diet | Symptoms causing altered dietary intake without medical intervention indicated | Symptoms causing severely altered dietary intake with medical intervention indicated | Life-threatening reduction in oral intake |
| *Nausea* | Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake | Persistent nausea resulting in decreased oral intake for 24-48 hours | Persistent nausea resulting in minimal oral intake for > 48 hours OR aggressive rehydration indicated (eg. IV fluids) | Life-threatening consequences (eg. Hypotensive shock) |
| *Vomiting* | Transient or intermittent vomiting with no or minimal interference with oral intake | Frequent episodes of vomiting with no or mild rehydration | Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (eg. IV fluids) | Life-threatening consequences (eg. Hypotensive shock) |
| **CARDIOVASCULAR** | | | | |
| *Prolonged QTc* | Asymptomatic, QTc interval 0,45 – 0,47 sec | Asymptomatic, QTc interval 0,48 – 0,49 sec | Asymptomatic, QTc interval ≥ 0,50 sec OR | Life-threatening consequences, eg. |

| CLINICAL | | | | |
|---|---|---|---|---|
| ***PARAMETER*** | **GRADE 1 MILD** | **GRADE 2 MODERATE** | **GRADE 3 SEVERE** | **GRADE 4 POTENTIALLY LIFE-THREATENING** |
| | OR increase interval < 0,03 sec above baseline | OR increase interval 0,03 – 0,05 sec above baseline | increase interval ≥ 0,06 sec above baseline | Torsade de pointes or other associated serious ventricular dysrhythmia |
| **NEUROLOGIC** | | | | |
| *Alteration in personality-behavior or in mood (eg. Agitation, anxiety, depression, mania, psychosis)* | Alteration causing no or minimal interference with usual social or functional activities | Alteration causing greater than minimal interference with usual social or functional activities | Alteration causing inability to perform usual social or functional activities | Behavior potentially harmful to self or others (eg. Suicidal and homicidal ideation or attempt, acute psychosis) OR causing inability to perform basic self-care functions |
| *Headache* | Symptoms causing no or minimal interference with usual or social or functional activities | Symptoms causing greater than minimal interference with usual social or functional activities | Symptoms causing inability to perform usual social or functional activities | Symptoms causing inability to perform basic self-care functions OR hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function |
| *Insomnia* | NA | Difficulty sleeping causing greater than minimal interference with usual social and functional activities | Difficulty sleeping causing inability to perform usual social and functional activities | Disabling insomnia causing inability to perform basic self-care functions |
| *Neuromuscular weakness (including myopathy and neuropathy)* | Asymptomatic with decreased strength on exam OR minimal muscle weakness causing no or minimal interference with usual social and functional activities | Muscle weakness causing greater than minimal interference with usual social and functional activities | Muscle weakness causing inability to perform usual social and functional activities | Disabling muscle weakness causing inability to perform basic self-care functions OR respiratory muscle weakness impairing ventilation |
| *Neurosensory alteration (including paresthesia and painful neuropathy)* | Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social and | Sensory alteration or paresthesia causing greater than minimal interference with usual social and functional activities | Sensory alteration or paresthesia causing inability to perform usual social and functional activities | Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions |

| CLINICAL | | | | |
|---|---|---|---|---|
| ***PARAMETER*** | **GRADE 1 MILD** | **GRADE 2 MODERATE** | **GRADE 3 SEVERE** | **GRADE 4 POTENTIALLY LIFE-THREATENING** |
| | functional activities | | | |
| *Seizures (new onset)* | NA | 1 seizure | 2 – 4 seizures | Seizures of any kind which are prolonged, repetitive (eg. Status epilepticus), or difficult to control (eg. Refractory epilepsy) |
| *Seizures (known pre-existing seizure disorder)* | NA | Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable medication in a previously controlled seizure disorder | Change in seizure character from baseline either in duration or quality (eg. Severity or focality) | Seizures of any kind which are prolonged, repetitive (eg. Status epilepticus), or difficult to control (eg. Refractory epilepsy) |
| *Vertigo* | Vertigo causing no or minimal interference with usual social and functional activities | Vertigo causing greater than minimal interference with usual social and functional activities | Vertigo causing inability to perform usual social and functional activities | Disabling vertigo causing inability to perform basic self-care functions |
| **RESPIRATORY** | | | | |
| *Dyspnea or respiratory distress* | Dyspnea on exertion with no or minimal interference with usual social and functional activities | Dyspnea on exertion causing greater than minimal interference with usual social and functional activities | Dyspnea at rest causing inability to perform usual social and functional activities | Respiratory failure with ventilatory support indicated |
| **OCULAR/VISUAL/AUDITIVE** | | | | |
| *Visual/Auditive changes (from baseline)* | Visual or auditive changes causing minimal or no interference with usual social and functional activities. | Visual or auditive changes causing greater than minimal interference with usual social and functional activities. | Visual or auditive changes causing inability to perform usual social and functional activities. | Disabling visual or auditive loss. |
| **ENDOCRINE/METABOLIC** | | | | |
| *Hyperthyroidism* | Asymptomatic | Symptomatic causing greater than minimal interference with usual social and functional activities | Symptoms causing inability to perform usual social and functional activities OR uncontrolled | Life-threatening consequences (e.g. myxedema coma) |

| CLINICAL | | | | |
|---|---|---|---|---|
| ***PARAMETER*** | **GRADE 1 MILD** | **GRADE 2 MODERATE** | **GRADE 3 SEVERE** | **GRADE 4 POTENTIALLY LIFE-THREATENING** |
| | | OR thyroid replacement therapy indicated. | despite treatment modification. | |

| LABORATORY | | | | |
|---|---|---|---|---|
| *PARAMETER* | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
| **HEMATOLOGY** | | | | |
| *Absolute neutrophil count* | 1000 – 1300/mm³ | 750 – 999/ mm³ | 500 – 749/mm³ | < 500/ mm³ |
| *Hemoglobin* | 8,5 – 10, 0 g/dl | 7,5 – 8,4 g/dl | 6,5 – 7,4 g/dl | < 6,5 g/dl |
| *Platelets, decreased* | 100.000 – 124.999 /mm³ | 50.000 – 99.999 /mm³ | 25.000 – 49.999 /mm³ | < 25.000 /mm³ |
| *WBC, decreased* | 2.000 – 2.500 /mm³ | 1.500 – 1.999 /mm³ | 1.000 – 1.499 /mm³ | < 1.000 /mm³ |
| **CHEMISTRIES** | | | | |
| *ALT (SGPT)* | 1,25 – 2,5 x ULN | 2,6 – 5,0 x ULN | 5,1 – 10,0 x ULN | > 10,0 x ULN |
| *AST (SGOT)* | 1,25 – 2,5 x ULN | 2,6 – 5,0 x ULN | 5,1 – 10,0 x ULN | > 10,0 x ULN |
| *Creatinine* | 1,1 – 1,3 x ULN | 1,4 – 1,8 x ULN | 1,9 – 3, 4 x ULN | ≥ 3,5 x ULN |
| *Uric acid* | 7,5 – 10,0 mg/dl | 10,1 – 12,0 mg/dl | 12,1 – 15,0 mg/dl | > 15,0 mg/dl |

### Annex 3. Data collection forms

DRTB FollowUp Forms 15.2.13.xls

HIV-related data will be recorded in the standard MoH forms implemented for the HIV care and follow up.

### Annex 4. Informed Consent form

Patient Informed Consent_1012 appro