Short treatment regimen for Multidrug Resistant Tuberculosis

Clinical treatment protocol for Swaziland

MSF Operational Centre Amsterdam

April 2013

1. Diagnosis and DST

Criteria for Xpert® MTB/RIF Testing and Baseline Smear Testing:

All patients visiting Matsapha Comprehensive Health Clinic and Mankayane Hospital TB Unit are screened for tuberculosis based on the presence of clinical criteria (cough, weight loss, night sweats and fever). All patients suspected of pulmonary tuberculosis will submit sputum samples for microscopy and Xpert® MTB/RIF assay.

Sample processing time is 2-3 hours, so all patients get results on the same (or the following) day. Xpert® MTB/RIF-test results indicate the presence of *M. tuberculosis* complex DNA, as well as mutations conferring Rifampicin-resistance. Sputum-smear microscopy serves only as baseline and for monthly follow up.

All Xpert MTB+/RIF+ patients will be included as soon as possible into the study (see annex 1) with study-treatment-regimen plus Rifampicin (empirical treatment regimen). A specimen from the original sample or a second sample will be submitted for MGIT-culture and FL-DST, performed at the National Reference Laboratory (NRL) in Mbabane, Swaziland as well as SL-DST, performed at Institute of Tropical Medicine in Antwerp (Belgium). In case of contamination of the culture, the patient will be asked to provide an additional sputum sample for repetition of culture and FL-DST & SL-DST.

For all Xpert MTB+/RIF-patients, a specimen from the original sample or a second sample will be submitted for MGIT-culture and FLDST, performed at the National Reference Laboratory (NRL) in Mbabane, Swaziland. Patients who are found to be MDR in FLDST will be offered to be enrolled in the study-treatment-regimen as soon as possible and a sample for SLDST will be sent to Institute of Tropical Medicine laboratories in Antwerp (Belgium). In case of contamination of the culture, the patient will be asked to provide an additional sputum sample for repetition of culture and FLDST.

For suspected extra-pulmonary TB patients, extra-pulmonary tissue samples will be analyzed with Xpert® MTB/RIF, smear microscopy and MGIT-culture, including FL-DST. Presumptive (based on Xpert MTB+/RIF+) or mycobacteriologically proven (by MGIT culture and FLDST) extra-pulmonary MDR TB are included in the study in the same way as pulmonary MDR TB. Involvement of bones and meninges are exclusion criteria for enrollment to the study regimen.

In children suspect of TB presumptive diagnosis by Xpert® MTB/RIF and mycobacteriological proof by MGIT culture and FL-DST is not always possible. However: all *clinically feasible* methods of gaining samples, including induced sputum or gastric aspiration or lymph node aspiration or sampling of other suspect tissue should be employed. Children who are clinically suspect of TB ***and*** are unable to deliver an adequate sample for analysis ***and*** are close contact of a proven MDR-TB patient are offered to be included in the study regimen without mycobacteriological proof and followed up clinically.

Criteria for culture and FL-DST:

1. All cases with Xpert MTB+ (either Xpert MTB+/Rif+ or Xpert MTB+/Rif-)

2. Others to be referred as clinically necessary according to the national TB-diagnostic algorithm (e.g.., suspected failure of TB-treatment with FLD).

Criteria for SL-DST:

1. All cases with Xpert MTB+/Rif+
2. All cases with mycobacteriological proof of Rifampicin-resistance in FL-DST.

2. Eligibility and inclusion criteria for short MDR TB Treatment regimen

The following patients will be offered inclusion in the study (as described in research protocol):

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 (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.

Preconditions before initiation of treatment with the study regimen:

1. Live or be willing to spend the entire treatment course in Manzini-region/Swaziland
2. No exclusion criteria;
3. Competition of the baseline test (according to chapter 5/6);
4. Competition of one preliminary adherence counseling session including appointment of a treatment supporter (see chapter 8)

3. Treatment delivery model

At both sites an ambulatory treatment model with direct observation of treatment (DOT) will be used. During the intensive phase, patients will receive treatment twice per day (morning and evening). Depending on what is most appropriate for the individual patient, morning DOT may take place at the health facility under supervision of a staff nurse or at the patient's home under supervision of a treatment supporter. Afternoon DOT will take place at the patient's home under supervision of a treatment supporter (treatment supporter see chapter 8). During the continuation phase, treatment is administered once per day in supervised direct observation and may take place either at the patient's home under supervision of a treatment supporter or the health facility under supervision of a staff nurse. Eventual medication for other medical conditions, including ART, will be given together with the MDR-TB drugs as far as medically possible and practically feasible.

When a patient necessitates inpatient care, s/he will be hospitalized in Mankayane Hospital DR TB Unit or to Moneni Hospital with close follow up by MSF clinicians. Once a patient is discharged, s/he will resume ambulatory treatment as described above.

4. Treatment Regimen

Patients will be started on "empirical treatment regimen" (shortened MDR TB treatment regimen plus Rifampicin) based on presumptive diagnosis after being diagnosed with Xpert MTB+/RIF+. Upon receipt of results from culture and FL-DST which confirm MDR TB, Rifampicin will be dropped from the regimen (See annex 1).
Patients who are primarily diagnosed by MGIT culture and FL-DST start shortened MDR TB treatment without Rifampicin.

The standardised short regimen for MDR TB and duration

	Intensive Phase	Continuation Phase
Duration	Pyrazinamide + Ethambutol + Isoniazid + Moxifloxacin + Kanamycin + Prothionamide + Clofazimine for at least 4 months and continue until sputum first culture is negative, maximum 7 months (time when 6-month-culture result becomes available.)	Pyrazinamide + Ethambutol + Moxifloxacin + Prothionamide + Clofazimine for 5 months, starting after 4 months or first negative culture, whichever is later.
Description	Seven drugs; Includes injectable & high dose Isoniazid	Five drugs; Only oral drugs in standard dosage.

Any missed doses will be added at the end of each phase.

Dosing of standardized MDR TB Drugs for adults and adolescents > 25 kg, including pregnant women

Drug	Formulation	Frequency	Weight range in Kg			
			<25	**25-32**	**33-50**	**>50***
Isoniazid (H)	300mg tab 100 mg tab	od	15-20 mg/kg	1	1 1	>55kg 2
Pyrazinamide (Z)	400mg tab	od	30-40 mg/kg	2.5	4	5
Ethambutol (E)	400mg tab	od	15-25 mg/kg	1.5	2	3
Moxifloxacin (Mfx)	400mg tab	od	7.5-10 mg/kg	1	1	1
Prothionamide (Pto)	250mg tab	od[#]	15/25 mg/kg	1	2	>55kg 3
Clofazimine (Cfz)	100mg cap	od	2-3 mg/kg	1	1	1
Kanamycin (Km)		od	15mg/kg			

*For Pto and H highest doses are given above 55kg

[#] Pto can be given twice a day in the intensive phase if maximum doses are used and the patient has major GI side effects not responding to anti-emetics.

Treatment will be given **7 days a week** with all doses given under DOT. Supervision of drug intake will be done by either the health care worker or by the treatment supporter according to the model described in chapter 3.

In case SL-DST shows resistance to Km/Am the regimen is changed to use Cm (at the same dose as Km). (This adjustment of the regimen will not be considered "withdrawal" from the original study protocol. However, resistance in SLDST to Km/Am *and* Ofl/Mfx (=XDR-TB) will lead to exclusion from the study and offer of an appropriate XDR-TB treatment). SLD resistance to Mfx will lead to exclusion of the short regimen and adjustment to adequate regimen.

General remarks:

- Pyridoxine at a dose of 25 mg/day will be added to the regimen as prophylaxis of peripheral neuropathy with the use of high dose Isoniazid (increased risk in HIV co-infected patients, malnourished, diabetic, alcoholic and pregnant women). If neuropathy appears it should be treated with higher dose of pyridoxine from 100-200 mg/day.
- Mfx must be administered separately from antacids, iron, magnesium, and vitamins by 4 hours.
- In cases of renal or hepatic failure, dosing of some medications need adjustment (see table 9.2 WHO Guidelines for the programmatic management of MDR TB emergency update 2008) and discuss with CRT and HIV/TB advisor.
- In cases of QT prolongation >500milliseconds (ms) or when the QTc exceeds >60ms compared with the baseline ECG QTc, patients will be withdrawn from the regimen. Appropriate clinical follow-up (which include tests for electrolyte abnormalities) and management will occur as needed. Standard MDR TB treatment will be offered (see table 9.2 WHO guidelines for the programmatic management of MDR TB emergency update 2008) and each case discussed with CRT and HIV/TB advisor.

Women in childbearing age, pregnancy and breast-feeding:

- Women in child bearing age who are not pregnant will be offered hormonal contraception and barrier methods.
- Women who get pregnant while on treatment are not automatically withdrawn from the regimen; however adjustment of the regimen is done according to the risk-benefit analysis of the treating medical doctor in collaboration with the CRT and advisory board.
- Women who are pregnant in the first 12 weeks of pregnancy at time of MDR-TB diagnosis should not be included in the regimen before end of 12^{th} weeks of pregnancy.
- Women who are breastfeeding or pregnant beyond the 12^{th} week of gestation can be enrolled into the regimen and they will be adequately informed and counselled of risks and benefits.
- Mfx, Cfz and Km are safety class C drugs and Cfz is excreted in breast milk. Pregnant or breastfeeding women will be informed about potential risk and benefits in a separate informed consent.

Children < 14 years of age:

- See in annex 3 MDR TB drug dosage and prescription for paediatric cases <25 kg

5. Baseline examination

All examinations and follow up are summarized in table 3. All patients will have a clinical examination prior to starting MDR TB treatment. The baseline examination includes the following:

1) Thorough history and clinical examination including:
    - Signs, symptoms, diagnosis, and documentation of co-morbidities including treatment;
    - Signs and symptoms of mental disorder (psychiatric assessment if indicated by either physician or psychosocial officer) including treatment;

- Psychosocial assessment with a focus on factors that may affect adherence (e.g. living situation, substance use/abuse, psychosocial support);
- Audiometry;
- Weight/height, BMI, weight-for-height z-score for children, blood pressure;

2) Xpert® MTB/Rif test, culture and DST, sputum smear microscopy;
3) Provider initiated counseling and testing for HIV (NB: PICT includes the "opt out" for HIV-testing.
4) Blood tests: See Table 3 below for required tests including pregnancy test for women;
5) Chest X-ray (desirable, not a precondition to start).
6) Electrocardiogram (ECG) to monitor QT interval

6. Monitoring

Exact follow-up needs will be individualized according to patient's clinical response and tolerance of medications. However there is a standard minimum of clinical and mycobacteriological monitoring including biochemistry. All those routine, minimum examinations are listed in table 3:

Clinical Monitoring:

<u>First two months of treatment:</u>

1) Weekly physician review: Clinical follow-up – cough; fever, weight, sputum production, side effects (including hearing, balance, vomiting and visual problems), ECG will be done at 2 weeks to monitor QT interval and at month 1 after treatment initiation. After that, ECG will be performed depending on clinical indication (syncope, dizziness…).
2) Daily DOT provision (by a nurse and/or treatment supporter) according to chapter 3
3) Specialist referral if clinically indicated (e.g. severe renal insufficiency)[1]

<u>Months 3 and following months of intensive phase and continuation phase</u>

1) Monthly physician review
2) Daily DOT provision (by a nurse and/or treatment supporter) according to chapter 3
3) Specialist referral if clinically indicated (e.g. severe renal insufficiency)[1]

<u>Mycobacteriological monitoring during treatment</u>

1) Specimen smear microscopy monthly on 2 specimens (spot and morning samples).
2) Specimen culture at baseline and monthly to the end of treatment.
3) Mycobacteriological follow-up of extrapulmonary manifestations will not be done routinely, but the patients will be followed up on clinical grounds

[1] The Raleigh Fitkin Memorial Hospital has a dialysis facility where patients will be sent for this treatment.

***Table 3*:** Monitoring Investigations for MDR TB

	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 Physical examination (weight)	x	First 2 months biweekly, then monthly						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									
Chest X-ray	x	Repeat only if clinically indicated							x
Electrocardiogram	x	x		x		If develops syncope or dizziness			
Hearing test (clinical and audiometry)	x	Monthly clinical assessment and audiometry to repeat if indicated							

Comment [msfuser1]: In the text above, it states weekly visit for the first 2 months, but in the Table here it says biweekly visits, please clarify.

7. Considerations for HIV positive patients

Every MDR TB patient will be offered HIV counseling and testing, regardless of self-reported status or current ART. All HIV positive patients diagnosed with TB will be initiated on ART regardless of CD4 cell count within 2-8 weeks after MDR TB treatment initiation and tolerance to treatment.

CD4 count will be measured at baseline, at 12 months after ART initiation and every six months thereafter, unless clinically necessary throughout treatment.
HIV RNA VL will be measured at baseline for patients already on ART and for all co-infected patients HIV RNA VL will be measured at the end of the MDR TB treatment and at the end of the follow up period after treatment completion.

Additional considerations for HIV positive patients include:

- All HIV positive patients will start or continue Cotrimoxazole prophylaxis.
- For patients who are already on 1st line ART, d4T will be replaced with AZT unless there are other contraindications.
- All ARVs can have overlapping toxicities with second line TB drugs; therefore all HIV positive patients will be discussed by the CRT prior to new ART-initiation.
- Efavirenz will be the preferred NNRTI except in patients with psychiatric co-morbidity.
- Tenofovir will be avoided during the intensive phase due to increased risk of renal failure when co-administered with injectable agents.
- Patients taking ddI will use enteric-coated capsules as the other buffered forms interfere with Mfx absorption.
- In general the preferred first line regimen will be AZT + 3TC + EFV in patients without anemia, but each case will be assessed by their Medical Doctor.

8. Psychosocial components and adherence support

Comprehensive psychosocial support

Psychosocial and adherence support will be integral components of MDR TB treatment for all patients. To ensure adherence among all patients, the study will provide treatment support, patient support and have patient-centred treatment services. All patients will undergo enhanced DOT for the duration of treatment. Patient support will include disease education sessions to empower patients to make informed health care choices and psychosocial support, including motivational communication and emotional support. Socioeconomic support will include transport fees for monthly follow-up health visits, nutritional support, and monetary incentives for treatment supporters. All services will be patient-centered involving a teamwork approach in an effort to build provider-patient relationships. Individual patient obstacles to receiving medications regularly and other issues impacting adherence will be addressed.

At initiation, all patients will be presented comprehensive information about MDR TB and the treatment regimen. Throughout treatment, adherence counselors and nurses will continue to reinforce this information and follow-up any questions a patient or family member might have. Each patient will appoint a treatment supporter. A treatment supporter will ideally be neighbour or friend of the patient (as opposed to relatives) and will assist the patient, observe and document daily their medications intake, monitor adherence and will be available as a second option for defaulter tracing. All treatment supporters will participate in a one-day training which covers elements of DOT, instructions on filling out

monitoring instruments, TB/HIV medical knowledge and side effects, and infection control. Treatment supporters will receive an adequate incentive (currently E400 per month) for their time and dedication. For patients who are not able to appoint a treatment supporter the CMT will assist in finding an appropriate person. A patient who refuses involvement of a treatment supporter will not be excluded from participation.

As a necessary component of MDR-TB treatment, patients will participate in routine adherence counseling during both phases of treatment. In addition to adherence support, available psychosocial components at both clinical sites include mental health assessment, assessment of psychiatric side effects, and general support of mental well-being.

Defaulter tracing strategy

Defaulter tracing will be conducted as soon as a patient misses one appointment (i.e. if a patient does not turn up to have DOT). Adherence officers will trace patients via telephone and home visitation. Adherence counseling will address specific reasons for defaulting in an effort to find solutions to prevent future missed DOT or appointments. Every effort will be made to convince the patient to continue treatment, and patients will be addressed in a sympathetic, friendly, and non-judgmental manner. Every effort will be made to address the patient's concerns and reasoning for treatment interruption to prevent it from recurring.

9. Contact tracing

All close contacts of MDR TB patients will be systematically clinically screened every 6 months and will be screened and tested with Xpert® MTB/Rif if symptomatic. Close contacts are those living in the same household as the patient or who spend a significant amount of time with the patient. Contacts of MDR TB patients will be instructed to report any symptoms of possible TB, at which point a careful assessment will be made.

10. Discontinuation of treatment

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 HIV/TB advisor. Consideration to MDR TB treatment interruption will be made in the following situations:

- Life threatening adverse effects of medications.
- Adherence problems including confirmed selling of medication, persistent failure to appear for DOT refractory to adherence support interventions.

11. Adverse Events and management

All possible adverse events will be documented by a systematic and standardized screening of clinical and/or laboratory data at each visit. We will utilize the DAIDS grading score to assess the type, severity and possible relationship of side effects.

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 cause by or related to that product.
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. All SAE will be discussed by the CRT and reported.

Subjects will be followed-up by phone or by visitation at least once per week for the first month following an adverse event. Following this, follow-up for adverse events will occur at a patient's monthly clinical visit, or more frequently, depending on clinical need.

In general, HIV-positive patients have a higher rate of side effects to both MDR TB and non-TB medications and the risk of these increases with a lower degree of immunosuppression.
Management of side effects will be done in close consultation with the CRT, utilizing algorithms from the 2008 WHO MDR TB management guidelines. All side effects will be systematically documented, including what influence they may have on a patient's treatment. Side effects will be identified early and treated immediately. Patients will be informed about certain side effects, including that Cfz may cause discolouration of the conjunctiva, lacrimal fluid, sweat, sputum, urine, faeces, nasal secretions, semen, breast milk and reddish to brownish-black discoloration of the skin (in light skinned individuals). This is however reversible after stopping treatment. Permanent dose reduction or definitive stopping of a drug is used as a last resort only when other possible solutions have failed and it is to be made in consultation with the CRT. Appendix 1 summarizes minor and major side effects and their management.

12. Infection control

Infection control guidelines for MDR TB will be the same as those for drug sensitive TB. Administrative and environmental measures include segregation of infectious patients, cough triage in waiting areas and the reinforcement of natural ventilation. All staff will wear high filtration masks (respirator) when in the MDR consultation rooms or ward in the hospital. Visitors are strictly limited to a single caretaker who should spend most time outside the patient's room, and should not sleep in the patient's room. No children are permitted in the ward. Visiting can take place outside in the open air.

Patients will be instructed to cover their mouth with a mask/handkerchief/tissue while coughing or sneezing and will use a sputum container with a screw top to collect sputum. The container and contents will be incinerated. Patients will wear surgical masks whenever there is a risk of transmission to others, e.g. moving inside the facility.

All sputum collection will be done outside and away from other patients and visitors. Patients will be instructed by an experienced cough officer on how to produce sputum samples. All laboratory personnel working with TB specimens will wear respirator masks. Specimen preparation will be done inside a properly-maintained biosafety cabinet.

Buildings at Matsapha clinic and Mankayane TB Unit have been designed to allow for as much air circulation as possible. The windows will be kept opened as much as possible. In case a patient needs to be hospitalised, the patient will be located in a private room or ward for MDR TB patients, but without mixing culture/smear positive and negative patients.

13. Data Handling and Recordkeeping

All patient files will be stored in a locked cabinet in the MDR TB consultation rooms at Matsapha Clinic and Mankayane TB Unit. All data will be collected in a password protected Koch'6 database. This database is an electronic patient monitoring system until follow up after treatment completion.

The simplified protocol will be implemented with a minimum number of forms which are kept as paper based versions in the patient's file. These forms are:

1. Ministry of Health DR TB Treatment Card
2. Monthly treatment monitoring form (1 form for monthly follow-up month includes all patient medications including MDR TB drugs, HIV drugs, side effect drugs)
3. Default form (filled in cases of missed appointments and defaults)
4. Patient consent to Treatment (filled once at start of treatment)

The clinical team will complete forms on paper. The MoH MDR TB Treatment Card and the Monthly Treatment Monitoring Form are sent to the data clerk after being filled out by the clinical team. The data clerk will then return the forms to the patient's file after data encoding.

The database will be backed up to a secondary external hard drive on a weekly basis.

Annex 1. Algorithm for Xpert MTB+/RIF+ (for use within the study; to be included following NTP MDRTB protocol)

Annex 2: Management of Main Side Effects of Treatment

Side effect	Possible responsible drugs	Side effect management	Extra considerations for patients on ARVs
Nausea, vomiting	**Most likely Pto**, H, E, Z, **Cfz, ARVs**	1.Treat dehydration, check electrolytes/for hepatitis if needed, 2.Split Pto/Eto in 3 doses if possible 3.Give metoclopramide ½ hr before doses 4.Treat reflux/gastritis if present 5.Supportive management of anxiety and consider low dose/short acting benzodiazepine at night (beware of CO2 retention in severe lung disease) 6.If fails to resolve after 2 days, give ondansetron ½ hr before doses for 5 days 7.Consult TB/HIV advisor if still a problem	Common and usu. self-limiting if early but also consider NNRTI induced hepatitis, possible sign of lactic acidosis if occurs after several months. Consider pancreatitis in patients on ddI or D4T with severe abdominal pain
Gastritis/reflux	**Pto**	1. Avoid anti-acids (Note: must be at least 2 hrs before or 3 hrs after anti-TB drugs due to interactions) 2. Omeprazole or ranitidine for 1 week 3. If severe/not resolving discuss with TB adviser	None
Diarrhea	PI especially Lpv, buffered ddI	1. Give hydration and electrolytes as needed (ORS), 2. Anti-diarrheal medication (loperamide) unless patient has fever or blood in stools	Consider opportunistic infections /other causes of diarrhea (C.difficile)
Electrolyte disturbances ($\downarrow K^+$ or Mg^{2+}, $\uparrow K^+$ in renal impairment)	**Km**, Am (and other injectable aminoglycosides), Cm, TDF (rare)	1. Follow levels of potassium, magnesium and replace as needed 2. Assess for diarrhoea / vomiting NOTE: If unable to measure Mg and potassium level fails to respond to replacement, give Mg also (see potassium and magnesium management guide in TB tool kit)	Risk of additive renal toxicity with TDF and injectables HIV-infected have increased risk renal toxicity and electrolyte abnormalities to injectables
Arthralgia	**Z,** fluoroquinolones	1. Non-steroidal anti-inflammatory therapy 2. Will often settle with time 3. If severe/not settling discuss with TB/HIV adviser regarding possible lowering of pyrazinamide Note uric acid often elevated in patients on pyrazinamide and not corrected by allopurinol=>don't check uric acid	None
Hepatitis	**Z,H,R**, Eto/Pto, E, fluoroquinolones, NVP, EFV, all PI, all NRTIs, cotrimoxazole	1. Temporarily withhold all therapy if ALT > 5x normal level or severe nausea/vomiting until improved, 2.consider other causes of hepatitis (meds, viral hepatitis.alcohol) and manage fluids/electrolytes 3. Discuss with TB/HIV adviser about re-introduction plan.	Timing of commencement of drugs and hepatitis may help identify most likely agent. Stop ARVs. Consider switch NVP to EFV. Also consider TMP/SMX

Side effect	Possible responsible drugs	Side effect management	Extra considerations for patients on ARVs
Skin rash	**All TB agents,** EFV**, NVP, ABC, CTX**	Maculopapular rash and prutuitus are common early side effects and may resolve after few weeks spontaneously. Antihistamine, topical hydrocortisone. If severe with generalized erythema, blistering or mucosal involvement, cease all immediately and consult TB/HIV advisor.	Usu. In first 3 months of ART. Antihistamine only for grades 1 & 2, stop ARVs, TB drugs + CTX and consult TB+HIV advisor for grades 3 & 4 Do not re-challenge with ABC
Renal toxicity	**S, Km, Am, Cm,** TDF (rare)	1. Temporarily Stop injectable agent, and manage fluid status. Assess electrolytes. 2. Discuss with TB/HIV adviser - Consider 3 times a week dosing or lower dose of injectable or change to capreomycin, 3. Readjust other drug doses to renal function	Risk of additive renal toxicity with TDF (if on both TDF + injectable consider switch from TDF to AZT or ABC) Many antiretrovirals need dose adjusting in renal insufficiency. HIV-infected have increased risk renal toxicity and electrolyte abnormalities to injectables
Seizures*	H, fluoroquinolones	<u>Control existing seizures</u> 1. Most self-limiting. If necessary give diazepam IV or PR 0.2-0.4 mg/kg (5-10mg and re-dose if required) 2. In hospital with capacity - Phenytoin 20 mg/kg IV: give slowly (not in D5W as precipitates)- watch for drop in blood pressure <u>For new onset on treatment</u>: 1. Increase pyridoxine to 200 mg/day 2. Commence anticonvulsant (carbamazepine or sodium valproate or phenytoin) discuss with TB/HIV adviser and continue until complete MDR TB Rx – consider dosing adjustment or withhold isoniazid	? Risk potentiated by alcohol containing syrups (pediatric LPV/r)
Peripheral neuropathy	**H**, S, Km, Am, Cm, Pto, fluoroquinolones, **d4T, ddI**	1. Increase pyridoxine to 200 mg/day 2. Amitriptyline if severe symptoms 3. If severe/worsening discuss with TB/HIV adviser to consider change injectable to Capreomycin or possible dose reduction/change medications	Generally avoid d4T or ddI with Cs or H. If must give D4T or ddI monitor closely, and change to TDF/ABC/AZT if develops peripheral neuropathy
Hearing loss	**S, Km, Am, Cm**	1. Document hearing loss (clinical or audiometry if possible). Note that hearing loss not reversible. 2. Discuss with TB/HIV adviser possibility of changing to Cm or 3x week dosing	None
Optic neuritis	**E,** ddI	Decreased red-green colour distinction seen early, Stop E, monitor with clinical eye examination	Opportunistic infections affecting eye (examine for OI vs optic neuritis)

Side effect	Possible responsible drugs	Side effect management	Extra considerations for patients on ARVs
Psychosis	H, fluoroquinolones, Pto, **EFV** This is low risk in 9 month regimen	1. Rule out other causes e.g. illicit drugs, alcohol 2. Commence risperidone or haloperidol if very agitated (See MSF Mental Health guidelines) and discuss with TB/HIV adviser	EFV has high rate of mild CNS effects during first 2-3 weeks treatment which usually resolve by themselves (confusion, impaired concentration, abnormal dreams, dizziness) Stop EFV if severe or not responding to withholding Cs. Discuss with TB/HIV adviser
Depression*	**Socio-economic circumstances, chronic disease,** fluoroquinolones, H, Pto, Cfz related to skin changes, EFV	1.Improve socio-economic conditions if possible, 2.Counseling, 3.Consider hospitalization if suicidal/assess for signs psychosis or symptoms hypothyroidism If antidepressant therapy needed, begin with fluoxetine 20mg daily. If not responding/ worsening by 4 weeks increase to 40mg and discuss with TB/HIV adviser	Substitute EFV if severe or not responding to treatment
Hypothyroidism	**Pto/Eto**	PAS+ Eto/Pto worse than either alone Treat if TSH >10 IU/mL. If symptomatic and raised TSH discuss with TB adviser Thyroxine therapy (begin with 25-50 mcg and increase 2-3 weekly. TSH monthly till stable Continue levothyroxine until 1 month after cessation MDR TB treatment – usually completely reversible	Mixed evidence. Some studies show ART (?D4T) associated with subclinical hypothyroidism
Bone marrow suppression	R, H, AZT, CTX	1. Mild anemia of chronic disease common – treat TB and monitor clinically 2. Consider other co-morbidities (gastritis/nutritional deficiency, etc)	Usu. occurs during the first 3 months of AZT treatment. If HB<8 or decreasing or poor respiratory reserve switch AZT for d4T,TDF or ABC Consider opportunistic infections (LIP, MAC, etc) CTX more likely if high dose (treating toxo or PCP)
Lactic acidosis	D4T, ddI, AZT, 3TC	None	Stop all ARVs until recovery. Replace d4T with TDF or ABC when restarting.
Lipodystrophy/ lipoatrophy	D4T, ddI, AZT, PIs	None	Switch NRTI to TDF/ABC.
Pancreatitis	D4T, ddI		Avoid use together, if already present stop agent and do not use again.

Side effect	Possible responsible drugs	Side effect management	Extra considerations for patients on ARVs
Abdominal pain	**Cfz, Pto, All ARVs**	Often benign Cfz has been associated with severe acute abdomen; in those cases it should be suspended.	Follow up patient as it may be an early sign of pancreatitis, hepatitis or lactic acidosis.
Skin, cornea, retina, sputum and urine discolouration	**Cfz**	Adequate counselling with advise to maintain regimen If very severe, discuss with TB advisor to explore drug change	
Icthyosis	**Cfz**	Topical hydration If very severe, discuss with TB advisor to explore drug change	
Decreased visual acuity, dry eyes or eye irritation	**Cfz**	Regular hydration of dry eyes with normal saline or water for injection If very severe, discuss with TB advisor to explore dose reduction	
QT prolongation (>500ms)	**Fluoroquinolones, Cfz**	1. Temporarily withhold all therapy 2.Obtain ECG and manage electrolyte abnormalities if any.	

Drugs in bold type are more strongly associated with the side effect than drugs not in bold.
Drug dosages should not be reduced without consultation with TB/HIV advisor. If a medication has to be ceased, please consult the TB/HIV advisor regarding a suitable substitute medication to prevent resistance developing.

Am=amikacin, Cm=capreomycin, Km=kanamycin, Pto=Prothionamide, Eto=Ethionamide, Cfz=Clofazimine, R=Rifampicin, H=Isoniazid, E=Ethambutol, d4T=stavudine, TDF=Tenofovir, 3TC=Lamivudine, AZT=Zidovudine, PI=protease inhibitors, Lpv=Lopinavir, ddI=didanosine, CTX=cotrimoxazole.

Annex 3. MDR TB paediatric drug dosage table

weight in kg	Capreomycin	Amikacin	Isoniazide high dose		Moxifloxacin		Prothionamide	Clofazimine	Pyrazinamide	Ethambutol	
dose	15-30mg/kg	15-30mg/kg	15-20 mg/kg		7.5-10mg/kg		15-20mg/kg	2-3 mg/kg	30-40mg /kg	15-25mg	
formulation	1g in 4ml dilution	2ml vial	tablet	tablet	tablet	Susp ??ml	tablet	Pharmacological preparation	tablet	tablet	tablet
	250mg/ml	250mg/ml	100mg	300mg	400mg	20mg/ml	250mg	mg	400mg	100mg	400mg
			Either of the dosages! Not additional!		**Either of the dosages! Not additional!**					**Either of the dosages! Not additional!**	
unit	**ml**	**ml**	**tbl**	**tbl**	**tbl**	**tbl**	**tbl**	**mg**	**tbl**	**tbl**	**tbl**
5	0.5	0.5	1			2	0.5	10-15 mg	0.5	1	
6	0.5	0.5	1			3	0.5	15 mg	0.5	1	
7	0.75	0.75	1			3	0.5	15-20 mg	0.5	1	
8	0.75	0.75	1.5	0.5		3	0.5	20 mg	0.75	2	0.5
9	1	1	1.5	0.5		4	0.5	20-25 mg	0.75	2	0.5
10	1	1	1.5	0.5	0.25	4	0.5	25 mg	1	2	0.5
11	1	1	2	0.5	0.25	5	1	25-30 mg	1	2	0.5
12	1	1	2	0.5	0.25	5	1	30 mg	1	2	0.5
13	1	1	2	0.5	0.25	6	1	30-35 mg	1	3	0.5
14	1.5	1.5	2	0.5	0.5	6	1	35 mg	1	3	0.5
15	1.5	1.5	3	1	0.5	6	1	35-40 mg	1.5	3	1
16	1.5	1.5	3	1	0.5	7	1	40 mg	1.5	3	1
17	2	2	3	1	0.5	7	1	40-45 mg	1.5	3	1
18	2	2	3	1	0.5	7	1.5	45 mg	1.5	4	1
19	2	2	3	1	0.5	8	1.5	45-50 mg	1.5	4	1
20	2	2	3	1	0.5	8	1.5	50 mg	1.5	4	1
21	2	2	3	1	0.5	8	1.5	50-75 mg	2	4	1
22	2	2	3	1	0.5	9	1.5	50-75 mg	2	4	1
23	2	2	3	1	0.5	9	1.5	50-75 mg	2	5	1
24	2	2	3	1	0.5	10	1.5	50-75 mg	2	5	1
25	2.5	2.5	3	1	0.5	10	1.5	50-75 mg	2	5	1