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MINISTRY OF HEALTH AND SOCIAL WELFARE
NATIONAL TUBERCULOSIS AND LEPROSY PROGRAMME

Operational Guidelines for the Management of Drug Resistant TB in Tanzania

First Edition

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NATIONAL TB AND LEPROSY PROGRAMME
Ministry of Health and Social Welfare
P. O. Box 9083, Dar es Salaam
Tel : 255 22 2124500
Fax : 255 22 2124500
E-mail : tantci@intafrica.com
Website: www.moh.go.tz/ntlp

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ABBREVIATIONS

AFB	Acid Fast Bacilli
AIDS	Acquired Immuno-Deficiency Syndrome
ART	Anti-Retroviral Treatment
BCG	Bacille Calmette-Guerin
BUN	Blood Urea Nitrogen
CPT	Cotrimoxazole Preventive Therapy
CTRL	Central Tuberculosis Reference Laboratory
CPC	Cetyl Pyridium Chloride
CXR	Chest X- Ray
DMO	District Medical Officer
DOT	Direct Observed Treatment
DOTS	Directly Observed Treatment, Short course
DR TB	Drug Resistant TB
DRS	Drug Resistance Survey
DST	Drug Susceptibility Testing
DTLC	District Tuberculosis and Leprosy Coordinator
EP	Extra-pulmonary
EQA	External Quality Assurance of AFB microscopy, culture
FDC	Fixed Dose Combination
FQN	Floroquinolones
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GLC	Green Light Committee
HCW	Health care workers
HIV	Human Immunodeficiency Virus
HEPA	High Efficiency Particulate Air
IC	Infection Control
LFT	Liver Function Tests
MDR TB	Multi-drug resistance TB
M/XDR-TB	Multi – drug resistance TB or extensively drug resistance TB
MIC	Minimum Inhibitory Concentration
MO	Medical Officer
MOTT	Mycobacteria Other Than Tuberculosis

MoHSW	Ministry of Health and Social Welfare
MSD	Medical Stores Department
NACP	National Aids Control Program
NTM	Non Tuberculous Mycobacteria
NTLP	National Tuberculosis and Leprosy Programme
OI	Opportunistic Infection
OPD	Out Patient Department
PTB+	Pulmonary Tuberculosis, sputum smear positive
PLHIV	People living with HIV
PITC	Provider Initiated Testing & Counseling
RLT	Regional Laboratory Technician
RMO	Regional Medical Officer
RTLC	Regional Tuberculosis and Leprosy Coordinator
SLD	Second Line Drugs
SRL	Supranational Reference Laboratory
TB	Tuberculosis
TLCU	Tuberculosis and Leprosy Central Unit
TSH	Thyroid Stimulating Hormone
WHO	World Health Organization
XDR TB	Extensively Drug Resistant TB

Anti-tuberculosis drug abbreviations

Am	Amikacin
Km	Kanamycin
S	Streptomycin
Cm	Capreomycin
Ofx	Ofloxacin
Lfx	Levofloxacin
Mfx	Moxifloxacin
FQ	Floroquinolone
Cs	Cycloserine
Eto	Ethionamide
Z	Pyrazinamide
PAS	P-aminosalicylic acid
E or EMB	Ethambutol
R	Rifampicin
H	Isoniazid

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Dr. Donan W. Mmbando
Ag. Chief Medical Officer
Ministry of Health and Social Welfare

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FOREWORD

The emergence of resistance to drugs that are used to treat tuberculosis (TB), and particularly Multidrug-resistant TB (MDR-TB), has become a significant public health problem in many countries, and is an obstacle to effective global TB control. In 2006, extensive drug-resistant TB (XDR-TB), a more severe form of drug resistant TB - was reported in all regions of the world, and the World Health Organization (WHO) classified XDR-TB, as a serious emerging threat to public health, especially, in countries with a high prevalence of the Human Immunodeficiency Virus (HIV).

In Tanzania, the MoHSW has taken specific measures through the National TB and Leprosy programme, to address the problem of MDR TB by conducting a drug resistance survey, which provided an insight into the extent and type of drug resistant TB strains. Currently MoHSW is providing appropriate treatment and management to identified patients, so as to halt the propagation and dissemination of drug resistant strains, in the general population, and prevent the high mortality, that is associated with MDR TB, especially in settings of high HIV prevalence.

The treatment of MDR TB is complicated and prolonged, and is supposed to be provided in isolated wards, at selected hospitals, until patients are no longer infectious. Thereafter, the treatment has to be continued at a health facility, under the care of qualified personnel, close to the patient's home. Since this is a new intervention, these guidelines are introducing new knowledge, and aim at disseminating current global recommendations on the management of MDR TB, to health care workers (HCWs), who are involved in the detection, diagnosis and treatment of drug

resistant TB, at all levels. In particular, the guidelines are intended to support the HCWs as a reading and reference tool, during their clinical practice, at MDR TB hospitals, district and health centre level facilities, where MDR TB patients will be managed, during the continuation phase of treatment. Also, new recording and reporting tools, for MDR TB hospitals, districts and regions, are introduced, so as to allow a systematic process for data analysis, and thus capture of important information, that can be used to inform policy makers and improve the management of Drug Resistant TB, in the country.

As this is a new and complex undertaking, I hope that you will find this document useful, in your daily work, and your feedback on areas that need revision and improvement, will be important, while preparing the next edition.

Regina L. Kikuli
Ag. Permanent Secretary
Ministry of Health and Social Welfare

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EXECUTIVE SUMMARY

Globally, Multidrug-resistant *Mycobacterium tuberculosis* (MDR TB) is emerging at an alarming rate and presents a major challenge for the clinical management of TB. There are estimated to be about 450,000 MDR TB cases world wide each year, 150,000 MDR TB deaths and approximately 25,000 of these cases are expected to have XDR TB. The most recent data from the National Drug Resistance Survey 2006 in Tanzania indicates that the proportion of MDR-TB among new and retreatment cases is about 1.1% and 3.1 % respectively.

MDR TB is a laboratory diagnosis confirmed after culturing *Mycobacterium tuberculosis* strains and performing drug susceptibility tests (DST). From a microbiological perspective, resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. An inadequate or poorly administered treatment regimen allows a drug-resistant strain to become the dominant strain in a patient infected with TB and that is why MDR TB is more common in patients with previous treatment of TB. Subsequent transmission of such bacilli to other persons may lead to new drug-resistant cases in the general population.

Currently in Tanzania, the Central TB reference laboratory (CTRL) can perform culture and DST. The MDR TB hospital laboratory is responsible for monitoring MDR TB patient treatment during the intensive phase while districts will utilize the zonal TB labs for cultures when monitoring treatment during the continuation phase. The national TB infection control (IC) guidelines apply to the management of MDR TB.

The Tanzanian MDR TB program recommends using a *standardized treatment regimen* approach with the intensive phase patients being hospitalised and continuation phase being provided at a health facility near the patient's home as possible. For patients who are seriously ill and have a high likelihood of MDR TB, empiric regimes should be started by the MDR TB Review Committee while awaiting DST results. Second line drugs are associated with many and sometimes intolerable adverse events, especially during the initial phase of treatment. Side effects should be managed aggressively so as to ensure that patients do not default from treatment.

Management of MDR TB drugs at the MDR TB centres and district levels are also outlined in these guidelines so as to ensure uninterrupted supply of second line drugs to MDR TB patients. The national data management team for MDR-TB developed a recording and reporting system for district, regional and national level. The guidelines introduce new standards for registering, monitoring and reporting the treatment outcomes of patients with MDR TB.

1. INTRODUCTION

Preamble

Globally, Multidrug-resistant *Mycobacterium tuberculosis* (MDR TB) is emerging at an alarming rate and presents a major challenge for the clinical management of tuberculosis and is a real threat for global TB control initiatives.

1.1 Magnitude of MDR TB

There are estimated to be about 450,000 MDR TB cases world wide each year and approximately 25,000 of these cases are expected to have XDR TB. Less than 5% of MDR TB cases are currently detected and only 3% of MDR-TB cases are being treated according to standards set by WHO. The number of MDR-TB cases among new and previously treated TB patients is greatest in the South-East Asia and Western Pacific Regions, the most populous areas of the world, followed by Eastern Europe.

Recognising the importance of monitoring the magnitude of MDR- TB in Tanzania, routine surveillance and drug resistance surveys have been undertaken by the National TB and Leprosy Programme since 1982. The most recent data available (National Drug Resistance Survey 2006) indicates that the proportion of MDR-TB among new and retreatment cases is about 1.1% and 3.1 % respectively.

Many African countries have limited laboratory capacity, resulting in an unknown true burden of MDR-TB and subsequently the management of drug resistant TB is largely ignored[1]. However,

1 Framework for the management of drug resistant TB in the African region WHO AFRO, 2008

WHO estimates that MDR TB is more widely prevalent in Africa than previously thought which is why most African countries now are now scaling up the programmatic management of MDR and XDR TB.

Numerous factors have been outlined as challenges in the management of MDR TB and these include:

- Therapy with second line drugs which are much more expensive but less effective and more toxic than the first line anti TB drugs
- Prolonged duration of therapy which is associated with high rates of side effects and poor outcomes (increased morbidity and mortality). This prolonged duration of therapy also increases the risk of transmitting the resistant bacilli to health workers (nosocomial outbreaks)
- Need for strong TB infection control measures in health facilities (infrastructural and administratively)
- Strengthened laboratory services for diagnosis and follow up of MDR TB patients
- Greater requirement for training of clinical personnel

1.2 Impact of HIV on MDR and XDR TB

Drug-resistant tuberculosis (TB) is emerging as a major clinical and public health challenge in areas of sub-Saharan Africa where there is a high prevalence of human immunodeficiency virus (HIV) infection. The combination of a large population of HIV-infected individuals who are susceptible to TB, a lack of airborne infection control in health facilities and congregate settings, limited drug-resistance surveillance, and an overburdened TB treatment

program provides ideal conditions for an M/XDR-TB/HIV epidemic. HIV is a strong risk factor for all forms of TB, and outbreaks of M/XDR TB among PLHIV have demonstrated high rates of mortality of up to 90% or more. Untreated or poorly treated patients with infectious drug-resistant TB bacilli are a source of primary transmission of drug-resistant TB strains in the community.

2. DEFINITIONS AND SITES OF DRUG RESISTANCE

MDR TB is a laboratory diagnosis confirmed after culturing *Mycobacterium tuberculosis* strains and performing drug susceptibility tests (DST). Resistant strains will be identified because they will be able to survive exposure to anti TB drugs which were previously toxic to them. Four different categories of drug resistance have been identified[2].

- **Mono-resistance:** Resistance to one anti-tuberculosis drug
- **Poly-resistance**: Resistance to more than one anti-tuberculosis drug, other than both isoniazid and Rifampicin (e.g. against both pyrazinamide and isoniazid).
- **Multidrug-resistance:** Resistance to at least isoniazid and rifampicin
- **Extensive drug resistance TB (XDR-TB):** Multidrug-resistance with additional resistance to any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin, and amikacin).

The two categories of drug resistance, Multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are of clinical and public health importance

Isoniazid is a potent mycobactericidal drug that ensures early sputum conversion and helps in decreasing the transmission of TB) and Rifampicin is a drug with mycobactericidal and sterilizing activities that prevent relapses. These two are keystone drugs in the current Short-Course Chemotherapy (SCC) regimen of 6 months duration.

2 *Guidelines for the programmatic management of drug resistant tuberculosis WHO/HTM/TB/2008.402*

XDR TB is the worst form of resistance. Its treatment is more complicated and outcomes are extremely poor, especially in HIV co-infected patients.

Primary resistance vs Acquired/Secondary resistance

Without genotyping of original and subsequent *Mycobacterium tuberculosis* isolates, it is impossible to discern whether previously treated patients have always been infected with drug-resistant strains, were re-infected with a new drug-resistant strain (primary resistance), or whether their strains evolved on treatment (secondary resistance). Hence the current terminology: drug resistance in new vs. previously treated cases[3].

- ***Drug resistance in a new TB case***

The presence of a resistant strain of M. tuberculosis in a patient newly diagnosed with TB who has not previously been treated with TB drugs (or therapy of less than one month duration) suggests 'primary' drug resistance. In these cases, patients were likely to have been infected with a strain that was already drug resistant.

- ***Drug resistance in a previously treated TB case***

The presence of a resistant strain in a TB patient who has previously received at least one month of TB therapy suggests 'secondary' or 'acquired' resistance. In these cases, patients are likely to have been initially infected with a drug-susceptible M. tuberculosis strain, but during the course of anti-tuberculosis treatment, drug resistance emerged.

3 *Drug resistant tuberculosis, a survival guide for clinicians. 2nd Edition. Available at www.nationaltbcenter.edu/drtb*

Site of drug-resistant tuberculosis disease (pulmonary and extra-pulmonary)

In general, recommended treatment regimens for drug-resistant forms of TB are similar, irrespective of site. Defining site is important primarily for recording and reporting purposes.

- **Pulmonary tuberculosis.** Tuberculosis involving the lung parenchyma. Miliary tuberculosis is classified as pulmonary TB because there are lesions in the lungs. A patient with both pulmonary and extrapulmonary TB should be classified as a pulmonary case.

- **Extrapulmonary tuberculosis.** Tuberculosis of organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. The definition of an extrapulmonary case with several sites affected depends on the site representing the most severe form of disease.

3. CAUSES OF DRUG-RESISTANT TUBERCULOSIS

From a microbiological perspective, resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. An inadequate or poorly administered treatment regimen allows a drug-resistant strain to become the dominant strain in a patient infected with TB.

Subsequent transmission of such bacilli to other persons may lead to a disease that is drug resistant from the outset (primary resistance), which can be a significant source of new drug-resistant cases in the general population.

There is a link between poor programme performance, or insufficient coverage of a good programme, and drug resistance. Previously treated cases, are more likely to be drug-resistant and to have resistance to more drugs than untreated patients.

Table 3.1 Common causes of drug resistant TB

HEALTH WORKER: INADEQUATE REGIMENS	− Inadequate initial treatment regimen: Wrong combination or doses, guideline noncompliance − Clinical errors: Adding a single drug to a failing regimen − Inadequate training on the management of drug susceptible TB − Lack of proper monitoring of treatment (Poor DOT) − The patient incorrectly diagnosed as having latent TB infection, rather than active TB, and treated with mono-therapy − Treatment “in the dark” for re-treatment cases: no drug susceptibility testing available, or results delayed

HEALTH SYSTEM: INADEQUATE DRUG SUPPLY/ QUALITY	- Poor drug quality, poor storage conditions - Unavailability of certain drugs (stock-out or delivery disruptions) - Wrong dose or combination - Drug-Drug interactions - Inappropriate or no guidelines - Lack of appropriate or timely laboratory testing
PATIENTS: INADEQUATE DRUG INTAKE	- Poor adherence, non-adherence or default - Lack of information / misunderstanding - Disbelief in the diagnosis, efficacy or necessity of treatment - Lack of money (to cover indirect cost of TB treatment) - Lack of transportation - Adverse drug reactions/intolerance - Social barriers - Neuropsychiatry disease - Substance dependency disorders - Mal-absorption of drugs

Adapted from WHO 2008, Guidelines for programmatic management of DR TB

Although its causes are microbial, clinical and programmatic, Drug-Resistant TB is essentially a man-made phenomenon.

4. CASE FINDING STRATEGIES FOR MDR-TB

Chapter Objectives

This chapter describes strategies for case finding and the diagnosis of patients with either suspected or confirmed DR-TB.

The chapter reviews case finding of patients with DR-TB with respect to:

- Risk factors for drug resistance;
- Strategies for case finding in programs with minimal access to DST and limited resources;
- Information on DST collection;
- The use of rapid DST methods to identify drug resistance;

Preamble

Clinically the symptoms of DR-TB are the same as for drug susceptible TB; in particular, cough for two weeks or more, fever and night sweats, chest and/or back pain, hemoptysis (coughing up of blood), weight loss and others. The diagnosis of DR TB therefore can only be confirmed by culture and drug susceptibility testing (DST) of sputum specimens. In order to facilitate the rapid identification of drug resistant TB, clinicians should have a high index of suspicion in certain high risk groups for MDR TB. A flow chart summarizing the major steps to identify DR TB suspects is available in annex 1.

4.1 Identification of DR TB suspects

MDR-TB is more common in previously treated than in new TB patients and all patients with prior history of TB treatment should be clinically evaluated for MDR TB. A delay in diagnosis leads to further amplification of drug resistance because MDR TB patients would unknowingly receive a ‘sub-optimal’ re-treatment regimen

with first line drugs. Early identification and treatment initiation would increase the chance of curing MDR TB and prevent the further spread of MDR TB.

The following patient groups should be targeted for rapid DST:

1. Patients who have failed, relapsed or returned after default of a re-treatment TB regimen **(formerly chronic excretors)**
2. Failure of first-line regimen; patients who are sputum smear-positive at 5 months or later during the course of standard new patient treatment regimen **(Cat 1 failures)**
3. Relapses and defaulters who are smear positive at month 3 of a retreatment **(late converters of a cat 2 regimen)**
4. Symptomatic close contacts of a known MDR-TB case

Start MDR TB treatment only after having proof of resistance, however, there are exceptions. Empiric MDR TB treatment can be started by the MDR TB review committee in patients with a high likelihood of MDR TB, such as; failures of a retreatment regimen (Cat. 2 failures), severely ill cases with still high positive smear at 3 months of well a supervised Cat. 2 regimen and child contacts of MDR TB cases who are unable to produce sputum and are severely ill. Starting empiric regimen pending DST is done to avoid further clinical deterioration and reduces the risk of transmission to contacts by rendering the patient less infectious.

TB patients who are *returning after defaulting* or *relapsing* from their first treatment course have a medium to low likelihood of MDR TB and should have routine DST performed and then receive a retreatment regimen containing first-line drugs (2HRZES/1HRZE/5HRE).

Previous TB treatment is a strong determinant of MDR TB and specimens for culture and drug susceptibility testing (DST) should be obtained from all previously treated TB patients at or before the start of a re-treatment regimen.

Case-finding should occur at any level of the HF and primarily at the district hospital level; DR TB suspects have to be recorded in the district DR TB suspect register and have specimens sent for DST to the Central TB Reference Laboratory in Dar es Salaam. This activity is coordinated by District TB and Leprosy Coordinators (DTLCs).

The required baseline investigations of any DR TB suspect include:

- comprehensive medical history including outcomes of prior TB treatment
- physical examination
- collection of 2 sputum samples (spot – morning) for smear microscopy, culture and DST
- Provider Initiated Testing and Counseling (PITC) for HIV
- education on cough hygiene
- chest X-ray examination

DST confirmed MDR TB patients shall be referred and transported by a special ambulance to the MDR TB Hospital where they will be admitted.

Medical services of prisons, army, police and refugee camps should also register DR TB suspects and have specimens sent for DST.

4.2 Case-finding in pediatric patients

Paediatric cases will require adjustments in diagnostic criteria and

indications for treatment. Multidrug-resistant tuberculosis should be suspected in the following situations:

- A child who is a close contact of an infectious MDR TB case.
- A child who is a close contact of a TB treatment failure or defaulter.
- A child with proven TB who is still bacteriologically positive after five months of appropriate treatment with first-line anti-TB medications. (Treatment failure).

Drug-resistant TB should be suspected under these circumstances, but confirming the diagnosis depends on sputum culture for M. tuberculosis strains and results of DST.

Efforts should be made to obtain specimens from all possible sources like gastric aspiration, sputum induction, or lymph node aspiration for culture and DST because MDR TB is a microbiological diagnosis even in children. Culture results can be available within two weeks (Liquid Media) and DST results are available after at least 6 weeks. The diagnosis of MDR TB in children is made by a review panel experts on MDR TB based on history, physical examination and laboratory findings. Children diagnosed with MDR TB should be reported to the DTLC for record and referred to an MDR TB Treatment Centre for further management

4.3 Identification of XDR TB suspects

The following patient groups are to be considered at risk for XDR TB:

- Failure of MDR TB treatment
- MDR TB cases who relapse or return after default
- Close contact with an individual with XDR TB or an individual for whom treatment with second-line drugs is failing

In those cases, DST of second line drugs (Injectable Agents and Fluoroquinolones) in addition to isoniazid and rifampicin must be performed. Adjustment of the regimen should be done according to DST results.

Key recommendations

- ☒ Patients at risk of DR-TB should be screened for drug resistance
- ☒ For the screening of DR-TB, rapid DST methods should be used whenever possible
- ☒ Patients at increased risk of XDR-TB should be screened for resistance with DST of isoniazid, rifampicin, second line injectable agents and a fluoroquinolone

5. LABORATORY TESTING FOR DR-TB

Chapter objectives

This chapter describes standards for laboratory services needed to diagnose and treat DR-TB in the context of the existing laboratory capacity.

Preamble

Optimal management of MDR-TB requires both mycobacterial and clinical laboratory services. At a minimum, the required mycobacteriology laboratory services include; culture, confirmation of *M. tuberculosis* and DST to Isoniazid and Rifampicin while clinical laboratory services include basic hematology, biochemistry, serology and urine analysis for adequate evaluation and monitoring of patients.

Currently in Tanzania, the Central TB reference laboratory (CTRL) can perform culture and DST, whereas 3 zonal TB laboratories and the National MDR TB hospital can perform culture and clinical laboratory investigations. The MDR TB hospital laboratory will be responsible for monitoring MDR TB patient treatment during the intensive phase while districts will utilize the zonal TB labs for cultures when monitoring treatment during the continuation phase.

Prompt turnaround time for laboratory results is of paramount importance in rapid diagnosis and appropriate treatment of drug resistant TB (DR-TB). Based on improved rapid diagnostic tests, the following turnaround times are recommended:

Table 5.1 Turnaround times for different available TB diagnostic tests

Procedurals for smear, culture and DST results	Solid culture (LJ)	Liquid culture (MIGIT)	Hain test (Line Probe Assays)	Gene Xpert (Molecular technique)
Processing of collected sputum	**Within 1 working day** after collection	**Within 1 working day** after collection	**Within 1 working day** after collection	**Within 1 working day** after collection
AFB smear reports reaching clinician	**Within 2 working days** after specimen receipt in the laboratory	**Within 2 working days** after specimen receipt in the laboratory	**Within 2 working days** after specimen receipt in the laboratory	**Within 2 working days** after specimen receipt in the laboratory
Positive culture identification	**Within 8 weeks** of specimen collection using solid media	**Within 17-21 days** of specimen collection using broth media	**Within 5 hours** after primary isolation	**Within 2 hours** after primary isolation
Isolate definitively identified as *M. tuberculosis* *	**Within 14 weeks** of specimen collection	**Within 23 days** of specimen collection	**Within 5 hours** after primary isolation	**Within 2 hours** after primary isolation
Drug susceptibility test results for Isoniazid, Rifampicin, Streptomycin and Ethambutol (HRSE) reported to the clinician	**Within 14 weeks** of specimen collection	**Within 4 weeks** of specimen collection	**Within 48 hours** of specimen collection	**Within 48 hours** of specimen collection

**Isolate identification done by PNB in solid culture and Capilia in broth media, PNB done concurrently with DST and definite identification obtained 42 days after a positive culture growth.*

5.1 Microscopy

The main use of microscopy for drug-resistant TB is in assessing the infectiousness of patients and triaging specimens to different methods of culture and DST. However, AFB sputum smear microscopy cannot distinguish between viable and non-viable bacilli hence its utility for monitoring patient infectiousness and response to treatment is limited. For example, even with adequate treatment, specimens from MDR-TB patients may remain sputum smear-positive after they become culture-negative, suggesting that the bacilli are non-viable.

5.2 Culture

Although the vast majority of mycobacterial isolates will be *M. tuberculosis*, mycobacteria other than tuberculosis (MOTT) can occur especially in patients living with HIV (PLHIV). MOTTs are inherently resistant to the commonly used first line anti TB drugs and clinically present as MDR TB (treatment failures). In the laboratory, unless the species is confirmed as *M. tuberculosis*, mycobacterial isolates appearing phenotypically resistant to first-line drugs may represent infection with MOTT, not drug-resistant TB.

Therefore, it is recommended that laboratories performing TB cultures conduct Paranitrobenzoic acid (PNB), niacin and nitrate tests (both positive in *M. tuberculosis* strains) so as differentiate MOTTs from drug resistant MTB strains.

5.3 Drug Susceptibility Testing (DST)

Susceptibility testing of mycobacteria utilizes the same solid media, broths, and inoculation methods as culture techniques. The systems are supplemented with anti-tuberculosis drugs. Growth of the organisms in the presence of anti-tuberculosis drugs is

compared to controls in order to interpret susceptibility or resistance

It is recommended that two sputum specimens be obtained for culture and that DST be performed with the specimen that produces the best culture.

Second line DST will be conducted in the Central TB reference Laboratory in Dar es Salaam in collaboration with the internationally recognized supranational laboratory of Antwerp, Belgium.

Rapid DST

Molecular-amplification assays such as line probe assays allow detection of rifampicin resistance (alone or in combination with isoniazid) within days of sputum specimens being obtained from the patient or cultures obtained from rapid liquid culture systems. Rapid molecular (and culture-based) DST should be targeted to high risk groups for MDR TB such as; (i) failure cases of Cat. 1 and 2, (ii) relapses of Cat. 2, (iii) late converters of Cat. 2 and (iv) contacts of MDR TB (if smear+ or at least symptomatic).

Conventional culture will continue to be used for definitive diagnosis of TB in smear-negative patients, while conventional DST will be used to determine drug susceptibility to drugs other than rifampicin and isoniazid. ie Ethambutol & Streptomycin

The accuracy of DST is highest for rifampicin and isoniazid and less accurate for streptomycin, ethambutol and pyrazinamide. Always correlate DST results with the patient's clinical condition.

5.4 Specimen transportation

- An adequate sputum specimen (3–5mls) is essential for the success of culturing *Mycobacterium tuberculosis.*
- Collect two specimens for culture, for at least one DST.
- The sputum are to be collected into Falcon tubes 50mls.
- Carefully labeled with name, hospital, TB district number, date of collection.
- Wrap with absorbent materials like, cotton wool or used newspapers so that if they are damaged or leak the sputum will be absorbed.
- Pack collected sputum specimens into used plastic containers used to store drugs like panadol or aspirin. These containers will protect the tubes from physical damage while on transit.
- Transport parcels to TB Culture laboratories if possible twice a week using EMS or local buses to the nearest TB culture laboratory.
- Always use CPC (1% Cetyl Pyridium Chloride in 2% sodium chloride transport medium) for specimens sent for DST, this will keep the TB alive even after more than one month (not just one week)
- Keep tubes with CPC at room temperature ALWAYS (also with the specimen in it). DO NOT REFRIGERATE
- For MGIT cultures (only recommended for diagnosis of smear-negative, and not suspect MDR TB) collect specimens in 50 ml Falcon WITHOUT CPC; keep cold; transport rapidly (if possible cold)
- Make sure that laboratory request forms are kept separate from specimen containers to prevent them from being contaminated if leakage occurs.

5.5 Laboratory quality assurance

Quality of laboratory processing is of crucial importance especially in DR-TB where diagnosis has profound implications to the individual patient. Delays in specimen transport, excessively harsh or insufficient decontamination, poor-quality culture media or incorrect incubation temperature can adversely affect the culture yield. Laboratory errors, such as mislabeling or cross-contamination between specimens during aerosol-producing procedures, may lead to false negative or false-positive results.

A comprehensive laboratory quality assurance program shall be place to ensure the accuracy, reliability and reproducibility of DST results. The CTRL in Dar es Salaam shall maintain a formal link with the Supranational Reference Laboratory (SRL) Tropical Medicine Antwerp, Belgium to ensure quality of laboratory services and the validation of DST results.

5.6 TB infection control measures in the Laboratory

Transmission of TB – including MDR- and XDR-TB - is a well-recognized risk for laboratory workers. *M. tuberculosis* is classified as a Risk Group 3 laboratory pathogen by WHO, requiring specific laboratory containment measures.

5.6.1 Specimen collection

Sputum specimen collection should take place in open air using a sputum container with a wide mouth so that the patient can expectorate easily inside the container without contaminating the outside. The patient must be educated on the need to prevent spread of TB infection and no one should stand in front of a patient producing sputum. After collecting sputum specimen, the lid should

be placed on the container and closed firmly. The HCW should wash hands with soap and water after completing the procedure.

One sample should be produced on spot (spot sample) and the second sample on early morning of day two (early morning sample) when a patient wakes up after rinsing the mouth with water (before brushing). The patient should be instructed to produce the sample in a well ventilated open space away from people after:

- Inhaling deeply 2-3 times.
- Coughing out deep from the chest (should avoid producing saliva)
- Opening the container and then s/he spits sputum into it.

Then the patient closes the container and immediately delivers the sample to the lab for processing. In the laboratory, the sample container is labeled appropriately.

Requirements:

Specimen collection container

Containers must be rigid to avoid crushing in transit and must possess a water-tight wide mouthed screw top to prevent leakage and contamination

1. Wide-mouthed (at least 35mm in diameter) so that the patient can expectorate easily inside the container without contaminating the outside
2. Volume capacity of 50ml for the disposable 'falcon' tubes and 28ml for standard universal containers.
3. Made of translucent material in order to observe specimen volume and quality without opening the container

4. Made of single-use combustible material to facilitate disposal
5. Screw-capped to obtain an airtight seal and to reduce the risk of leakage during transport
6. The container should be sterile
7. Easily-labeled walls that will allow permanent identification

An alternative container is the 28ml Universal bottle (McCartney bottle), which is a heavy glass, screw-capped bottle with a wide neck. This container is reusable after thorough cleaning and sterilization.

5.6.2 Specimen processing

Every laboratory processing sputum specimens should have at least two rooms, one for reception and the other one for performing the test. The smear preparation should be performed in a well ventilated room with sunlight. Fresh bleach (5% sodium hypochlorite) diluted 1:10 in water should be used for cleaning sputum and for decontamination of equipment (e.g. microscope, glasses for mixing reagents). Laboratory safety precautions for specimen handling and transportation including wearing gloves and laboratory coats should be observed. During sputum specimen preparation, the wire loop should be disinfected and burned before re-use, otherwise, if a wooden applicator is used instead, it has to be disinfected before being discarded.

5.6.3 Specimen disposal and decontamination

The room should have a container with plastic bags, made of polyethylene if available, for the proper disposal of waste. A good water drainage system during the process of staining smears is mandatory and used sputum cups, applicator sticks and slides should be disposed (e.g. place in a discard bag, then burnt or

buried or autoclaved) after being used. In case of accidental spillage of a specimen on the floor or bench, fresh bleach (5% sodium hypochlorite) or 5 % phenol should be poured on the specimen and left for 30 minutes before cleaning the area (refer to subheading on disinfectants and waste disposal for a complete list of disinfectants). Culture media, sputum containers and glass slides should be autoclaved or burned in the incinerator prior to disposal.

5.6.4 Infection control and biosafety in the laboratory

The relative hazards of infective micro-organisms handled in the laboratory are classified by WHO according to their risk of causing human disease, the potential for laboratory spread and whether effective treatment and prevention measures are available. *M. tuberculosis* is classified by WHO as a Risk Group 3 laboratory pathogen with procedure such as Mycobacteriological culture and DST generating high-concentration aerosols requiring biosafety level 3 containment precautions.

Laboratory standards require the following essential measures to be in place and enforced:

- Appropriate and specific administrative controls (including good laboratory practice, standard operating procedures and accident management plans);
- Appropriate engineering controls functioning adequately as designed;
- Personal protective equipment appropriate for the tasks being performed;
- Proper waste management procedures;

- Proper procedures for general laboratory safety (including physical, electrical and chemical safety).

Guidelines on biosafety level 3 precautions should be rigorously followed. Laboratory managers shall ensure that health and medical surveillance of laboratory personnel involved in mycobacteriological culture and DST is done. Surveillance shall include a detailed medical history, targeted baseline health assessment, monitoring of respiratory signs and symptoms, and a proactive plan for appropriate medical investigations when indicated.

Laboratory workers should disclose their HIV status to Laboratory managers and HIV-infected ones should be offered safer work responsibilities and discouraged from working with DR-TB specimens. Pregnant women working in the laboratory should be reassigned other duties until after childbirth and lactation.

The use of a safety cabinet may not be necessary for laboratories performing direct sputum examination only, e.g. most of the peripheral laboratories. However, for laboratories performing culture and Drug Susceptibility Testing (DST) the minimum level of containment requires a class II safety cabinet with a double/single filter.

N95 respirators should always be used by the laboratory technicians when handling known or suspected DR TB specimens.

5.6.5 Disinfectants

The following disinfectants are recommended for disinfection procedures in a TB laboratory:

- Glutaraldehydes 2%

- Sporicidin 2%
- Chlorhexidine 4%, centrimide 5%
- Hydrogen peroxide 6%
- Chlorine 0.5%

For the optimal performance of these disinfectants, users should always follow the manufacturer's instructions and ensure that the agents has not expired and are used according to the established SOPs.

5.6.6 Laboratory waste management

Laboratory waste including used sputum collection containers, cultures and devices used to transfer, inoculate and mix cultures should be managed as follows, depending on availability:

- Properly handled by autoclaving at a temperature of 121oC at 1 bar for at least 30 minutes; or
- Burnt in an incinerator; or
- Discarded in a deep pit at least 1,5 meters depth; or
- Disinfected overnight in a solution of sodium hypochlorite in concentrated form and then discarded with hazardous health care waste; or
- If none of the above treatment options can be ensured, packed in a specific bag that should be sealed and directly discarded with the hazardous health care waste
- Highly infectious waste from TB isolation wards shall always be incinerated on-site

Key recommendations

- All patients suspected of DR-TB need access to laboratory services for adequate and timely diagnosis of DR-TB;
- Laboratories should follow all standardized protocols for infection control and biosafety;
- Quality control and quality assurance should be in place for microscopy, culture and DST. Links with supranational TB reference laboratories are strongly encouraged including exchange of TB strains.
- Safe management of waste is key to reduce nosocomial infections inside a hospital and to ensure that the outside environment is well protected.

6. TREATMENT OF DR TB

Chapter objectives

This chapter provides guidance on the strategy options, specifically the standardized approach, to treat MDR-TB as well as the more highly resistant strains such as XDR-TB.

Preamble

Treatment duration for MDR-TB is much longer than treatment for non-MDR TB (up to 2 years). However, as with drug-susceptible TB, treatment for MDR-TB consists of two different phases, the intensive phase of treatment whereby a patient takes at least 4 effective drugs, including an injectable and the continuation phase with the patient talking the same drugs except the injectable.

Once a patient has confirmed MDR-TB it is vital that the patient take all their medications correctly to be cured minimizing the risk of relapse. **The treatment of MDR-TB in many of these patients represents the last opportunity for them to be cured**. Patients with MDR-TB can have very high mortality rates, even on treatment.

Health workers must take an active role to ensure that every patient takes the recommended drugs, in the right combinations, on the correct schedule, for the appropriate duration using the directly observed treatment (DOT) strategy. Supervised treatment for MDR-TB patients is necessary throughout the entire period of treatment.

The National TB & Leprosy Programme (NTLP) has designed an MDR TB treatment strategy based on DRS data and on the frequency of use of first line anti-tuberculosis drugs in Tanzania.

6.1 Baseline procedures and investigations for confirmed MDR TB cases

The required baseline pre-treatment investigations and procedures of any MDR TB patient include:

- Inform the patient and family about MDR-TB and its treatment
- collect medical history
- conduct physical examination, including weight measurement and prepare the patient's MDR-TB Treatment Card
- conduct Provider Initiated Testing and Counseling (PITC), if the patient does not already have a positive HIV test
- educate on cough hygiene
- perform blood test (serum creatinine, serum potassium, thyroid stimulating hormone, liver enzymes and a pregnancy test among women of reproductive age)
- perform a chest radiograph
- Give the patient a brief orientation on the drugs that will be taken and the expected adverse reactions associated with each drug

6.2 Definition of Patient's categories

Every confirmed MDR TB case should be categorized and recorded in the MDR TB treatment card as follows:

- **New MDR TB patients**: patients who have never received anti-tuberculosis treatment e.g. MDR TB contact or who have received first line anti-tuberculosis treatment for less than one month.
- **Retreatment after first line therapy only:** patients who have been treated for one month or more with first-line drugs only. These are further categorized as:
    - **Default**: A patient who returns to treatment, bacteriologically positive with drug resistant TB, after

having interrupted first line treatment for two months or more and who had been on treatment for drug susceptible TB for more than 4 weeks.

- **Relapse:** Patient declared cured or treatment completed for drug susceptible TB but who reports back to the health service and is found to be bacteriologically positive with drug resistant TB,.
- **Failure(**1**):** MDR TB patient who had failed first line standard new patient regimen by being AFB positive at 5 months or later during the course of first line treatment.
- **Failure (**2**):** MDR TB patient who had failed first line retreatment regimen by being AFB positive at 7 months or later during the course of first line treatment.

- **Retreatment after second line therapy:** patients who have been treated for one month or more with second-line drugs. These are further categorized as:
    - **Default:** A patient who returns to MDR TB treatment after having interrupted treatment for two months or more and had more than 4 weeks of MDR TB treatment.
    - **Relapse:** Patients previously treated for MDR tuberculosis who have been declared cured or treatment completed, and then diagnosed with MDR-TB.
    - **Failure:** Patients who return after the first treatment of MDR TB has failed
- **Transfer in**: MDRTB patients who have been transferred from another register for treatment of drug-resistant TB to continue MDR TB treatment. Their outcomes should be reported to the transferring unit so that it can report their outcomes in the

cohort in which they originally started MDR-TB treatment.

- **Other**: MDR TB patients who do not fit the above definitions. This group includes MDR TB patients who were treated outside NTLP.

6.3 Treatment management of DR TB

6.3.1 Treatment of Mono- and poly-resistant TB other than MDR

Cases with mono- or poly-resistance will be identified during the course of case-finding for MDR-TB. Treatment of patients infected with mono or poly-resistant strains using standardized regimens with first line drugs has been associated with increased risk of treatment failure and further acquired resistance, including the development of MDR-TB. The following are recommendations for managing such cases;

1. Patients who have isolated INH resistance should have an excellent outcome with a standard retreatment regimen and that is the preferred regimen to continue or initiate.
2. Proof of rifampicin resistance in Hain, Gene Xpert or LJ DST is sufficient (even without INH), to start MDR TB treatment; in case of doubt, send another specimen for rapid DST using the same test
3. INH + ethambutol + streptomycin resistance can be treated as MDR TB. If still smear-positive at time the DST result arrives; repeat rapid DST before starting MDR TB treatment
4. Treat other resistance patterns with a retreatment regimen

(Category 2) and follow evolution; repeat DST if late converter (sputum smear +ve at month 3), is a failure or relapse of the cat 2 regimen. DO NOT to add one or two second-line drugs to a first-line regimen.

6.3.2 Treatment of MDR TB

The Tanzanian MDR TB program recommends using a **standardized treatment regimen** approach.

Standardized treatment: Regimens are designed according to representative Drug Resistance Surveillance (DRS) data in well-defined patient populations. All patients in a patient group or category receive the same regimen. Suspected MDR TB should be confirmed by DST whenever possible.

Overview of Second Line Drugs

The classes of anti-tuberculosis drugs have traditionally been divided into first and second-line drugs, with isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin being the primary first-line drugs. TB drugs have also been classified using a WHO group system based on efficacy, which is described in Table 6.1 below.

Table 6.1 Grouping anti-TB agents

Group	Drugs
Group 1 – First-line oral agents	isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z)
Group 2 – Injectable agents	kanamycin (Km); amikacin (Am); capreomycin (Cm); streptomycin (S)
Group 3 - Fluoroquinolones	ofloxacin (Ofx); moxifloxacin (Mfx); levofloxacin (Lfx)

Group	Drugs
Group 4 – Oral bacteriostatic second-line agents*	ethionamide (Eto); protionamide (Pto); cycloserine (Cs); terizidone (Trd); *p*-aminosalicylic acid (PAS)
Group 5 – Agents with unclear role in treatment of drug resistant-TB**	clofazimine (Cfz), linezolid (Lzd), amoxicillin/clavulanate (Amx/Clv), thioacetazone (Thz), imipenem/cilastatin (Ipm/Cln), high-dose isoniazid (high-dose H), clarithromycin (Clr)

**The drugs in Group 4 may be started at a low dose and escalated over two weeks; the approach of slowly escalating drug dosage is referred to as "drug ramping".*
*** Can be of use in constructing XDR-TB regimens. They should be used in consultation with an MDR TB*
*** High does H is defined as 16 - 20 mg / kg / day*

While drug resistant TB is generally treatable, it requires extensive chemotherapy (up to 2 years of treatment) with second-line anti-TB drugs which are more costly than first-line drugs and which produce adverse drug reactions that are more severe, though manageable. Quality-assured second-line anti-TB drugs are available for use in Tanzania, through the Green Light Committee (GLC) mechanism of the World Health Organisation (see annex 2 for a summarized drug information guide).

The recommended standardized regimen includes Amikacin (Am), Ofloxacin (Ofx) / Levofloxacin (Lfx), Pyrazinamide (Z), Ethionamide (Eto)**,** Cycloserine (Cs) **and** Ethambutol (E) (if no resistance to Ethambutol is documented)

Always include Ethambutol in the regimen since DST results for ethambutol are lest accurate among anti TB agents and the drug is not toxic. In addition, Capreomycin (Cm) will be available for patients with intolerance or contraindication to one or more of the agents in the standard regimen above.

Standardized MDR TB treatment regimen for Tanzania:
6Z Amk(5) Ofx Eto Cs±E /12Z Ofx Eto Cs±E

- **Intensive Phase (minimum 6 months, or 6 months post culture conversion**)
    - Amikacin or Kanamycin
    - Ofloxacin or Levofloxacin
    - Pyrazinamide
    - Ethionamide
    - Cycloserine
    - Ethambutol

- **Continuation Phase (minimum 12 months or 18 months post culture conversion)**
    - Ofloxacin or Levofloxacin
    - Ethionamide
    - Pyrazinamide
    - Cycloserine
    - Ethambutol

Intensive phase

A *multi-disciplinary MDR TB team* composed by Medical Doctors, nurses, pharmacists, laboratory technicians, counsellors, and social workers at the MDR TB hospital will be responsible for clinical management and close monitoring of MDR-TB patients during the intensive phase of treatment. Physicians from zonal and referral hospitals provide backup support in the clinical management of MDR-TB. The intensive phase lasts at least 6 months and is provided under directly observed therapy (DOT) during which the patient should be admitted.

Continuation phase

In the continuation phase, when patients are potentially non infectious, they will be referred back to their respective health facilities (or prison health facilities) for the continuation phase treatment and follow up. The continuation phase will in principle be provided on an ambulatory basis, at a health facility as close to the patients home as possible.

The *district MDR TB team* (composed by DTLC, clinician and the DOT nurse from the nearest health facility to an MDR TB patient's home) will be trained on MDR TB and TB Infection Control. The team will be responsible for daily DOT and monitoring progress of treatment of the patient including management of side effects for the entire continuation phase. Other district health workers will be trained on MDR-TB treatment, monitoring of treatment, management of adverse effects, reporting and recording of MDR-TB treatment and follow up of defaulters. Continuation phase will be provided for a total of 12 months.

District and Regional TB and Leprosy Coordinators (DTLCs and RTLCs) are responsible, on behalf of the respective DMOs and RMOs for overall coordination at the district and regional levels, referral of specimen for DR TB suspects, follow up of MDR-TB cases and recording and reporting. The flow of the MDR TB case management activities is described in annex 3.

Daily DOT in both the intensive and continuation phase should be recorded on the MDR TB daily DOT record from (annex 4).

The recommended drugs' dosage is described in the tables 6.2 and 6.3.

Table 6.2: Recommended Drug Dosages

Drug	*dose*	*Remarks*
Amikacin or Kanamycin	15mg/kg IM or IV daily 5X week	10 mg/kg if 60 years or older. In impaired renal function (CrCl of < 30 or on dialysis) reduce the frequency of the dose to 2-3 times a week
Ofloxacin	800 mg daily	- usually in 2 divided doses
Levofloxacin	750 mg daily	- Single close
Pyrazinamide	20-30 mg/kg daily	-
Ethionamide	15 mg/kg daily, usually 750 mg, maximum 1gm daily	the dose should be gradually increased every 3-4 days from 250 to 500 to 750 mg; it is advised to administer in 2 divided doses
Ethambutol	15-25 mg/kg daily	start with 25 mg/kg and decrease to 15 mg/kg after 2 months
Cycloserine	10-15 mg/kg daily	the dose has to be gradually increased from 250 mg to 500 mg after 3-4 days

Table 6.3: Dosages for additional drugs if standard regimen cannot be used

Drug	*dose*	*Remarks*
PAS	(as granules) 150 mg/kg, usually 4 gms twice a day	gradually increase the dose every 3-4 days from 2gms to 4 gms to 6 gms to 8 gms in 2 divided doses; administer the drug with acidic food
Capreomycin	15 mg/kg IM or IV daily 5 X week	10 mg/kg if 60 years or older; use only if amikacin is not tolerated. In impaired renal function (CrCl of < 30 or on dialysis) reduce the frequency of the dose to 2-3 times a week. Capreomycin is preferred over Amikacin as the injectable of choice in renal insufficiency

Most drugs should be started at full dose except cycloserine, ethionamide, and PAS, in which case the dose of the drug can be increased over a 2-week period. The patient is begun on a low starting dose and the dose is increased every few days until the targeted dose is reached.

Vitamin B6 (pyridoxine) should be given to all patients receiving cycloserine to prevent neurological adverse effects.
The recommended dose is 50 mg pyridoxine for every 250 mg of cycloserine.

Corticosteroids

The use of corticosteroids in MDR-TB patients can be beneficial in cases of severe respiratory insufficiency and central nervous system involvement. Use prednisolone at a starting dose of approximately 1 mg/kg, with gradual decrease in the daily dose by 10 mg per week when a longer course is indicated.

In patients with an exacerbation of obstructive pulmonary disease, prednisolone may be given in a short tapering course over 1–2 weeks, starting at approximately 1 mg/kg and decreasing the dose by 5–10 mg per day. Injectable corticosteroids are often used initially when a more immediate response is needed.

6.3.3 Cross resistance among anti TB agents

Cross-resistance occurs when resistance mutations (in *M. tuberculosis* bacteria) to one anti-TB drug confers resistance to some or all of the members of the drug family and, less commonly, to members of different drug families.

There is well-known cross-resistance between some of the

antibiotics used in treating Tuberculosis as summarized below;

- All rifamycins (Rifampicin, Rifabutin) have high levels of cross-resistance.
- Fluoroquinolones are generally believed to exhibit complete class effect with cross-resistance between the lower - generation fluoroquinolones (cipro-floxacin and ofloxacin) being almost complete. However, in vitro data shows that higher generation fluoroquinolones such as Levofloxacin or Moxifloxacin remain susceptible when lower generation fluoroquinolones are resistant.
- Amikacin and kanamycin are considered to be very similar and have very high cross-resistance. Capreomycin and Viomycin have high cross-resistance.
- Aminoglycosides (Amikacin and kanamycin) and polypeptides (Capreomycin) have low cross-resistance.
- Prothionamide and ethionamide have 100% cross-resistance. Ethionamide can have cross-resistance to Isoniazid if the *inhA* mutation is present (low level isoniazid resistance).

6.3.4 Management of XDR-TB patients

The approach to designing a treatment regimen is the same as with MDR-TB. First, begin with any first-line drugs that demonstrate in vitro activity, followed by second- and third-line drugs. The following steps are recommended:

- Begin with any first line agents to which the isolate is susceptible (PZA and EMB are commonly not susceptible)
- Add an injectable drug based on susceptibilities (amikacin, capreomycin or kanamycin) and consider an extended duration of use (12 months or possibly the whole treatment). If resistant to all injectable agents it is recommended to use one the patient has never used before;

- Use a higher generation fluoroquinolone such as high dose Levofloxacin or Moxifloxacin;
- Use all Group 4 agents (oral second-line drugs) that have not been used extensively in a previous regimen or any that are likely to be effective;
- Use two or more agents from Group 5;
- Consider high-dose H treatment if low-level resistance is documented.
- Consider adjuvant surgery if there is localized disease;
- Ensure strong infection control measures;
- Treat HIV as per Chapter 7;
- Provide comprehensive monitoring (see Chapter 8) and full adherence support (see Chapter 12).
- if the above combinations are not possible, consider consultation with an XDR TB expert

The minimum duration of an XDR TB regimen should be 18–24 months beyond culture conversion. Surgery should be a strong consideration in patients with XDR-TB.

6.3.5 Mycobacteria other than tuberculosis (MOTT)

Mycobacteria other than tuberculosis (MOTT), also known as **environmental mycobacteria**, **atypical mycobacteria** and **nontuberculous mycobacteria** (NTM), are mycobacteria which do not cause tuberculosis or leprosy

Mycobacteria are a family of small, rod-shaped bacilli that can be classified into 3 main groups for the purpose of diagnosis and treatment:

- The closely related species, *Mycobacterium tuberculosis, M. bovis, M. africanum, M. microti and M. canetti* that form the

M. tuberculosis complex (MTBC) are the causative agents of tuberculosis (TB) in human and animals.

- *M. leprae* which causes Hansen's disease or leprosy.
- Nontuberculous mycobacteria (NTM) are all the other mycobacteria which can cause pulmonary disease resembling tuberculosis, lymphadenitis, skin disease, or disseminated disease.

NTM are ubiquitous species widely distributed in the environment, particularly in soil, food, water and animals, and are not generally considered to be contagious. Most NTM disease cases involve the species; *M.avium complex (MAC), M. kansasii, M. abscessus, M. fortuitum, M. gordonae* and *M. chelonae.*

Unlike tuberculosis, which is spread from person to person, MOTT infections are not contagious. There is no evidence that the infection can be transmitted from one person to another hence MOTT is not a public health threat.

Like tuberculosis, about 90% of cases involve the pulmonary system; the rest involve lymph nodes, skin, soft tissues, and bones. Pulmonary disease occurs predominantly in patients with underlying lung disease and/or with a history of chronic lung disease like cystic fibrosis or old tuberculosis. Pneumonia and/or disseminated infection can also occur in persons with immunosuppression due to HIV. MOTT pulmonary infection is caused primarily by *M. avium complex (MAC)* and *M. kansasii.* Other species that cause lung disease include *M. abscessus, M. fortuitum, M. xenopi, M. malmoense, M. szulgai*, and *M. simiae.*

MOTTs are inherently resistant to the commonly used first line anti TB drugs and clinically present as MDR TB suspects (treatment

failures). In the laboratory, species identification of all mycobacterial isolates appearing resistant to first-line drugs will identify MOTT cases on LJ, Hain or MGIT but NOT Gene Expert, in case of doubt, send more samples for culture identification or Hain.

Generally MOTT should be considered as an opportunistic infection or colonization in cured TB cases (or even just contamination if isolated only once and are the same species).

If found in suspect MDR TB who has never shown to have MDR TB (positive DST), counsel the patient as the disease is often times incurable and refer to a pulmonary specialist. Do not treat as TB or MDR TB.

Stop MDR TB treatment if patients has already started empirically based on a presumptive diagnosis and MDR TB was never document by DST results.

Key recommendations

- Promptly diagnose DR-TB and initiate appropriate therapy;
- Do not use ciprofloxacin as an anti-tuberculosis agent;
- Treat for 18 months past culture conversion;
- Use adjunctive measures appropriately, including surgery and nutritional and social support;
- Aggressively treat XDR-TB whenever possible;
- Treat adverse effects immediately and adequately.
- Treatment of MOTT is entirely different from the treatment of drug resistant TB, refer to pulmonary specialists.

7. TREATMENT OF MDR-TB IN SPECIAL SITUATIONS

Chapter Objectives

The management of drug resistant tuberculosis require particular consideration in special situations outlined below:

- Contraceptive
- Pregnancy
- New born child of an MDRTB mother
- Paediatric patients
- HIV co-infection
- Renal disease
- Liver disease
- Extra pulmonary MDR TB
- Diabetes mellitus
- Psychiatric disorders

7.1 Contraceptives

There is no contraindication to the use of oral contraceptives with the non-rifamycin containing regimens. However, patients who vomit soon after taking an oral contraceptive have increased risk of reduced absorption of the medications, and hence reduced efficacy. These patients should be advised to take their contraceptive apart from the time that they may experience vomiting due to anti-tuberculosis medications or use a barrier method until medications are tolerated.

7.2 Pregnancy

All female patients of child bearing age should be tested for pregnancy on initial evaluation. If a patient is found to be pregnant, she must be carefully evaluated, taking into consideration the

gestational age and severity of the MDR-TB. The risks and benefits of treatment should be carefully considered, with the primary goal of smear conversion prior to delivery to protect the health of mother and child.

There are four options for treatment to be considered.

1. Use the best possible albeit weak regimen, avoiding the known potential teratogens: aminoglycosides, capreomycin and ethionamide. At least three and preferably four drugs with demonstrated efficacy against the infecting agent should be used to avoid failing of the second line regimen
2. Use a strong regimen including an injectable agent. Because there may be less teratogenicity with capreomycin, it is preferred. It is essential to discuss risks and benefits with patient and family
3. Postpone treatment until after delivery if patient very stable.
4. If mother's life is at risk without known teratogenic drugs, pregnancy termination is sometimes reluctantly considered

The pregnant MDR TB patient should be evaluated for the severity of her disease and the different options discussed with the patient.

- Patients who are relatively stable and without severe manifestations of their MDR-TB can be considered for the first and third options. However, the pregnant woman must be counseled at this time that if treatment is to be postponed until after delivery, she will be separated from her newborn infant because of the risk of MDR-TB to the very young child.
- Patients who are very ill and in danger of mortality should be considered for the second and fourth options. If the second option is chosen, then capreomycin should be selected as the injectable agent. Cycloserine and PAS can be used along with the ofloxacilin or levofloxacin, PZA and the injectable agent,

avoiding ethionamide if possible.

- Unless immediately life threatening, treatment should be deferred until after the first trimester of pregnancy, when the majority of teratogenic effects occur.

7.3 Management of newborn child of a mother with MDR-TB

- If the mother is no longer contagious and decentralization for the continuation phase at the community level has already occurred, the infant may be cared for by the mother. However, most TB medications are present in breast milk and to avoid unknown adverse effects, consideration of using infant formula should be given, if resources are available.
- For patients who are no longer contagious, but still in the intensive phase of treatment at the MDR TB Hospital, family members may bring the child for visits which should occur outdoors. Consideration should be given to early transfer to a health facility near the patient home for continuing MDR TB care and management.
- If mother is untreated, or still infectious (still smear positive) despite treatment, the mother and infant should be **separated,** and family members should care for the infant. Infant formula will be necessary, and if there are financial difficulties, there should be provision in the MDR TB program to supply the infant formula.

Women of childbearing age who are not pregnant and have MDR-TB should be counselled to use contraception and avoid pregnancy during treatment.

Table 7.1: Safety of some MDR TB medications during pregnancy[4]

Medication	Comments
Ethambutol	Safe to use.
Pyrazinamide	Safe to use.
Amikacin	**Avoid use**. Documented ototoxicity
Fluoroquinolones	Can be used.
Ethionamide	**Avoid use.** Teratogenic effects observed in animal studies; significantly worsens nausea and vomiting associated with pregnancy.
Cycloserine	Safe to Use; no significant evidence of toxicity in pregnant patients.
PAS	Can be used
Capreomycin	Carries the risk of ototoxicity but is the injectable drug of choice if an injectable agent cannot be avoided.

7.4 Pediatric MDR TB patients

Children defined as aged 14 years and below, with MDR-TB generally have primary resistance transmitted from an index case with MDR-TB. Although children often have paucibacillary TB disease and are culture negative, a strong effort should be made to confirm the diagnosis with culture and DST to avoid exposing children unnecessarily to toxic drugs.

In children with clinical evidence of active TB and contact with a documented case of MDR TB, and there are no culture or DST results available from the child, treatment should be guided by DST of the presumed source case. If a child has MDR-TB, the benefits of treatment far outweigh any potential risks of the anti-TB medications used for MDR-TB, and the standard regimens outlined above should be used. Of note, children typically have a lower organism load than adults and generally tolerate MDR-TB

4 The PIH guide to medical management of multi-drug resistant tuberculosis. International Edition. 2003

medications better with fewer side effects.

While fluoroquinolones have been shown to retard cartilage development in animal studies, experience with the use of fluoroquinolones in children has not demonstrated similar effects in humans[5],[6]. It is considered that the benefit of fluoroquinolones in treating MDR-TB in children outweighs any risk.

Table 7.2: Pediatric dosing of second line anti-tuberculosis drugs

DRUG	DAILY DOSE (mg/kg)	FREQUENCY	MAX DAILY DOSE
Amikacin	15-22.5	Once daily, 5 times a week	1g
Kanamycin	15-30	Once daily	1g
Capreomycin	15-30	Once daily	1g
Ofloxacin	15-20	Twice daily	800mg
Moxifloxacin	7.5-10	Once a day	400mg
Levofloxacin	7.5-10	Once a day	750mg
Ethionamide	15-20	Twice a day	1g
Cycloserine	10-20	Once or twice a day	1g
PAS	150	Twice or thrice daily	12g
PZA*	30-40	Once daily	-
EMB*	15-25	Once daily	-

**First line anti tuberculosis drugs*

All drugs, including the fluoroquinolones, should be dosed at the higher end of the recommended ranges whenever possible. Although ethambutol was previously omitted from treatment regimens for children, due in part to concerns about toxicity (particularly optic neuritis), a literature review indicates that it is safe in children. Ethambutol is bactericidal at higher doses, so daily doses up to 25 mg/kg should be used in children being treated for

5 *The PIH guide to medical management of multi-drug resistant tuberculosis. International Edition*

6 *Guidelines for the programmatic management of drug resistant tuberculosis WHO/HTM/TB/2008.402*

MDR-TB.

In children who are not culture-positive initially, treatment failure is difficult to assess. Weight loss, failure to thrive or failure to gain weight adequately, is of particular concern and often one of the first (or only) signs of treatment failure. Always monitor weight carefully in children to adjust doses as the child gains weight.

7.5 HIV Co-infection

HIV co-infection is a significant challenge for the prevention, diagnosis, and treatment of MDR-TB. In line with the national policy on TB/HIV collaborative services, early diagnosis, prompt treatment with adequate regimens, sound patient support, and strong infection control measures are essential components in the management of MDR-TB in HIV positive persons. Co-trimoxazole preventive therapy (CPT) should be started as soon as possible and antiretroviral therapy (ART) should be initiated promptly to all MDR TB patients irrespective of CD4 count and within eight weeks of starting MDR TB treatment

All MDR-TB patients should undergo provider initiated HIV counselling and testing

Factors affecting MDR TB/HIV co-management

A number of factors make the treatment of MDR-TB in patients who are infected with HIV more complex.

- Drug toxicity may be worsened by underlying conditions or other drugs the patient is taking.
- The sheer volume of medications needed for both conditions can be challenging to the patient.

- In patients who are not immunocompromised, we rely on the immune system to help control the TB. In patients with HIV disease, we must rely on the drugs alone to control and cure the MDR TB disease.
- Malabsorption is quite common in HIV disease and may result in lower blood levels of the anti TB drugs, sometimes no longer reaching therapeutic levels needed to inhibit or kill the TB organism.
- There can be drug-drug interactions, or additive toxicities.
- After the initiation of ART, paradoxical reactions with immune reconstitution, usually referred to as the immune reconstitution inflammatory syndrome (IRIS) may occur in up to 30% of patients, particularly if the initial CD4 count was very low. Manage IRIS according to the available National TB/HIV guidelines
- Many HIV patients will have smear-negative TB or extrapulmonary disease complicating the diagnosis of MDR-TB.

Little is known about drug-drug interactions between second line anti-tuberculosis agents and antiretroviral therapy. Quinolones and didanosine have demonstrated such interactions. Buffered didanosine contains an aluminium/magnesium-based antacid and, if given jointly with fluoroquinolones, may result in decreased fluoroquinolone absorption, it should be avoided, but if it is necessary it should be given six hours before or two hours after fluoroquinolone administration. The enteric coated (EC) formulation of didanosine can be used concomitantly without this precaution.

With regard to additive toxicities, the clinician should be aware of the side effects of the various agents used, and monitor more

closely if two drugs are used with a similar toxicity. If serious or life-threatening adverse events occur, all medications should be suspended, and then serially re-introduced with the least suspected agents started first. Anti-TB therapy should be initiated prior to restarting ART. This should be done in consultation with MDR-TB experts in the MDR TB hospital and HIV specialists.

Table 7.4: Potential overlying and additive toxicity of ART and TB treatment

TOXICITY	ART	Anti-TB Treatment	COMMENTS
Peripheral neuropathy	D4T, ddI, ddC	Cs, H	Avoid using D4T, ddI, ddC in combination with Cs
CNS toxicity	EFV	Cs	Efavirenz has a high rate of CNS side-effects (confusion, trouble concentrating, abnormal dreams, and insomnia) in the first 2-3 weeks, which typically resolve on their own. If the problem persists consider substituting for another drug. Concurrent use is accepted practice with close monitoring for CNS toxicity. Frank psychosis is rare with EFV alone
Depression	EFV	Cs	Consider substituting EFV if severe depression occurs
Hepatotoxity	NVP, EFV, All PIs, All NRTIs	H,R,E,Z	Follow hepatotoxic treatment recommendations in annex 5. Consider CTX as a source of hepatotoxicity
Skin Rash	ABC, NVP, EFV, D4T	H,R,Z, PAS	Do not re-challenge with ABC or an agent that caused Steven-Johnson syndrome
Nephrotoxicity	TDF	Amino-glycosides, Cm	Use TDF cautiously in patients receiving aminoglycosides or Cm. Monitor Creatinine as in annex 6.

During initiation of ART in MDR TB/HIV co-infected patients, an AZT-based regimen is preferred to a D4T-based regimen due to

the risk of lactic acidosis with D4T. In case of AZT-related anemia, d4T may be substituted for AZT.

Given the extremely serious nature of MDR-TB and HIV co-infection, provide DOT for both anti-TB therapy and ART throughout the TB treatment course and not only in the initial phase

7.6 Renal Disease

Many of the drugs used to treat MDR-TB are primarily renally excreted and therefore require dose modification. Generally, it is the interval between doses that is lengthened, rather than decreasing the amount of drug given per dose. For the evaluation and management of a patient with renal failure, refer to annex 7.

The following drugs need to have the dose adjusted in impaired renal function (CrCl of < 30 or on dialysis)

Table 7.5: TB drugs dose adjusted in impaired renal function

Drug	Dose	Frequency
PZA	25-35 mg/kg/dose	3 times/week (not daily)
EMB	15-25 mg/kg/dose	3 times/week (not daily)
Cycloserine	500 mg/dose	3 times/week (not daily)
Ofloxacin	600 – 800 mg dose	3 times/week (not daily)
Amikacin/capreomycin	12-15 mg/kg/dose	2-3 times/week*

** increased risk of both ototoxicity and nephrotoxicity, capreomycin preferred injectable in renal insufficiency*

Ethionamide, Moxifloxacin, PAS, Isoniazid and Rifampicin do not need dose adjustment. Avoid sodium salt formulations of PAS which may result in sodium retention in renal failure.

Estimated creatinine clearance calculations:

Men: ideal body Weight (kg) X (140 – age) / 72 X serum creatinine (mg/dl)

Women: 0 .85 X ideal body Weight (kg) X (140 – age) / 72 X serum creatinine (mg/dl)

7.7 Liver Disease

Patients with a history of liver disease can receive the usual MDR-TB chemotherapy regimens provided there is no clinical evidence of severe chronic liver disease, recent history of acute hepatitis, or excessive alcohol consumption. However, hepatotoxic reactions to antituberculosis drugs may be more common in these patients and should be anticipated. Refer to annex 6 on how evaluate and manage a patient with drug induced hepatotoxicity

Pyrazinamide, Ethionamide, and PAS can all cause liver toxicity but pyrazinamide is associated with the most severe toxicity and should be avoided in patients with chronic liver disease.

If a patient has severe liver disease, consider avoiding all hepatotoxic drugs. The use of ofloxacin, EMB, an aminoglycoside, and cycloserine should be considered, if appropriate. Very rarely fluoroquinolones can be associated with hepatitis, so they should be used with caution

If the patient is resistant to Ethambutol, use of ethionamide or PAS as the fourth drug is justified, and the patient should be closely followed for signs of deterioration in liver function.

A patient with TB may have concurrent acute hepatitis that is

unrelated to TB or antituberculosis treatment, in this case clinical judgment is necessary.

7.8 Extra pulmonary MDR-TB

Most forms of extra-pulmonary MDR-TB can be treated with the same regimens as for pulmonary TB. The exception is tuberculosis meningitis. EMB, PAS, and Amikacin penetrate poorly into the CSF with uninflamed meninges, but better with inflamed meninges. Capreomycin does not penetrate the CNS at all. Pyrazinamide, ethionamide and cycloserine, have good CNS penetration. Fluoroquinolones have variable CSF penetration, with better penetration seen in the later generations i.e. Moxifloxacin and levofloxacin. Ofloxacin has the least CSF penetration of the floroquinolones (FQs) and is not recommended. Therefore, in patients with MDR-TB meningitis, the optimum regimen will be Amikacin, levofloxacin, pyrazinamide, ethionamide and cycloserine. Dosages should be at the higher end of the therapeutic range. Consider the use of high dose INH at 16-20 mg/kg/day because of its excellent CNS penetration and possible efficacy.

Table 7.6: CNS penetration of second line anti-tuberculosis medications

Drug	CNS penetration
Cycloserine	Extremely good penetration.
Isoniazid	Good penetration. Equal to serum.
Pyrazinamide	Good penetration.
Ethionamide	Good penetration.
Kanamycin	Penetrates inflamed meninges only.
Amikacin	Penetrates inflamed meninges only.
Capreomycin	Penetrates inflamed meninges only.

Quinolones	Fair. For ofloxacin, the penetration is 5-10% and with inflamed meninges 50-90%.
Ethambutol	Generally low. In the presence of inflammation (4–64%).
p-Aminosalicylic Acid (PAS)	Poor.

7.9 Diabetes mellitus

Diabetic patients on MDR TB treatment are at risk of poor outcomes if blood glucose levels are not well controlled. In addition, diabetes may potentiate adverse effects, especially renal dysfunction and peripheral neuropathy. Therefore:

- Diabetes must be managed closely throughout treatment.
- Patients should be educated about the required diabetic diet, weight control, exercise, foot care and symptoms of hypo- and hyperglycemia.
- Creatinine and potassium should be monitored weekly for the first month and then at least monthly thereafter. If the creatinine rises, a creatinine clearance should be checked and tuberculosis medications should be adjusted accordingly (see renal insufficiency). Once the dose is adjusted, the creatinine should be checked weekly until it has stabilized;
- Fasting blood sugar monthly.

7.10 Psychiatric disorders during MDR-TB Chemotherapy

Due to disease chronicity, stigma and socioeconomic problems related to the MDR TB, patients have a high baseline incidence of depression and anxiety. Any psychiatric illness identified at the start of or during treatment should be addressed fully.

- Treatment with psychiatric medications, individual counseling, and/or group therapy may be needed to manage the patient suffering from a psychiatric condition or adverse effects. Group

therapy has been very successful in providing a supportive environment for the MDR tuberculosis patient and may be helpful for patients with or without psychiatric conditions

- The patient with a substance dependency poses a difficult challenge. Complete abstinence from alcohol or drugs should be strongly encouraged, and treatment for addiction should be offered. Alcohol or drug use is not an absolute contraindication to treatment. However, if treatment is repeatedly interrupted due to the patient's addiction, MDR-TB therapy should be suspended until treatment for the addiction is successful. Good DOT provides the contact with and support from health care providers that often help in reducing substance dependency.
- Cycloserine has a higher incidence of adverse effects in both the psychiatric patient and the alcohol or drug dependent patient. However, the benefits of using this drug may outweigh the potentially higher risk of adverse effects. Close monitoring is recommended if cycloserine is used in patients with psychiatric disorders.
- All clinicians treating MDR TB patients should have a system in place for monitoring psychiatric emergencies, including psychosis, suicidal indication, and any situation that involves the patient posing a danger to himself or to others.

Key recommendations

- Perform PITC in all DR TB suspects and confirmed DR TB, MDR TB, XDR TB cases
- In HIV infected patients, introduce antiretroviral therapy promptly in DR-TB/HIV patients and provide cotrimoxazole preventive therapy
- In HIV infected patients, monitor for overlying toxicity with ART and MDR-TB therapy
- Drug-resistant TB meningitis is challenging to treat due to the incomplete CSF penetration of many second-line drugs.
- Isoniazid (INH), rifampicin (RIF), ethionamide, and PAS are not cleared by the kidney, and their dosing does not require adjustment for renal failure. Most other anti-tuberculosis drugs require dose adjustment for significant renal insufficiency.
- INH and PZA are the anti-tuberculosis medications most often associated with hepatotoxicity
- Second-line anti-tuberculosis medications are less commonly associated with hepatotoxicity

8. MONITORING PROGRESS OF STANDARDIZED MDR TB TREATMENT

Chapter objective

This chapter provides information on the identification and management of adverse effects caused by second-line antituberculosis drugs. It addresses the following:

- monitoring requirements for the treatment of MDR-TB;
- monitoring actions for early detection of adverse effects;
- adverse effects associated with different second-line drugs;
- strategies for the treatment of adverse effects;
- adverse effects in HIV-coinfected patients.

8.1 Pre treatment Screening and Evaluation

The required initial pre-treatment clinical investigation includes a thorough medical history and physical examination. The initial evaluation serves to establish a baseline and may identify patients who are at increased risk for adverse effects or poor outcomes. The monitoring of treatment and the management of adverse effects may have to be more intensive in patients with pre-existing conditions or conditions identified at the initial evaluation (diabetes mellitus, renal insufficiency, acute or chronic liver disease, thyroid disease, mental illness, drug or alcohol dependence, HIV infection, pregnancy, lactation and others).

8.2 Monitoring Progress of treatment

During monitoring refer to the MDR TB care plan (annex 7). Hospitalized patients are monitored at least daily by physicians and other providers. After discharge MDR TB patients should continue treatment at a local health facility near their homes which should be able to manage simple adverse effect with support from the DTLC.

Both direct and indirect monitoring methods should be utilized. Direct and active monitoring includes collection of specimens for smear and culture, blood testing, radiographic imaging, audiology testing and physical examination whereas indirect monitoring involves observation of the patient's affect, mentation, etc.

8.2.1 Clinical monitoring

The patient should be monitored by taking and recording regular history and physical examination in the monthly follow up form (annex 22). The classic symptoms of TB (productive cough, weight loss and fever) generally improve within the first few months of treatment.

Check weight monthly throughout the course of treatment and follow-up. As a measure of clinical response to therapy, monitor weight more frequently in a patient who has sustained substantial weight loss, or if the drug-resistant TB patient is an infant. Ensure dose adjustments are made as weight increases or decreases even when the patient is in the continuation phase of treatment (refer to table below).

Table 8.1 Adult drug dose adjustments according to changes in patient's weight for the two drugs used in the continuation phase.

Ethambutol (1 pill = 400mg)		Pyrazinamide (1 pill = 500mg)	
Weight (kilograms)	**Dose**	**Weight (kilograms)**	**Dose**
22 → 33	400 mg		
34 → 44	600 mg	34 → 44	1000 mg
45 → 63	800 mg	45 → 54	1250 mg
64 → 81	1000 mg	55 → 64	1500mg
82 → 99	1200 mg	65 → 75	1750mg
100 → 117	1400 mg	≥ 76	2000 mg

Chest radiography (CXR) is recommended for MDR TB patients, as follows:

- At baseline
- Every 6 months
- At the end of therapy
- When a surgical intervention is being considered i.e. for a pneumothorax
- When the patient's clinical situation has worsened

The CXR may be unchanged or show only slight improvement, especially in re-treatment patients with chronic pulmonary lesions.

The daily monitoring of the patient includes also the drug intake monitoring.

8.2.2 Monitoring treatment efficacy and safety through lab tests

The most important objective evidence of improvement is conversion of the sputum smear and culture to negative. While sputum smear is still useful clinically because of its much shorter turnaround time, sputum culture is much more sensitive and is necessary to monitor the progress of treatment.

Persistently positive sputums and cultures for acid fast bacilli should be assessed for Mycobacterium other than TB (MOTT) as overgrowth with MOTT in damaged lung secondary to TB is not uncommon.

Sputum conversion is defined as two consecutive negative smears and cultures taken 30 days apart and is slower in DR-TB than in drug-susceptible TB. Paucibacillary culture results should not be automatically regarded as negative when treating DR-TB. Acquired drug resistance and treatment failure often begin with the growth of one or two colonies on a sputum culture. Culture conversion should not be considered to be equivalent to cure. A certain proportion of patients may initially convert and later revert to positive sputum culture. The timing of smear and culture conversion among smear and/or culture positive patients receiving MDR TB treatment is important. After conversion, the minimum period recommended for bacteriological monitoring is monthly for smears and every 2 months for cultures. Objective laboratory evidence of improvement often lags behind clinical improvement.

Routine toxicity monitoring for patients with MDR-TB frequently includes the following

- Obtain complete blood counts at baseline and intermittently, as clinically indicated
- Obtain creatinine twice monthly for the first month and at least monthly thereafter for patients receiving aminoglycosides or capreomycin. Interpret the creatinine carefully in patients with small body weight, over 50 years of age, and in those with diabetes (creatinine over 1.0 mg/dl is elevated in these patients). Baseline creatinine clearance should be documented in persons with serum creatinine greater than expected, or if any concerns arise.
- Send liver function tests (LFTs) monthly (AST, ALT, Total Bilirubin) in the intensive phase and quarterly in the continuation phase for patients on PZA
- Monitor potassium monthly while patient is on an injectable

agent, if potassium is low, obtain calcium and magnesium as well

- Test thyroid function (TSH) at baseline and every 6 months for patients receiving ethionamide or PAS. Monitor TSH sooner if symptoms of hypothyroidism develop or if baseline thyroid shows abnormalities. Use thyroid replacement if hypothyroidism is documented. Refer to annex 9
- Perform audiology and vestibular function monthly for patients receiving aminoglycosides or capreomycin (dizziness or ear ringing can also result from cycloserine and fluoroquinolones). Refer to annex 10. While most drugs can be continued safely, in general, a patient who suffers vestibular toxicity from an aminoglycoside or capreomycin should not receive those drugs in the future.
- Perform visual acuity and color discrimination screens monthly and watch for evidence of uveitis for patients on EMB, rifabutin, and clofazimine.

Table 8.2. Treatment monitoring of children with MDRTB

Parameter	Frequency
Fever, cough and loss of appetite	monitor daily
sputum for smear, culture	Monthly
Weight	Daily in hospital, monthly in the continuation phase
Height	Monthly
Full blood picture	Baseline and quarterly
Creatinine	Twice monthly for the first month, then monthly in intensive phase and in continuation phase if indicated
Potassium	Monthly, If low, obtain calcium and magnesium.
AST, ALT, total bilirubin	Monthly.
TSH	Baseline then quarterly
Audiology and vestibular function	Monthly in the intensive phase then quarterly
Chest x-ray	At baseline, every 6 months, and at end of therapy

8.3 Management of adverse effects

When on MDR TB treatment many patients may experience some difficulties or drug intolerance; timely detection and adequate management of these adverse reactions is vital for a successful treatment outcome. Most reactions occur during the first few months of treatment, some resolve spontaneously, others need to be treated with drugs according to the symptoms experienced by the patient. In general, treat adverse reaction and encourage the patient to tolerate these effects until they resolve by themselves. Reducing the drug dose and the withdrawal of the drug or its replacement should be taken as a last resource measure. Adverse reactions are one of the main reasons for defaulting, and some patients may need additional support especially at the beginning

of treatment (annex 11).

Document all adverse reactions, treatment interruption, and other significant events related to the patient's treatment, actions or interventions taken in the 'Comments' section of the MDR-TB Treatment Card and in the side effect monitoring form (annex 13). Write down the type of problem the patient experienced such as an adverse reaction and the suspected drug, or absence from supervised treatment, and the action taken such as prescribing symptomatic treatment. Exhaust all options before changing MDR-TB regimen when a patient has adverse reactions. If a patient has a moderate or severe adverse reaction, refer to hospital immediately for proper management (annex 12)

8.4 Hypersensitivity reaction to Second Line anti-TB Drugs

When any of the severe allergic reactions are present, all anti-tuberculosis medications should be suspended. Treat allergic reactions with epinephrine, as well as corticosteroids and antihistamines. Then efforts should be undertaken to determine which drug caused the reaction. Once the patient has improved, anti-tuberculosis therapy can be reinstated as a "challenge"– a partial dose – in a serial fashion (refer to annex 14), with the most likely allergen administered first. However this challenge described should not be used for agents that may have caused an anaphylactic reaction.

Key recommendations

- The monitoring of patients with drug-resistant TB requires a systematic, organized approach. Elements which require monitoring include: drug administration, weight and nutrition, drug interactions, substance abuse and mental health, respiratory and systemic symptoms, symptoms of drug toxicity, blood tests, visual screens, audiology and vestibular testing, bacteriology, therapeutic drug monitoring and radiology
- Monitor both smear and culture monthly to evaluate treatment response
- Ancillary drugs for the management of adverse effects should be available to the patient.

9. TREATMENT OUTCOME DEFINITIONS FOR MDR-TB PATIENTS

Preamble

The following mutually exclusive MDR-TB outcome definitions that rely on the use of laboratory smear and culture are recommended to be used as a monitoring tool.

Cured

MDR TB patient who has completed treatment according to NTLP guidelines and has at least 5 consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. A patient will still be considered cured if only one positive culture is reported during that time and there is no concomitant clinical evidence of deterioration, and this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.

Treatment Completed

MDR-TB patient who has completed treatment according to NTLP guidelines but does not meet the definition for cure or failure due to lack of bacteriological results (fewer than five cultures were performed in the final 12 months of treatment).

Died

MDR-TB patient who dies for any reason during the course of MDR-TB treatment.

Treatment failure

- MDR-TB patient with two or more positive cultures in the last 12

months of treatment, with a minimum of five cultures performed during the last 12 months.

- MDR-TB patient with one positive culture among the final three cultures taken during the final 12 months of treatment
- MDR-TB patient who is persistently culture-positive and a clinical decision has been made to terminate treatment early
- MDR-TB Patients permanently removed from treatment due to drug intolerance

Treatment default

MDR-TB patient whose MDR-TB treatment was interrupted for two or more consecutive months without medical approval.

Transfer out

MDR-TB patient who has been transferred to another region and for whom the treatment outcome is unknown.

10. MDR TB CASE HOLDING

Chapter objectives

This chapter outlines the strategies for treatment delivery that will improve adherence among patients receiving treatment for DR-TB. The main adherence promotion strategies include DOT, socioeconomic support, emotional support and management of adverse effects.

Preamble

The management of DR-TB depends on a steady supply of medicines provided to patients free of charge through a reliable network of educated providers. DR-TB treatment can be successful, with high overall rates of adherence, when adequate support measures are provided.

10.1 Adherence Counseling

To be eligible for the initiation of the MDR-TB management, the patient has to successfully complete adherence counselling and preparation sessions. These sessions will be conducted by district MDR TB teams before referring patients to the MDR TB hospital to ensure readiness for treatment (annex 15).

During the adherence counselling and preparation sessions, particular attention has to be given to re-treatment patients who were previously defaulters, because strict adherence to the new second-line treatment is highly recommended.

Then, counselling must be done at admission to the hospital and regularly every month till discharge. Any counselling session must cover at least the following issues:

- *Nature of disease and infectiousness*
- *Adherence to treatment and DOT*
- *Early and effective management of drugs side effects*
- *Drug collection system*
- *Follow up examinations*

At the time of the discharge specific exit adherence counselling sessions have to be delivered to the patient and the family members to prepare the patient for the continuation phase in the community (annex 16). Continuum of counselling after discharge has to be provided by the DOT nurse or DTLC on monthly basis and at any time the patient requests it. Missed-dose patients and defaulter patients must attend a counselling session once traced. It has to be done by the counsellor or any HCW at the hospital level and district level who have received proper training on counselling according to NTLP and NACP guidelines. Patients coinfected with MDR TB/HIV should receive enhanced adherence support for both MDR TB drugs and ART

Education of Patients

Health education has to be provided by clinicians and nurses at the MDR TB hospital, the DTLC and any other HCW at the TB clinic, and MDR TB treatment supporters at the community level. It has to be given to the patient and respective family using a multimedia approach including pamphlets, posters and TV/video shows. Health education can be delivered individually or in a group and should be offered at admission in the hospital, at discharge and at the community level during the continuation phase of treatment. Health education should focus on prevention of TB transmission, MDR TB adherence to treatment, side effects, cough hygiene and MDR -TB/HIV co-infection.

10.2 Treatment of MDR-TB at the district hospital

When MDR TB patients have completed the intensive phase of treatment and are potentially non infectious, they will be discharged to the district for the continuation phase of treatment and follow up. At the district, MDR TB treatment, care and follow up will be provided at a district health facility nearer an MDR-TB patient's home. The health facility will be responsible for the supervised treatment of an MDR-TB patient six days a week.

When an MDR-TB patient comes in for treatment, ask how the patient is feeling (and try to solve any problems identified) and record the administration of drugs. Remind the patient when the next dose should be taken. This daily interaction with MDR-TB patients is very important to provide constant support and identify potential problems and fix them before they become obstacles to treatment.

Patient who had defaulted in the past, lack of economic resources to use for transportation or to buy food, have work constraints, or are substance abusers should be identified and monitored closely. There are times when an MDR-TB patient will not be able to go to the district health facility for supervised MDR-TB treatment because of an intervening event such as a travel or a funeral. These are counted as absences and should be avoided to the extent possible while the patient is on MDR-TB treatment. **Do not give drugs to MDR-TB patients for self-administered treatment.** Rather, the missed doses due to absences will be made up and treatment time will be extended.

Roles of DTLC and DOT nurse:

- To supervise MDR-TB treatment and document adherence, e.g. daily recording if treatment was received

- To continuously provide information to MDR-TB patients and their families during treatment.
- To ensure that MDR-TB patients continue taking their treatment and trace MDR-TB patients who do not come in to receive their medications
- To promptly recognize, document and manage minor and moderate drug reactions and refer MDR-TB patients to Referral MDR TB Centres for uncontrolled or severe reactions.
- To ensure that MDR-TB patients continue their clinical and laboratory follow-ups monthly and as scheduled
- To manage second-line as well as first-line anti-TB drugs and other medical supplies for MDR-TB

MDR-TB patient's who misses treatment

24 hours of a missed appointment, call or make a home visit to the patient using the contact information written in the MDR-TB Treatment Card. Find out the reason for the missed the dose and offer a solution if this continues to pose a problem for the subsequent doses. In a respectful manner, remind the patient to avoid further missing treatment as this may lead to increased drug resistance, spread of MDR-TB and death.

Give one dose of treatment to the patient once they are located and give the missed doses one day at a time. Do not give an extra dose on any day, instead, extend the treatment period until all of the drugs are taken. For patients who interrupt treatment for more than 2 weeks, but less than 2 months or for more 2 months, refer to chapter 11.

Every attempt by district health facility to address treatment interruptions must be documented, such as telephone calls, text

messages, home visits, talks with patient and family, etc. Document these on the patient's MDR-TB Treatment Card.

Coordinate medical referrals of MDR-TB patients

MDR-TB patients may need to be referred to a specialist or to a hospital for care of an acute or chronic problem. If this happens at the district health facility, the MDRTB Centre needs to be informed of this referral within 24 hours from the time of referral to the hospital.

When a referral is necessary, discuss the referral with the patient. Inform the patient and family of the need to return to the health facility to continue MDR-TB treatment after discharge from the clinician or hospital. Ensure that the patient continues treatment for MDR-TB while receiving special care outside the facility.

Coordinate MDR-TB patients' transfer between district health facilities

MDR-TB patients may need to be transferred to a different health facility to continue treatment. Some reasons for this may be that they are:

- Changing residence
- Having difficulty getting to their present place of treatment
- Having difficulties in transportation and access

In all cases of transfers DTLC must be notified and fill out the necessary transfer forms.

Key recommendations

- To ensure high rates of adherence, a comprehensive package of services, including disease education, DOT, socioeconomic support, emotional support, management of adverse effects and monitoring systems to improve adherence should be offered to MDR TB patients

11. MANAGEMENT OF MDR TB PATIENTS WHO RETURNED AFTER DEFAULT FROM SECOND LINE TB TREATMENT

Chapter objectives

The objectives of this chapter are:

- To describe the clinical approach to manage MDR-TB patients returning after default
- To discuss indications for re-starting treatment

Preamble

As for patients on first-line TB treatment, all efforts have to be made to prevent MDR TB patients from defaulting; through the provision of attractive patient-tailored services and ensuring that the patient and a family member fully understand the disease and its treatment.

Health care workers should ensure that patients fully understand that their MDR-TB treatment should not be interrupted and the consequences of this happening. These may include poorer prognosis, putting family members and contacts at risk, and having to receive more complicated and longer treatments. Only in exceptional cases will patients who default from MDR-TB treatment will not be allowed to re-start treatment.

Table 11.1 Patients returning after default from second-line TB treatment

Patient returning after default	Action to be taken
A patient who returns to MDR TB treatment after having interrupted treatment for two months or more and had more than 4 weeks of MDR TB treatment, and is sputum smear-positive	1. Collect 2 sputum specimens for Culture and request DST on first-line and second-line TB drugs 2. Give counseling to the patient and his family members 3. Discuss the case with a MDR-TB management team, and decide social eligibility to continue second-line TB treatment 4. Re-register the patient 5. Re-start original MDR TB treatment regimen from the initial phase 6. Adjust regimen when DST results are available
A patient who returns to MDR TB treatment after having interrupted treatment for two months or more and had more than 4 weeks of MDR TB treatment, and is sputum smear-negative	1. Collect two sputum specimens for Culture and request DST on all first-line and second-line TB drugs 2. Continue the previous MDR TB treatment regimen from where it was interrupted Culture is positive: – Re-start from the initial phase a second-line TB treatment regimen, based on DST results. – Give a final treatment outcome as defaulter from previous regimen – Re-register the patient with a new registration number for the new treatment episode Culture is negative: – Continue previous MDR-TB regimen from where it was interrupted – Delete earlier “default” outcome and report – Provide final treatment outcome from current regimen

Patient returning after default	Action to be taken
A patient who returns to MDR TB treatment after having interrupted treatment for two months or more and had less than 4 weeks of MDR-TB treatment and is sputum-smear positive	Restart the MDR-TB treatment regimen which the patient interrupted previously
A patient who returns to MDR TB treatment after having interrupted treatment for two months or more and had less than 4 weeks of MDR-TB treatment and is sputum-smear negative	Continue MDR-TB treatment regimen from the point where it was interrupted

Key recommendations

- MDR TB patients returning after default and are sputum smear negative should in general continue the previous regimen and restart from the initial phase only if they had 4 or more weeks of MDR TB treatment and the culture result is positive
- MDR TB patients returning after default who are sputum smear positive should in general restart the MDR TB regiment from the initial phase

12. MANAGEMENT OF MDR-TB PATIENTS AFTER TREATMENT FAILURE

Chapter objectives

The objectives of this chapter are:

- To describe the clinical approach in suspected MDR-TB treatment failure.
- To discuss indications for suspending treatment for patients in whom a MDR TB treatment regimen has failed.
- To outline the supportive care options for patients in whom all the possibilities of MDR-TB treatment have failed.

Preamble

Patients who do not show signs of improvement after four months of treatment are at risk for treatment failure. All patients who show clinical, radiographic or bacteriological evidence of progressive active disease, or reappearance of disease after month 4 of treatment, should be considered as being at high risk for treatment failure.

12.1 Identification of patients at risk for MDR TB treatment failure

The presence of one of the following signs should be considered as possible MDR TB treatment failure:

- recurrence of TB symptoms after sputum conversion
- patient who initially has culture conversion and later reverts to positive sputum culture
- persistent positive smears or cultures past month 8-10 of treatment
- patient who shows clinical or radiographic or bacteriologic evidence of progressive active disease occurring after 4

months of standardized MDR TB treatment

- overall deteriorating clinical condition that includes weight loss and respiratory insufficiency
- progressive extensive and bilateral lung disease on CXR with no option for surgery
- high-grade resistance (often XDR) with no option to add two additional agents

In children who are not culture-positive initially, treatment failure is difficult to assess. Weight loss, failure to thrive or failure to gain weight adequately is of particular concern and often one of the first (or only) signs of treatment failure.

Patients who are confirmed failing MDR TB treatment should be evaluated for XDR TB by performing second line DST

12.2 Actions to be taken for patients suspected of MDR TB treatment failure

In patients who are suspected of MDR TB treatment failure, it is recommended to:

- Assess adherence to treatment by reviewing the patient treatment card and interviewing the MDR TB treatment supporter. If this reveals problems, they should be corrected and the need to select a different treatment supporter should be considered
- Repeat DST and at the same time perform second line DST. However, one single positive culture in the presence of an otherwise good clinical response can be caused by laboratory contamination or error. Positive smears with negative cultures

can be caused by the presence of dead bacilli and therefore do not indicate treatment failure in the absence of other supporting evidence.

- Evaluate for other illnesses that may decrease absorption of medicines (such as chronic diarrhea) and correct if possible, or consider increasing the doses of medication.
- Review of the treatment regimen in relation to history of previous drug treatment, and DST reports. If the regimen is thought to be inadequate, a new regimen should be designed, with at least four effective drugs. Adding one or two drugs to a failing regimen should be avoided. For example, if a patient was being treated with Pyrazinamide (PZA), Amikacin, ofloxacin, ethionamide and cycloserine and was progressing poorly at 4 months, the regimen could be changed to PZA, capreomycin, ofloxacin, PAS, ethionamide, and cycloserine, and a group 5 drug such as clofazimine, with capreomycin, PAS, and clofazimine as the three new drugs.
- If surgical resection is feasible, it should be considered.

Patients who are persistently positive on smear and culture at month 4 but are doing well clinically and radiographically may not need a regimen change.

Changes to treatment can be made as early as 4-6 months if conversion of sputum to negative is not seen and there is clinical deterioration.

It takes 3-4 months to evaluate whether a change in treatment plan has been effective. If a patient continues to deteriorate despite the measures described above, treatment failure should be considered. Treatment can be considered to have failed and suspension of

therapy recommended in cases where medical personnel are confident that all of the drugs have been ingested and there is no possibility of adding other drugs or carrying out surgery.

Therapy should not be interrupted before the patient and family understand and accept the reasons to do so, and agree to the supportive case offered. It is very important that medical visits continue and that the patient is not abandoned.

12.3 Supportive care for patients in whom all the possibilities of MDR -TB treatment have failed

A number of supportive measures can be used once the therapy has been suspended. It is very important that medical visits continue and that the patient is not abandoned. The supportive measures are summarized as follows:

- Pain control and symptom relief. Paracetamol, or codeine with paracetamol, gives relief from moderate pain. Codeine also helps control cough. Other cough suppressants can be added. If possible, stronger analgesics, including morphine, should be used when appropriate to keep the patient comfortable.
- Relief of respiratory insufficiency. Oxygen can be used to alleviate shortness of breath. Morphine also provides significant relief from respiratory insufficiency and should be offered if available.
- Nutritional support. Small and frequent meals are often best for a person at the end of life. It should be accepted that the intake will reduce as the patient's condition deteriorates and during end-of-life care. Nausea and vomiting or any other conditions that interfere with nutritional support should be treated.
- Regular medical visits. When therapy stops, regular visits by the treating physician and support team should not be

discontinued.

- Continuation of ancillary medicines. All necessary ancillary medications should be continued as needed. Depression and anxiety, if present, should be addressed.
- Hospitalization, hospice care or nursing home care. Having a patient die at home can be difficult for the family. Hospice-like care should be offered to families who want to keep the patient at home. Inpatient end-of-life care should be available to those for whom home care is not available.
- Preventive measures. Oral care, prevention of bedsores, bathing and prevention of muscle contractures are indicated in all patients. Regular scheduled movement of the bedridden patient is very important.
- Infection control measures. The patient who is taken off antituberculosis treatment because of failure often remains infectious for long periods of time. Infection control measures should be continued

Key recommendations

- Suspension of therapy should be considered only after all other options for treatment have been explored. Suspending therapy in a patient who has failed MDR-TB treatment is a delicate situation and difficult for family members and caregivers; but it is especially difficult for the patient as treatment is often viewed as his or her only hope. Strong support, care and sympathy must be given to the patient and family.

13. TB INFECTION CONTROL MEASURES

Chapter objectives

This chapter addresses special considerations for reducing transmission of DR-TB through infection control measures. Infection control practices are discussed in more detail in the *"National guidelines for prevention of Tuberculosis in healthcare facilities, MOHSW 2010".*

Preamble

Drug resistant TB is transmitted in the same manner as drug-susceptible TB. Well documented outbreaks of highly drug-resistant strains of TB constitute convincing evidence that MDR TB is transmissible, especially among highly vulnerable populations (i.e. among PLHIV) and in institutional settings. Moreover, MDR TB patients respond to treatment slower and hence remain sputum smear positive for longer periods than other drug susceptible TB patients, therefore they may infect more contacts.

The management of MDR TB does not alter the basic TB infection control (IC) strategies. TB infection control has three components: administrative controls environmental measures and personal respiratory protection. The administrative controls (work practices) are the most effective and least expensive and therefore take the highest priority. Environmental controls and personal protective equipment will not work in the absence of solid administrative control measures.

13.1 Administrative measures

Administrative control measures (work practices) include policies and procedures intended to reduce the amount of TB germs

generated into room air when a TB patient coughs. They are the first and most important control measures therefore the following measures should be in place:

- A written TB infection control plan should be available in all MDR TB hospitals
- MDR TB suspects should be identified early at the HF level by the clinician, educated on cough hygiene and directly referred for smear, culture and DST
- Turnaround times for culture and DST should be minimized to start DR TB treatment early by implementing rapid diagnostic tests for drug resistance
- Confirmed MDR TB/XDR TB patients should be directly referred to and hospitalized at the MDR TB hospital
- MDR-TB patients should be placed in an isolation ward that is not overcrowded; the ward should be disinfected on daily basis. Waste disposal (such as gloves, syringes, mask, needles, sputum cups etc) has to be carried out by proper containers with lids and has to be incinerated in the specific area of the hospital compound or has to be burned in the pit.
- MDR TB wards should be preferably fenced off from the rest of the hospital with restricted entry via a gate with a sign post
- Each MDR-TB patient has to receive sputum cup with lid into which discard any expectorate; the cups' contents have to be disinfected (5% sodium hypochlorite or glutaraldehydes 2%) and then discarded in the incinerator on a daily basis.
- Whenever MDR-TB patients have to leave the ward for any reason (e.g. investigations or recreational period) and when health personnel enter the ward, they have to wear disposable surgical masks.
- DR/MDR/XDR TB patients have to be instructed to turn their heads and cover their mouth and nose with a handkerchief,

tissues or forearm when coughing and sneezing, dispose of waste in the trash, wash their hands with water and soap, and avoid indiscriminate spitting.

- Nurses in charge at the MDR ward, under the supervision of the MDR TB clinician, are responsible for distributing cups and masks and monitoring the correct use of these items.
- Non-infectious MDR TB patients should be referred back to the community during the continuation phase
- DR/MDR/XDR TB patients and their families should be counseled and educated on MDR TB and TB infection control and household contacts should be screened
- Training on MDR TB and TB IC should be conducted for health workers
- Communities should be sensitized on MDR TB and TB IC
- Infectious patients with XDR-TB, whether infected with HIV or not, should be isolated until they are no longer infectious

Visitors' precautions

Preventive measures directed at visitors are important for high risk patient wards, such as MDR-TB wards. Family and household members visiting TB patients should be restricted to enter MDR TB wards. Restricting visitors' access to the MDR-TB isolation wards can be achieved by posting a sign that instructs family members and visitors not to enter the ward. If the need arise, family or household members who enter MDR TB ward should also wear properly fitted N95 masks. MDR TB patients are recommended to meet any visitor in the outside space, to wear a surgical mask and avoid shaking hands.

13.2 Environmental measures

Environmental measures aim to reduce the concentration of

infectious bacilli in the air in areas where contamination of air is likely. Measures include natural and assisted ventilation. Natural ventilation is highly recommended in our settings and are being implemented by the NTLP. Natural ventilation is controlled when windows or doors are deliberately secured open to maintain air flow and enhance cross ventilation. Air mixing increases the effectiveness of natural ventilation and therefore the use of propeller fans is also recommended.

13.3 Respiratory protection

Respiratory protection aims to protect personnel who work in environments with contaminated air. Health workers who enter MDR-TB wards should always wear N95 respirators, which are special masks designed to protect the wearer from tiny (1–5 μm) airborne infectious droplets and hence are effective in filtering out *M. tuberculosis* bacilli. Fit testing should be conducted prior to use of the respirator and thereafter repeated annually. Respirators can be re-used repeatedly for a week if they are not damaged and are properly stored. The main factors responsible for the deterioration of respirators are wetness, dirt and puncture, tears or any breach of the respirator and crushing and stretching out of the elastic band. Respirators should be labeled with the wearer's name and hung on a peg in a clean dry location

It is also recommended that health staff working with MDR TB patients receive counseling and testing for HIV. HCWs living with HIV as well as pregnant or breastfeeding HCWs who are working at the MDR-TB hospital and laboratories performing culture and DST should be given the option of reassignment to an area or activity that has a low risk for exposure to *M. tuberculosis*,. However, this

choice should be the personal decision of the HCW.

HCWs working in MDR-TB hospitals and laboratories performing culture and DST should undergo chest X-ray examination and sputum smear and culture on an annual basis regardless of the results of symptom screening.

Key recommendations

- Infection control, including administrative and engineering controls and personal protection, should be made a high priority in all DR-TB control programmes.
- XDR-TB patients should be placed in isolation until no longer infectious

14. CLOSE CONTACTS OF MDR TB INDEX CASE

Chapter objective

This chapter outlines the management of symptomatic adults and children who have or have had a known contact with an MDR-TB patient.

Preamble

Close contacts are people who share the same household, or spend many hours a day together with an MDR TB patient in the same indoor living space. A list of close contacts should be made for each confirmed MDR TB patient and these contacts should be examined for active tuberculosis

14.1 Adult contact of index MDR TB case

Adult contacts of the index MDR TB patient should undergo physical exam, sputum collection for AFB smear and culture, and chest X-ray.

If the contact is found to have active tuberculosis (i.e., is sputum smear-positive), then two separate sputum specimens should be sent for culture and DST. In the meantime, the patient should be managed with a treatment regimen based on the susceptibility pattern of the index case, or with the standardized MDR TB treatment regimen if a DST is not available. The regimen should be adjusted as soon as DST results become available.

If the initial investigation is not suggestive of active TB but the contact remains symptomatic, physical examinations, chest X-ray, smears and cultures should be repeated monthly until there has been three months of follow up. Antibiotics that are not active

against TB should be used during this evaluation period (e.g. do not use fluoroquinolones, amikacin, or kanamycin).

Close contacts without active tuberculosis should receive health education on tuberculosis, MDR-TB and infection control principles while at home.

14.2 Pediatric contact of index MDR TB case

Close contacts of drug-resistant TB patients who develop TB disease most commonly have drug-resistant disease. All symptomatic children (age ≤ 14 years) who are household contacts to an infectious TB case should be screened for TB disease.

Screening should be conducted and includes;

- A symptom screen,
- Sputum for AFB smear and culture and,
- A CXR even if asymptomatic.

HIV counseling and testing should also be done to all pediatric contact of MDR TB cases. HIV-infected children with no evidence of TB disease should receive appropriate TB preventive therapy and/or close follow-up.

Preventive therapy in children exposed to MDR and XDR-TB is not recommended in Tanzania. The alternative to chemoprophylaxis in MDR-TB contacts (and therefore also XDR-TB contacts) is careful clinical follow-up, every 2-3 monthly for the first 6 months and thereafter 6-monthly for at least 2 years. If active disease develops, prompt initiation of treatment with a regimen designed to treat MDR-TB and using the index case's DST pattern is recommended.

If a child's clinical condition is highly suggestive of TB, or

progressively deteriorates, MDR TB therapy can be started in accordance with the susceptibility pattern of the strain from the index case.

Preventive therapy with second-line anti-TB drugs **is not** recommended in Tanzania.

Key recommendations

- DR-TB contact investigation should be given high priority, and contact investigation of XDR-TB contacts has to be conducted emergently
- Close contacts of DR-TB patients should receive careful clinical follow-up.

15. MDR TB DRUG MANAGEMENT

Chapter objectives

This chapter provides information on the procedures for procurement and management of the second-line drugs used in the treatment of MDR-TB at all levels.

Preamble

The management cycle of drugs comprises six elements: drug selection, quantitative assessment of drug requirements, management of procurement, distribution, assurance of drug quality and ensuring rational drug use. Access to second-line drugs must be accompanied by measures to ensure rational drug use. Misuse of the drugs will result in loss of susceptibility to the second-line agents, producing circulating strains that will be extremely difficult to cure with currently available medicines.

15.1 MDR TB drugs procurement, forecasting, storage and distribution

The Procurement of second line anti-TB drugs will be done by the National TB and Leprosy Program (NTLP) in collaboration with the Medical Stores Department (MSD). Forecasting should be a consumption-based approach, with projections of future needs based on records of past consumption of individual drugs. This method assumes that the data are complete, accurate, and properly adjusted for stock-outs and expected changes in demand and use. Factors to be considered in forecasting include long lead times and short shelf lives of MDR TB drugs. Forecasting should be done quarterly from a central level and a review of drug status is done monthly at the MDR TB Hospitals and health facility level in order to ensure an uninterrupted supply of drugs.

The entire consignment of MDR TB drugs has to be stored at the MDR TB hospital pharmacy. To preserve quality, the drugs should be stored and transported by the supplier and the NTLP following "good storage practices" and the recommendations of the manufacturer regarding temperature and humidity. The MDR TB hospital will make drug requests using the TB Drug Requisition Form quarterly (annex 17). The MDR TB hospital will supply the local health facilities quarterly on the basis of the patient decentralized to that facility.

15.2. Ensuring an uninterrupted drug supplies for patients

15.2.1 Second line drug supplies at MDR TB treatment centres

Determining the quantity of drugs needed every quarter.
Two weeks before the beginning of each quarter (except for the first quarter of the year when the request is made on the first week of December to give allowance for the holidays) make an inventory of the drugs that the MDR-TB patients are receiving. Each patient may have a different regimen so the quantity of each drug must be calculated. Look at each patient's MDR-TB Treatment Card in the section "MDR-TB Regimen" and record the drugs that should be taken, per day row by row in a table.

Ordering for second line drugs
There are two steps in making a drug request at the MDR TB Hospital:

Determining the total consumption for each drug daily, monthly and quarterly.

a. Based on the MDR-TB Treatment Card of the patients in

the MDR TB Hospital, record the drugs to be taken per day per patient.

b. Calculate the DAILY consumption per drug by all patients receiving it.
c. Calculate the MONTHLY consumption by multiplying the daily consumption by 26 days.
d. Calculate the QUARTERLY consumption by multiplying the monthly consumption by 3.

For instance, you want to know the total consumption of prothionamide in a MDR TB hospital. If you have 4 patients taking 3 tablets of 250mg Ethionamide a day, and 1 patient taking 2 tablets of the same drug per day, the next table shows that the total daily need would be 14 tablets; the monthly need would be 364 tablets (daily consumption X 26); and the quarterly need would be 1092 tabs (monthly consumption X 3). Repeat this procedure for all patients and drugs.

How to calculate drug needs

Drug	Patient						Day	Month	Quarter
	1	2	3	4	5	6	Total	X26	X3
Z 500									
E 400mg									
Amk 1gm									
Ofx 400mg									
Eto 250mg	3	3	3	3	2		14	364	1092
Cs 250mg									

2. Once drugs needs are calculated, TB Drug Requisition Form has to be filled out based on the total consumption.

a. To write the name of the MDR TB Hospital and the quarter the request is made for.
b. In the first column of the TB Drug Requisition Form, write the drugs which are requested.
c. To write the projected quarterly consumption, the one month buffer, same as quantity in the “Month” column.
d. To follow the formula indicated.
e. Always double check the calculations.
f. The last two columns of the form has to be completed by the warehouse when the order is filled and sent to the requesting facility.

Once the need for each drug for the quarter is determined, one month’s supply has to be added to that sum as a buffer stock to have on hand in case of emergencies. After determining the total quarterly need plus one month buffer stock, the TB Drug Requisition Form has to be completed by subtracting the stock-on-hand from this number. The stock on hand is how much stock of each drug is presently in the facility.

15.2.2 Quantity of MDR TB drugs required for initial patient decentralization

Every time a patient is decentralized from the MDR TB Hospital, drugs for one quarter will have to be sent to the local facility. This first drug shipment does not require a TB Drug Requisition Form since the MDR TB Hospital will determine the quantities to send.

The quantity of drugs to be sent to the local facility by the MDR TB Hospital during this initial decentralization will depend on the timing

of the decentralization. Since decentralization of patients may not always be on the first day of the first month of a quarter, a table below will serve as a guide as to the quantity to be prepared and delivered. If the decentralization happens on the 1st month or the 2nd month of the quarter, prepare drugs for the remaining days of the quarter. Count the actual remaining doses for the month, and count 26 doses for a full month. If the decentralization happens on the 3rd month of the quarter, send drugs for the remaining days of the quarter plus the entire coming quarter.

Month of decentralization	**Quantity to prepare**
1st month of the quarter	Remaining days of the quarter + 1month buffer
2nd month of the quarter	Remaining days of the quarter +1 month buffer
3rd month of the quarter	Remaining days of the quarter + next quarter +1 month buffer

Example

A local health facility receives patient ZC on January 15 (1st month of the quarter). The MDR TB Hospital will need to prepare the following quantities of drugs for delivery to a local facility:

- Actual remaining days of January (count the actual remaining doses; January 15 - 31 = 15 doses excluding Sundays)
- February and March (2 x 26=52)
- One month buffer (26)

The quantity of drugs to send to the local facility will be for 93 days (15+52+26). The local health facility would request drugs on the 2nd week of March for the quarter April-June.

15.2.3 Second line drug supplies at the local health facility

At a local health facility, the same principles as the MDR TB Hospital should be used for verifying drug supplies, although the quantities will be less and you will not order the drugs but instead verify that the drugs you receive are sufficient. Use the same table shown in the previous section to calculate the drug consumption for your MDR-TB patients. Follow these steps:

1. *List the daily number of tablets, capsules, vials or sachets per drug in the treatment regimen for every patient in the local health facility.*
2. *Calculate the quantity of each drug used per day, and the monthly and quarterly consumption.*
3. *Complete the quarterly need with one month's buffer, and compare with the stock on hand*
4. *If the correct quantities for the quarter have not been received yet, contact MDR TB Hospital to correct the order.*

Always double check the calculations

15.3 Check drugs received

Upon delivery of drugs, check that the correct drugs were received in the correct quantities and with expiration dates allowing full use. If not, request the missing drugs and return any extra or expired drugs that were sent in error. If there are no discrepancies, sign the invoice receipt indicating the correct quantities, batch numbers and expiration dates.

At the local health facility, drugs are checked upon delivery but discrepancies are reported directly to the MDR TB Hospital where the drugs were prepared and packed.

When a drug delivery is received:

1. Sort through the drug delivery:
   a. *Inspect packages for damaged drugs, discolored tablets, distorted boxes or canisters, etc.*
   b. *Check expiry dates.*
   c. *Identify number of tablets received and their preparations by inspecting full containers and partial containers.*
   d. *Compare the quantities of each drug received with quantities delivered according to the Invoice.*
2. Sign the invoice receipt.
3. Note discrepancies (e.g. insufficient quantity of a particular tablet, incorrect strength of tablet, or expired drugs). Sign any changes with your initials. Inform your pharmacist (or the contact at the MDR TB Hospital if you work at the local facility) of these changes.
4. Put the drugs in stock, placing them on the shelves behind the stock that is nearer expiration and update bin card
5. Update the respective drug ledger within the facility

Accept only drugs that can be utilized within the expiry date. Some of the drugs which are received might have expiry dates that are very close. This is due to the fact that the procurement process is a long one. It is normal to receive second line anti-TB drugs with expiry dates that are close; for this reason it is important to make sure that the drugs are monitored regularly and used according to the First Expiry, First Out (FEFO) rule so that the drugs expiring soonest are used first. All expired drugs are documented, stored separately from “good” drugs and returned to the MDR TB Hospital

15.4 Monthly, check drug stock inventory

With experience, you will be aware of the number of MDR-TB cases entering treatment each quarter or month and the quantities of drugs needed to treat them. If you think that your facility's stocks do not contain sufficient quantities for the period, a special order may be needed. Take action or inform the person responsible for drug supplies. A monthly check of drug supplies will also be performed by the monitoring staff of the programme.

For local health facilities, check the monthly consumption of drugs and stocks available against the drugs required until the date of the next expected quarterly supply. If there will be insufficient drugs (quarterly requirement plus 1 month buffer stock) or drugs in excess of 2 months, inform the referring MDR TB Hospital so that the quarterly order can be adjusted.

There are a number of instances when drugs should be sent back to MDR TB Hospital or, if you work at a MDR TB Hospital, to the central pharmacy. Drugs will need to be retrieved when the following situations occur:

- *changes in regimen*
- *patient defaults*
- *patient deaths*
- *patient finishes treatment*
- *expired drugs*
- *damaged drugs*

15.5 Plan for other needed supplies

Make sure that your health facility maintains an adequate supply of disposable needles and syringes, sterile water for injections and sufficient sputum collection containers. It should also have adequate supply of ancillary drugs that are used to counter adverse drugs reactions of patients. Remember that unaddressed adverse

reactions may lead to patient irregular attendance and default; hence, ancillary drugs should not be prescribed for patients to buy but should be readily available for the patient at the MDR TB Hospital. Estimate the quantities needed of each of these supplies, and periodically check the quantities in the storeroom. If supplies will not meet the needs, request more according to usual procedures.

15.6 Estimate ancillary drugs

It is not easy to estimate the quantity of ancillary drugs that should be kept in a MDR TB Hospital or local health facility. There are drugs that are frequently used, e.g., vitamin B6, and some that are used only as side effects are experienced. In addition you may need a supply of co-trimoxazole if it is used for HIV infected patients.

MDR TB Hospital, which handle a considerable number of patients, where the intensive phase of treatment happens and where adverse reactions are most frequently encountered, should have a stock of most if not all the ancillary drugs. Local health facilities, where there are only a few patients at a time, and where the adverse reactions are rather predictable and not occurring frequently since patients are in the continuation phase of treatment, will not keep a stock of ancillary medicines except vitamin B6.

Key recommendations

- The forecasting should be a consumption-based approach
- The entire consignment of MDR TB drugs has to be stored at the MDR TB hospital pharmacy
- Health facilities that will manage patients in the continuation phase will receive an initial 6 months consignment from the MDR TB hospital

16. RECORDING AND REPORTING

Chapter objectives

This chapter describes the information system for MDR TB patients, with the objective of recording information needed to monitor programme performance and treatment outcomes. It presents the instruments and minimum variables necessary to implement and monitor MDR TB treatment.

Preamble

The national data management for MDR-TB shall record and report at the district, regional and national level on the use of second-line anti-TB drugs for MDR TB and XDR TB. Confirmed mono or poly drug resistant TB cases should not be entered in the MDR TB recording and reporting system, but registered in the standard national TB register. Therefore, NTLP is recommending reporting on and evaluating only MDR TB cases.

16.1 MDR TB Recording system

The following MDR TB recording forms/cards/registers are recommended to be used:

- District DR TB suspect register (annex 18)
- MDR TB Patient Identity Card (annex 19)
- MDR TB Treatment Card (annex 20)
- MDR TB register (annex 21)
- Drug Resistant TB Side-Effect Monitoring Form (annex 13)
- Monthly Follow up Form (annex 22)
- Laboratory TB Register for culture and DST (annex 23)
- Drug Resistant TB Referral/Transfer Form (annex 24)

District DR TB suspect register

Each DR TB suspect is registered in the district DR TB suspect register; the register is kept at the DTLC office and the DTLC is responsible for entering the DR TB suspects.

MDR-TB Patient Identity Card

Each MDR TB patient has the MDR-TB Patient Identity Card. This is a card which is held by the patient, and it is kept by the MDR-TB patient for the entire period of the clinical follow up.

MDR TB Treatment Card

Each MDR TB patient should have an MDR TB Treatment Card for monitoring the intake of drugs with the card updated daily by ticking off the supervised administration of drugs. Smear and culture results during treatment and any changes or adjustments to the regimen should be recorded in the MDR TB Treatment Card. On this card, also the treatment outcome of the previous anti-TB treatment has to be recorded (failed, defaulted or relapse). It is also important to record whether the patient ever previously received second-line drugs.

The card represents the primary source of information to complete and periodically update the MDR TB Register. The card, or a copy of the card, must always follow the patient (e.g. from a MDR TB hospital to a district health facility where the patient will continue with the continuation phase of treatment). A copy of the card may be used as a notification form and later also to report the final outcome of treatment.

MDR-TB register

Patient starting second line TB drugs are recorded in the MDR-

TB register; the register is kept at the MDR TB hospital and in districts managing MDR TB patients in the continuation phase of treatment. Medical officers in MDR TB hospitals and district TB and leprosy coordinators are responsible for entering the confirmed MDR TB cases in the register. When a patient is starting MDR TB treatment he/she should be entered in the MDR TB register, the date of registration should be the day when the health staff enters the patient in the MDR TB Register. The register should be updated regularly from the MDR TB Treatment Card and from the laboratory registers. Patients should be recorded consecutively by their date of registration. There should be a clear separation (extra line) when a new quarter is started.

Those mono and poly-resistance TB patients with relatively simple resistance patterns i.e. H, HS and HE; whose regimens do not require second-line drug should be maintained in the regular district TB register where adjustment of their regimen should be recorded.

Mono or poly-resistant TB cases involving complicated resistance patterns of rifampicin or HES; that require treatment with second line drugs should be entered into the MDR TB Register at the MDR-TB hospital. Some patients started on MDR TB regimens may be found to have drug-susceptible disease. Patient in this situation are removed from MDR TB treatment and placed on appropriate first-line therapy. Then the patient is crossed out of the MDR TB register (but the name left legible) and a comment noted in the last column that s/he has drug-susceptible disease. All patients who are switched should be registered in the District Tuberculosis Register (if they are already registered in the district register the final outcome should be documented in the original line of registration (do not create a new registration).

These patients do not need to appear on the Quarterly Report on MDR TB Detection and MDR TB Treatment Start, Six month interim outcome assessment of confirmed MDR-TB cases and Annual report of treatment result of confirmed MDR-TB patients starting MDR TB forms as they do not have MDR-TB.

The MDR TB registration number is filled as follows:

0457 / KK01 / 2010 / 01

0457	*refers to the referring district number*
KKS01	*refers to the MDR TB treatment centre*
2010	*refers to the year of registration*
01	*refers to the patient serial number*

KKS stands for Kifua Kikuu Sugu (Swahili for MDR TB) and 01 is the coding number assigned to the MDR TB treatment centre (in this case it refers to Kibong'oto hospital); the next MDR TB centre is going to be coded as KKS02.

Drug Resistant TB Side-Effect Monitoring Form

This form is used to notify adverse effects, it is filled by the District MDR TB Team and it is sent to Tanzania Food and Drug Authority.

Toxicity Monitoring Sheet

This form is filled by a nurse/physician and is kept in the MDR TB patient file at the MDR-TB hospital; after discharge it is kept at district level, and filled by the DTLC.

Laboratory TB Register for culture and DST

This register is used by the Laboratory personnel performing culture and DST.

Drug Resistant TB Referral/Transfer Form

This form is filled by a physician when the MDR TB patient is transferred to other hospital or referred for other services and is kept in the MDR-TB hospital or DTLC's office.

MDR TB daily DOT form

This form is to be filled by the DOT nurse and kept at the MDR TB patient file. Individual drug intake and doses should be recorded daily and the DOT nurse should put initials for every dose observed. Side effects for each of the specific second line drugs should also be recorded on this form.

Drug Resistant TB Treatment Follow-Up Form

This form shall be filled by a physician and is kept at the MDR TB patient file in the MDR-TB hospital or DTLC's office.

16.2 MDR TB Reporting system

The following MDR TB reporting forms are recommended to be used:

- Six Month Interim Outcome Assessment of confirmed MDR-TB cases (annex 25)
- Quarterly Report on MDR TB Detection and MDR TB Treatment Start (annex 26)
- Annual report of treatment result of confirmed MDR TB patients (annex 27)

Six Month Interim Outcome Assessment of Confirmed MDR-TB Cases

This form is filled by a physician working at MDR TB hospital and is kept at the MDR-TB hospital and should be used to report bacteriological status (negative, positive or no information) of those still on treatment at 6 months, and for those who have already defaulted, died or transferred out, this can be recorded as the final outcome. Bacteriological results are based on the smear and culture data during months 5 and 6 of treatment. Consider the 6-month outcome assessment unknown for a particular patient if a culture or smear result is unknown for either month 5 or 6.

All cases from the MDR TB Register should be included in this report. The form should be completed 9 months after the closing day of the cohort. This allows culture information at month 6 of treatment to be included for all patients in the cohort. For instance, TB patients who started treatment during the first quarter of a year (1 January to 31 March), should have the form filled in from 1 January of the following year.

Patients who do not meet the traditional definition of failure but are switched to MDR TB treatment regimens because of resistance (DST during category I, II or III) should be included in the outcome analysis of category I, II, III – the regimen they were in initially before switching.

Quarterly Report on MDR-TB Detection and MDR TB Treatment Start

This report is used to assess the number of MDR-TB cases detected (distribution and trends) and the number of MDR-TB cases who start treatment.

The report should be made quarterly by the MDR-TB hospital focal person and sent to the NTLP. Copy of the report will be kept in a reports folder at the MDR TB hospital.

The quarterly report includes:

- The number of patients, with date of result showing MDR-TB during the relevant quarter taken from the Laboratory Register.
- The number of MDR-TB patients started on MDR TB treatment during the quarter, taken from the MDR TB Register

If relevant, the number of XDR-TB cases registered (after cross-checking DST results with type of resistance) and the number of XDR-TB cases started on XDR-TB treatment should be added.

Patients who start treatment during the quarter may not be the same as those detected with DR-TB. This information will assist the NTLP to calculate the average delay between detection of DR-TB and treatment start.

Cohort analysis – Annual report of treatment result of confirmed MDR-TB patients starting MDR TB treatment

An MDR TB treatment cohort is defined as a group of patients who start MDR TB treatment during a defined time period. The MDR TB treatment cohort will consist of a subset of patients recorded in the MDR TB Register, i.e. those who actually started MDR TB treatment during the same quarter.

To account for the long duration of MDR-TB treatment regimens, cohort analysis should be carried out at 24 months and repeated at 36 months after the last patient starts treatment. The analysis is done at 24 months because most of the patients will have finished treatment, allowing preliminary assessment of cure rates. Since a few patients may be on treatment longer than 24 months, the

cohort analysis is repeated at 36 months after the last patient starts treatment. The 36-month evaluation is considered the final treatment cohort analysis result.

All patients should be assigned the first outcome they experience for recording and reporting purposes. Programmes may wish to record subsequent outcomes among patients followed systematically. (For example, a patient defaults on the first MDR TB treatment and then returns 14 months later to be re-registered and is cured with a second MDR TB treatment. This patient should receive a final outcome of “defaulted” in the cohort in which he or she was first registered and “cured” in the second cohort.) Patients who remain on treatment at the end of a designated cohort treatment period must be identified as “still on treatment”. This is a provisional outcome until a final outcome is available.

For each cohort, an interim status should be assessed at 6 months after the start of treatment to monitor programme progress.

Some patients may be registered twice during one cohort period (failure or default patients who are re-registered); therefore, the cohort analysis should identify the total number of treatment episodes. Stratifying cohort analysis by category of patient (new, re-treatment) will prevent the repeated inclusion of a patient in a single analysis.
All diagnosed MDR-TB patients should be started on MDR-TB chemotherapy. If any MDR-TB patients are left untreated, the reasons for not receiving an MDR-TB treatment regimen should be explicitly delineated.[7]

7 Some examples of reasons for exclusion from treatment include the following: a) Died before treatment initiated; b) Patient unwilling to be treated

The performance of the MDR-TB management is eventually measured in a cohort analysis using three different registration categories.

Table 17.2: reporting form of MDR TB cohort analysis

MDR-TB case categories	Total in cohort	Cured	Treatment Completed	Failed	Died	Default	Transfer Out
Patients who are sputum smear-positive at month 2 **and** remain smear positive at month 3 of first line regimens							
Failure of first-line regimen (patients who are sputum smear positive at 5 months **or** later during the course of standard new patient treatment regimen)							
Re-treatment regimen who failed							
Re-treatment regimen who relapsed							
Re-treatment regimen who returned after default							
Close contacts of a known MDR-TB case with active TB disease							

**or treated for less than one month (4 weeks)*

Key recommendations

- The standardized national system for MDR TB recording and reporting should be implemented

17. ROLES AND RESPONSIBILITIES FOR MDR TB MANAGEMENT

The chapter describes roles and responsibilities of NTLP, the TB reference laboratory, zonal and district levels and all key stakeholders involved in implementing the MDR TB Programme**.** The roles of MDR TB treatment panels are also outlined.

National Level I (The National TB and Leprosy Central Unit):

- Overall coordination of all stakeholders and partners involved in MDR TB activities, including the private sector in line with the Public – Private Partnership (PPP) strategy and prison authorities.
- Train regional and district healthcare workers including TB and TB/HIV coordinators on issues related to MDR TB management and TB infection control.
- Ensure an uninterrupted supply of second line drugs
- Conduct supportive supervision on MDR TB activities in the country in collaboration with all relevant stakeholders.
- Conduct monitoring and evaluation of MDR TB: aggregate national MDR TB data, perform cohort analyses, conduct MDR TB program evaluation and share data and provide feedback to regional and district level coordinators.
- Mobilise resources to support and sustain the scale up of programmatic management of MDR TB

National Level II (The Central TB Reference Laboratory – CTRL)

- Perform Culture/DST for first line drugs and second line drugs
- Collaborate with supranational laboratories to perform second

line DST so as to ensure external quality assurance

- Depending on availability, validate and perform newer molecular technologies for the diagnosis of MDR TB (i.e. Hain tests, GenExpert)
- Build capacity of zonal TB labs to perform cultures and DST and newer diagnostic technologies for MDR TB

District Level (MDR TB team - DTLC and DOT nurse):

MDR TB treatment will be provided in the continuation phase at a health facility as close as possible to the patient. At the district level, the MDR TB team will be responsible for;

- Supervising MDR-TB treatment and document adherence, e.g. daily recording if treatment was received
- Continuously provide information to MDR-TB patients and their families during treatment.
- Ensure that MDR-TB patients continue taking their treatment and trace MDR-TB patients who do not come in to receive their medications
- Promptly recognize, document and manage minor and moderate drug reactions and refer MDR-TB patients to zonal MDR TB Centres for uncontrolled or severe reactions.
- Ensure that MDR-TB patients continue their clinical and laboratory follow-ups monthly and as scheduled
- Manage second-line as well as first-line anti-TB drugs and other medical supplies for MDR-TB

Regional Tuberculosis and Leprosy Coordinator (RTLC):

- Responsible for the management (Planning, supervision, implementation, monitoring and evaluation) of MDR TB activities at regional level
- To regularly visit (at least once every 3 months) all the districts in the region in order to supervise and support the DTLCs and health workers involved in MDR TB management in the region

- To assist and advise the CHMT, DTLC and other health staff in the diagnosis and management of MDR TB
- To ensure a three months supply of second line anti-tuberculosis drugs in the region in collaboration with the pharmacist and provide feedback to TLCU
- To facilitate and coordinate health education and training activities through training sessions of the NTLP, in seminars, learning institutions and on-the-job within the region
- To compile disseminate and use regional data of tuberculosis and leprosy for making an informed decision
- To ensure that all sputum specimens for culture and DST of MDR TB suspect patients and MDR TB patients on follow up of continuation phase of treatment
- To advice the CHMT/RHMT on MDR TB activities to be included in the district/region health plan

Zonal Level (MDR TB hospitals):

- Centre of excellence for MDR TB management in the zone
- Provide hospital based DOTS for confirmed MDR TB cases for the intensive phase of treatment
- Ensure clinical training (ward rounds) for district MDR TB teams
- Storage of MDR TB drugs and dispensing to districts with a discharged MDR TB patient on a quarterly basis
- Refer MDR TB patient back to the district for completion of MDR TB treatment
- Record and report to the National TB and leprosy Program Data collection unit at the MoHSW

Prison Facilities

- Transmission in prisons may be an important source of spread of MDR-TB
- Implementation of strong TB infection control measures so as to reduce MDR TB incidence among inmates

- Refer inmates with documented MDR TB to MDR TB treatment centres
- Ensure MDR TB inmates continue with treatment in prison health facilities after completion of the intensive phase of treatment in MDR TB centres

Policy, Regulatory and operational documents

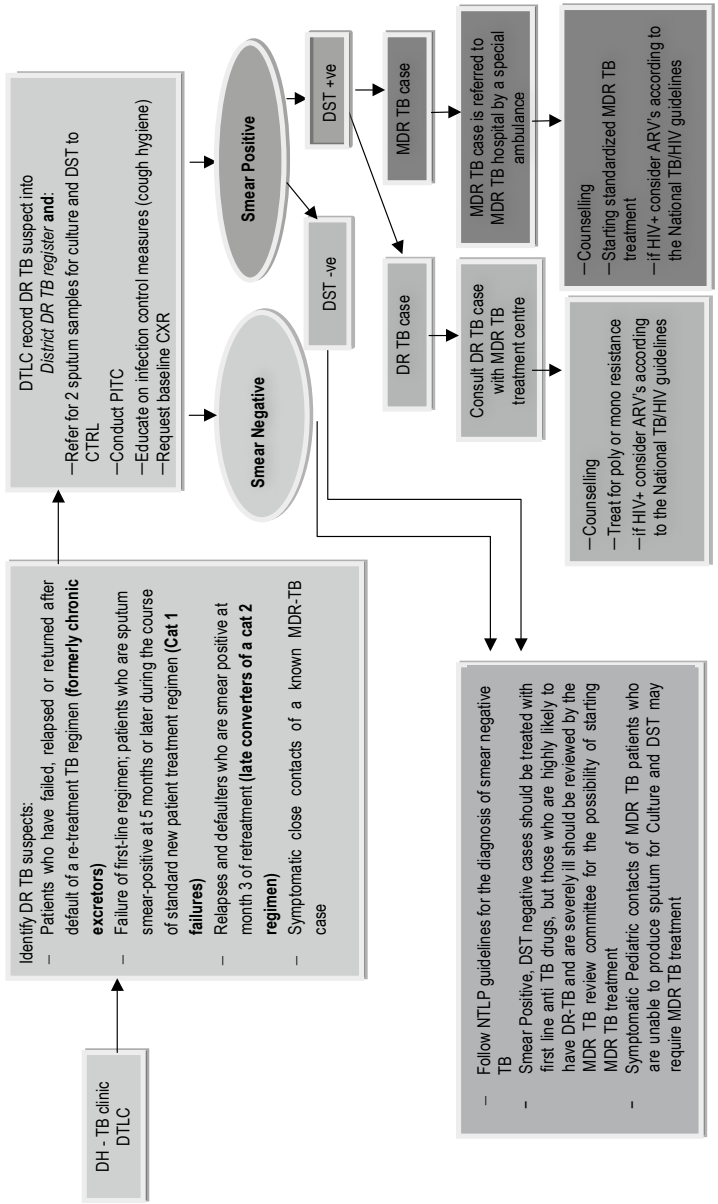
NTLP shall lead the development of DR-TB policies as a foundation for any subsequent legal, administrative and technical support necessary for the initiation, implementation and monitoring of the programme.

MDR-TB Review panels.

- The MDR-TB Review Panel is a case management committee composed of health care workers both locally and international with expertise on MDR-TB management.
- The panel will be composed of MDR TB lead clinician, MDR TB head nurse, MDR TB Lab expert, MDR TB Psychosocial expert, MDR TB International Consultant and MDR TB programmatic lead person from the NTLP
- This committee will meet regularly (monthly) to confirm the diagnosis, determine treatment regimens, assess response to treatment, and determine final outcome through a consensus using standards based on the NTLP Guidelines for Programmatic Management of Drug-resistant TB.
- Review the presentation of MDR-TB cases for enrolment; Approve the proposed enrollment regimen, regimen change, decentralization, treatment outcome or any action point relevant to the case presented;
- Arrive at a consensus on decisions when management of an MDR-TB patient is ambiguous and/or complicated.

ANNEXES

Annex 1: Management of DR TB suspect



Annex 2: Second line Drug Information Guide

Amikacin (Amk)

- Aminoglycoside:
- Interferes with protein synthesis through disruption of ribosome
- Bactericidal with strong antibacterial activity.
- Dose: 1 g IM/IV (15-20 mg/kg)
- Side effects
  - Nephrotoxicity
  - Ototoxicity
  - Electrolyte imbalance (hypokalemia and hypomagnesemia)
- Adjust dose for renal failure
- Avoid use in pregnancy due to congenital deafness
- Complete cross-resistance with kanamycin,

Kanamycin (Km)

- Structurally very similar to Amikacin
- Bactericidal
- Dose: 1 g IM/IV (15-20 mg/kg)
- Side effects (same as Amikacin)
  - Nephrotoxicity
  - Ototoxicity
  - Electrolyte imbalance (hypokalemia and hypomagnesemia)
- Adjust dose for renal failure
- Avoid use in pregnancy due to congenital deafness

Capreomycin (Cm)

- Cyclic polypeptide:
- Bactericidal with strong anti-TB activity; inhibits protein synthesis.
  - Similar to aminoglycoside
- Dose: 1 g IM/IV (15-20 mg/kg)
- Side effects:
  - Nephrotoxicity
  - Ototoxicity
  - Electrolyte abnormalities
- Some cross-resistance with kanamycin/amikacin
- Adjust dose for renal failure

Ofloxacin (Ofx)

- Fluoroquinolone:
  - Inhibits DNA-gyrase
- Bactericidal
- Dose: 800 mg once orally (PO)
- Side effects
  - Generally well tolerated
  - GI upset, rash, CNS disturbance
- Cross-resistance among FQs near-complete
- Adjust dose for renal failure

Moxifloxacin (Mfx)

- Fluoroquinolone:
  - Inhibits DNA-gyrase
- Bactericidal
- Dose: 400 mg once daily PO
- Side effects:
  - Generally well tolerated
  - GI upset, rash, CNS disturbance
  - Rare tendon rupture
- Moxifloxacin may be more active than earlier generation quinolones
- May still be effective against some strains resistant to CPX/OFX
- Adjust dose for renal failure

Ethionamide (Eto)

- Derivative of isonicotinic acid
- Bacteriostatic, blocks mycolic acid synthesis.
- Dose: 500-1000 mg daily in divided doses PO
- Side effects
  - GI upset and anorexia (maybe intolerable), best take at bedtime
  - Hypothyroidism
  - Neuropathy
- Hepatically metabolized
- Co-administer Vitamin B6
- Monitor TSH levels during treatment

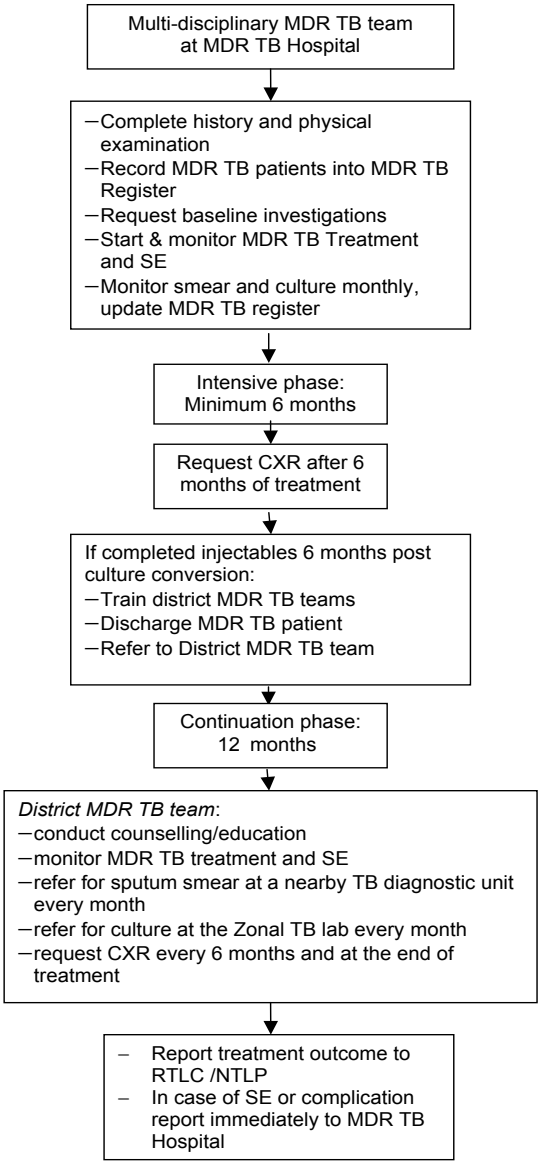
Cycloserine (Cs)
- Alanine analogue
– Interferes with cell-wall proteoglycan synthesis
- Bacteriostatic
- Dose: 500-1000 mg daily in divided doses
- Side effects
– Seizures, psychosis, depression
– Irritability, headache
- Renally excreted
- Best taken on an empty stomach
- Effective CNS penetration
- Co-administer with Vitamin B6

PASER
- Para-aminosalicyclic acid
- Bacteriostatic
- Delayed-release microcapsules
- Dose: 4 g (1 sachet) twice daily PO
- Side effects
– GI upset, hypothyroidism
– Hepatitis, electrolyte abnormalities
- Hepatic acetylation, renally excreted
- Administer with acidic food or drink
- Store packets in the refrigerator or freezer.
- Monitor TSH levels

Prothionamide (Pto)
- Structurally similar to ethionamide (a pro-drug)
- Complete cross-resistance with ethionamide
- Dose: 500-1000 mg daily in divided doses PO
- Side effect profile similar to ethionamide
- GI side effects may be less than with ethionamide

PAS sodium
- Many formulations,
- Dose: varies by formulation
- Side effects
– GI upset, hypothyroidism
– Hepatitis, electrolyte abnormalities
- Hepatic acetylation, renally excreted
- Contraindications (because of sodium load):
– Chronic renal failure
– Congestive heart failure

Annex 3: Management of MDR TB case



Annex 4: MDR TB Daily DOT Record

Ministry of Health and Social Welfare
National Tuberculosis and Leprosy Programme

MDR TB Daily DOT Record

Treatment Facility: _____ **Month / Year:** _____/_____

Patient Name: _____ **Patient Weight / Date:** _____/_____

MDR TB TREATMENT REGIMEN:

Drug	Dosage	Frequency	Date Started	Date Stopped
Ofloxacin/ Levofloxacin		Every Day		
Amikacin (Am)/ Capreomycin (Cm)		5 days/wk		
Cycloserine (Cs)		Every Day		
Ethionamide (Eto)		Twice Daily		
Pyrazinamide (Z)		Every Day		
Pyridoxine (Vit B6)		Every Day		
Ethambutol (E)		Every Day		
PAS		Twice Daily		

*Side Effect Codes	
1	Abdominal pain
2	Constipation
3	Decreased hearing
4	Depression
5	Diarrhea
6	Dizziness
7	Fatigue
8	Fever
9	Headache
10	Joint pain
11	Nausea
12	Psychosis
13	Insomnia

Oflaxacin (Ofx) 400mg tabs; Cycloserine 250 mg tabs; PZA 500 mg tabs; Ethionamide 250 mg tabs; Levofloxacin (Lfx) 250mg tabs; Ethambutol 100mg and 400mg tabs.

DAILY DOT RECORD: Record number of pills or cc's given and write your initials under DOT Initials. Mark "R" if patient refused medication. Mark "H" if medication was held.

Day	Ofx/ Lfx	Am/ Cm	CS	Eto		Z	Vit B6				DOT Initials		SE*
				am	pm						am	pm	
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
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Annex 5: Gastric Aspiration

Gastric aspiration is used to collect gastric contents to try to confirm the diagnosis of TB by microscopy and mycobacterial culture in young children when sputum cannot be spontaneously expectorated nor induced using hypertonic saline.

During sleep, the lung's mucociliary system sweeps mucus up into the throat where it is swallowed and remains in the stomach until the stomach empties. Therefore, the highest-yield specimens are obtained first thing in the morning. Gastric aspiration on each of 2 consecutive mornings should be performed for each patient.

Performing the test properly usually requires two people (one doing the test and an assistant). **Children with a low platelet count or bleeding tendency should not undergo the procedure.**

A. Required equipment:

5. Gloves
6. Naso-gastric tube (usually 10 French or larger)
7. 5, 10, 20 or 30 cm^3 syringe, with appropriate connector for the nasogastric tube
8. Litmus paper
9. Specimen container
10. Pen (to label specimens)
11. Laboratory requisition forms
12. Sterile water or normal saline (0.9% NaCl)
13. Sodium bicarbonate solution (8%)
14. Alcohol/chlorhexidine

B. Procedure:

The procedure can be carried out as an inpatient first thing in the morning when the child wakes up, at the child's bedside or in a procedure room on the ward (if one is available), or as an outpatient (provided that the facility is properly equipped). The child should have fasted for at least 4 hours (infants for 3 hours) before the procedure.

1. Prepare all equipment before starting the procedure.
2. Position the child on his or her back or side. The assistant should help to hold the child.
3. Measure the distance between the nose and stomach, to estimate distance that will be required to insert the tube into the stomach.
4. Attach a syringe to the nasogastric tube.

5. Gently insert the nasogastric tube through the nose and advance it into the stomach.
6. Withdraw (aspirate) gastric contents (2–5 ml) using the syringe attached to the nasogastric tube.
7. To check that the position of the tube is correct, test the gastric contents with litmus paper: blue litmus turns red (in response to the acidic stomach contents). (This can also be checked by pushing some air (e.g. 3–5 ml) from the syringe into the stomach and listening with a stethoscope over the stomach.)
8. If no fluid is aspirated, insert 5–10 ml sterile water or normal saline and attempt to aspirate again.
    a) If still unsuccessful, attempt this again (even if the nasogastric tube is in an incorrect position and water or normal saline is inserted into the airways, the risk of adverse events is still very small).
    b) Do not repeat more than three times.
9. Withdraw the gastric contents (ideally at least 5–10 ml).
10. Transfer gastric fluid from the syringe into a sterile container (sputum collection cup).
11. Add an equal volume of sodium bicarbonate solution to the specimen (in order to neutralize the acidic gastric contents and so prevent destruction of tubercle bacilli).

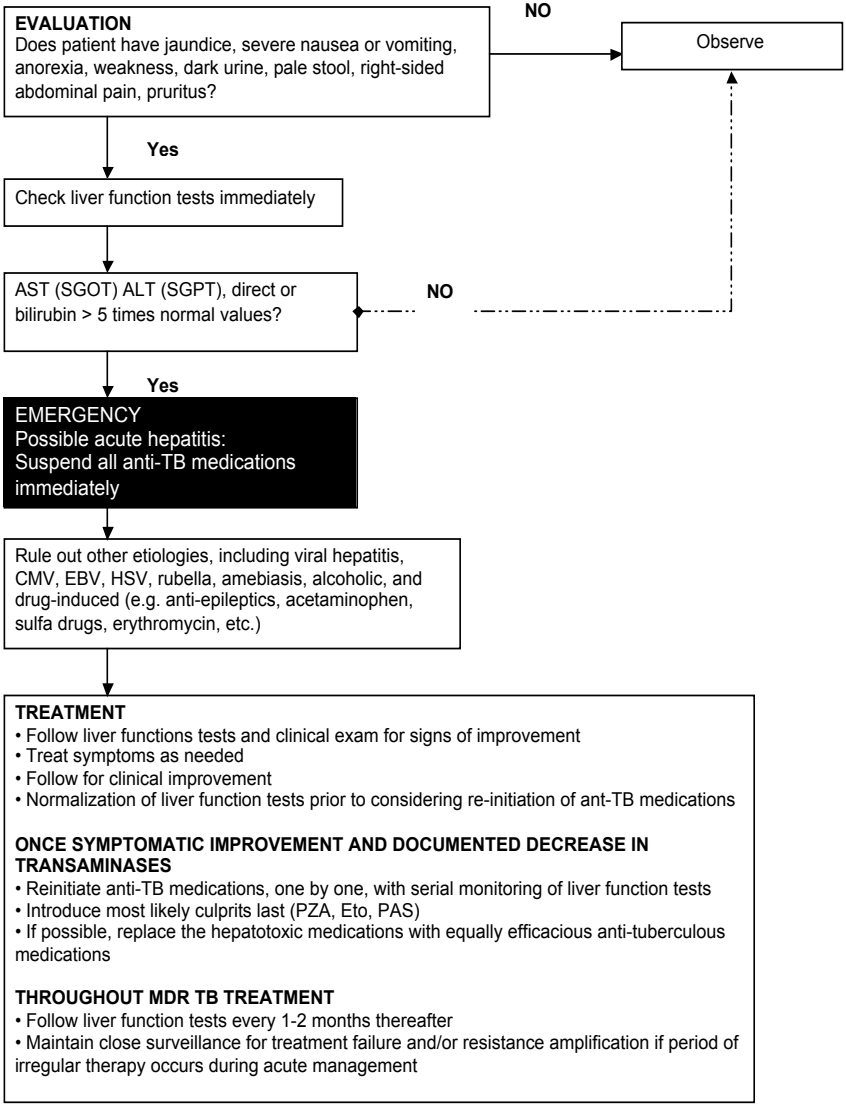
C. After the procedure:

1. Wipe the specimen container with alcohol/chlorhexidine to prevent cross-infection and label the container.
2. Fill out the laboratory requisition forms.
3. Transport the specimen (in a cool box) to the laboratory for processing as soon as possible (within 4 hours).
4. If it is likely to take more than 4 hours for the specimens to be transported, place them in the refrigerator (4–8 °C) and store until transported.
5. Give the child his or her usual food.

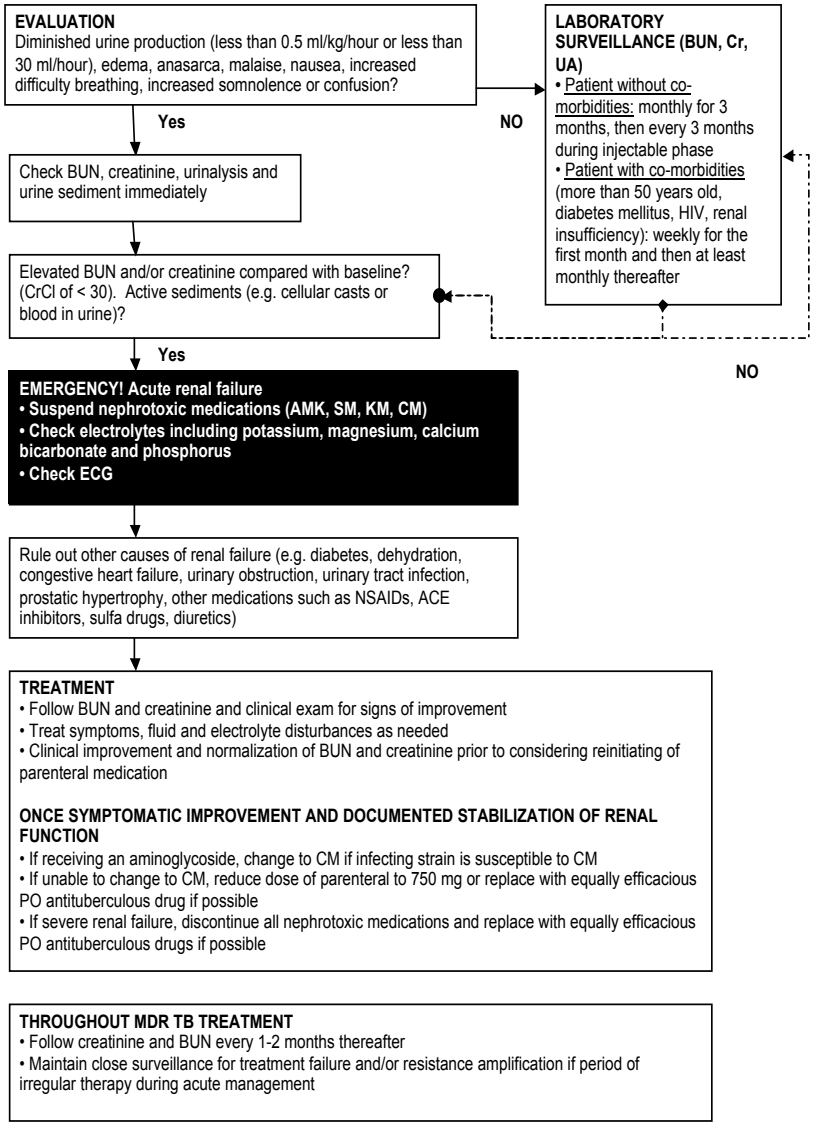
D. Safety:

Gastric aspiration is generally not an aerosol-generating procedure. As young children are also at low risk of transmitting infection, gastric aspiration can be considered a low risk procedure for TB transmission and can safely be performed at the child's bedside or in a routine procedure room.

Annex 6: Management of a patient with hepatic failure anagement of a patient with hepatic failure



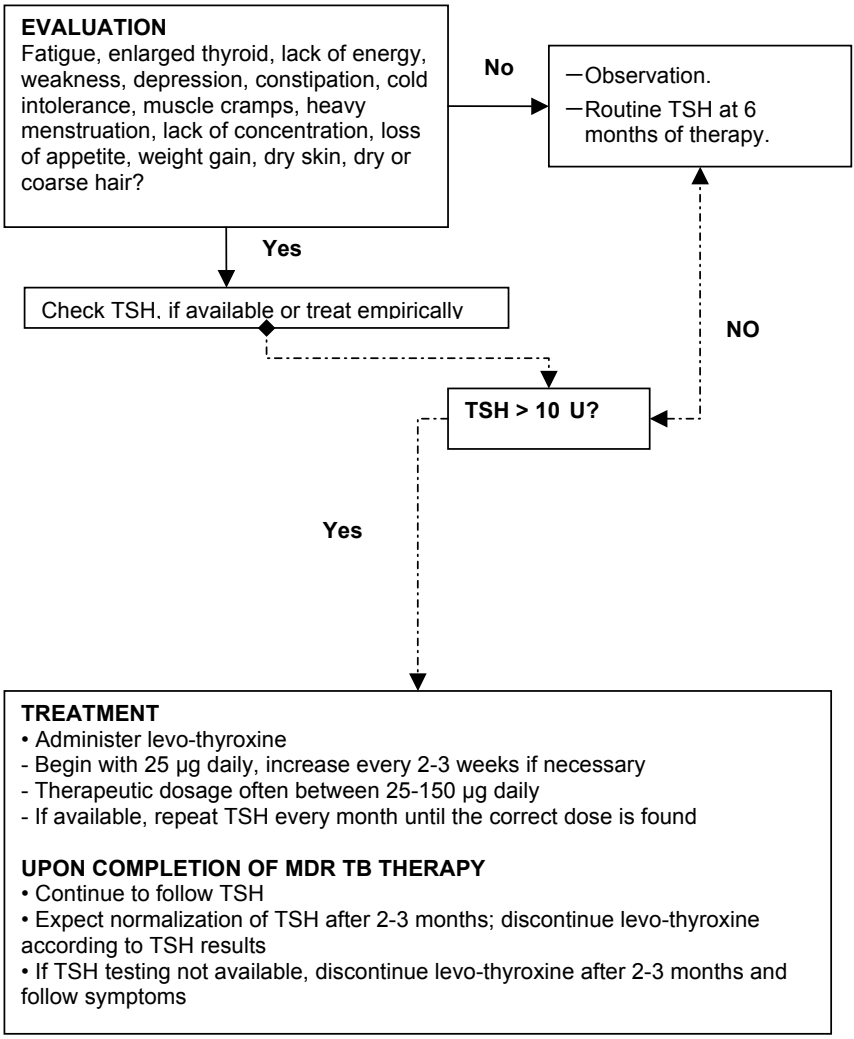
Annex 7: Management of nephrotoxicity



Annex 8: MDR TB care plan

SN	Description	Baseline	Treatment initiation	Month 1	Month 2	Month 3	Month 4	Month 6	Month 9	Month 12	Month 18	Month 24
1	Chest radiograph evaluation	CXR: PA/Lat; compare to old films						CXR		CXR	CXR	CXR
2	Clinical evaluation	Request & review old records	Clinician assesses weekly	Clinician assesses every 1-2 weeks	Clinician assesses every 1-2 weeks	Clinician Assesses monthly.	→	→	→	→	→	→
3	MDR TB daily DOT recording	Create MDR TB daily dot record	Update MDR TB daily dot record	Update MDR TB daily DOT record	→	→	→	→	→	→	→	→
4	Toxicity monitoring: Hematology	Review prior labs: FBP, CBC,	At baseline and	thereafter	intermittently	or as	clinically	indicated				→
5	Toxicity monitoring: renal toxicity	Review prior labs: RFT'S, Cr,	Cr twice monthly	Cr monthly	Cr monthly	Cr monthly	continue Cr	monthly until injectable →	stops			
6	Toxicity monitoring: Electrolytes & Glucose	review prior labs: K+, Ca+, Mg++, glucose	K+ monthly when on an injectable agents	Glucose done quarterly	K+	K+, Ca+, Mg++, glucose 3 monthly	K+	K+, Ca+, Mg++, glucose 3 monthly	→	→	→	→
7	Toxicity monitoring: hypothyroidism	review prior labs: obtain TSH						TSH 6 mo- levothyroxine if elevated TSH	→	→	→	→
8	Toxicity monitoring: Hepato-toxicity	review prior labs: LFT, alt, alt, total bilirubin	Request: LFT, alt, alt, total bilirubin			Quarterly for patients receiving PZA	→	→	→	→	→	→
9	Provider Initiated Testing & Counseling	HIV screen with pre/post counseling	If positive, CD4	If positive evaluate for ART		repeat HIV test	if clinically	indicated				
10	bacteriology	Review prior sputum results. Repeat sputum	Sputum x 2 for AFB smear and culture	Sputum x 2 for AFB smear and culture; monthly for first 6 months	→	→	→	Sputum smear and culture X 1 every 2 months until end of Rx	→	→	→	→
11	resistance pattern	Review DST; request extended DST				Repeat DST if culture positive	→	→	→	→	→	→
12	infection control measures	AFB Isolation	Continue until culture conversion	→	→	→	→	→	→	→	→	→
13	injectables	review renal function, hypersensitivity reactions	Amikacin and/or Capreomycin IV/IM 5 days /wk			Change to 3x/wk after 3 months if culture neg.	→	→	Stop after culture negative x 6 mo.	→	→	→
14	oral medications	review DST results	4-6 oral drugs	Cycloserine peak drug level 2 hrs post dose	→	→	→	→	→	→	→	→
15	treatment monitoring	review prior adherence	DOT initiated/Pt. educated	Educate as needed	→	→	→	→	→	→	→	→
		Baseline weight	Weigh monthly**	→	→	→	→	→	→	→	→	→
16	supportive care	review prior neuropathy, drug interactions (d4T)	Pyridoxine 100mg - G 0mg.	As long as Ethionomideor cycloserine given or if HIV+	→	→	→	→	→	→	→	→
17	Contact Evaluation	review history, trace contacts										
18	Nutritional Assessment	Nutritional supplement as	needed – Eo milk	product within 2 hours of floroquinolone use	→	→	→	→	→	→	→	→
19	**oto & vestibular toxicity**	**Audiogram/Vestibular Screen. Continue monthly as long as amikacin/capreomycin given**			→	→	→	→	→	→	→	→
20	**visual toxicity**	**Vision screen. Continue monthly as long as ethambutol given**			→	→	→	→	→	→	→	→
21	**others**	**Asses and address} Substance abuse/psychological factors influencing compliance and educational needs**			→	→	→	→	→	→	→	→

Annex - 9: Management of Hypothyroidism



Annex 10: Audio and vestibular assessment for Patient on Amikacin or Capreomycin

Point-to-Point Movement Evaluation

Ask the patient to extend their index finger and touch their nose, and then touch the examiner's outstretched finger with the same finger. Ask the patient to go back and forth between touching their nose and examiner's finger. Once this is done correctly a few times at a moderate cadence, ask the patient to continue with their eyes closed. Normally this movement remains accurate when the eyes are closed. Repeat and compare to the other hand.

Dysmetria is the clinical term for the inability to perform point-to-point movements due to over or under projecting ones fingers.

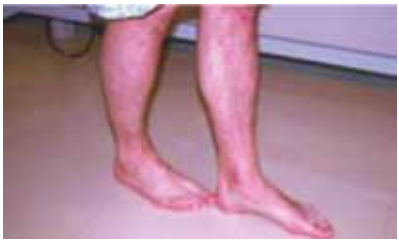
Rhomberg Test

Perform the Romberg test by having the patient stand still with their heels together.

Ask the patient to remain still and close their eyes. If the patient loses their balance, the test is positive.

To achieve balance, a person requires 2 out of the following 3 inputs to the cortex: 1) visual confirmation of position, 2) non-visual confirmation of position (including proprioceptive and vestibular input), and 3) a normally functioning cerebellum. Therefore, if a patient loses their balance after standing still with their eyes closed, and is able to maintain balance with their eyes open, then there is likely to be lesion in the cerebellum. This is a positive Rhomberg.

Heel to Toe



Gait is evaluated by having the patient walk across the room under observation. Gross gait abnormalities should be noted. Ask the patient to walk heel to toe across the room. Abnormalities in heel to toe walking (tandem gait) may be due to ethanol intoxication, weakness, poor position sense, vertigo and leg tremors. These causes must be excluded before the unbalance can be attributed to a cerebellar lesion. Most elderly patients have difficulty with tandem gait purportedly due to general neuronal loss impairing a combination of position sense, strength and coordination.

Annex 11: monitor and manage minor side effects and educate patient

Mild Adverse Reactions Adverse Reactions	Suspected Agents	Suggested Management
Anorexia	Z, Eto/Pto, FQ	Appetite stimulant, eg. Vitamin B complex
Arthralgias	**Z,** FQ	Non steroidal inflammatory drugs(NSAID), paracetamol, exercise therapy
Change in behavior (talkativeness, irritability)	**Cs**, Ofx	Haloperidol
		Pyridoxine 50mg per 250 mg of Cs up to 200 mg/day as maximum
Cutaneous reactions	H, R, Z, E, Eto/ Pto, Cs, PAS, S and other aminoglycosides	Antihistamines
		Hydrocortisone creams
Depression	**Cs**,H, FQ, Eto/Pto	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)
Diarrhea	PAS	Re-hydration
		Loperamide
Excessive salivation	Eto/Pto	Ice chips, metoclopromide
Flu like syndrome	R	Paracetamol
Gastritis	**PAS, Eto/Pto**	Antacids (eg. Calcium carbonate) H2 blockers, proton pump inhibitors)
Gynecomastia	**Eto/Pto**	Reassurance, surveillance
Headaches	**Eto/Pto**	Non steroidal inflammatory drugs(NSAID), paracetamol, exercise therapy
Insomnia	**FQ**	Antihistamine
Metallic taste	**Eto/Pto**	assurance
Musculoskeletal pain	No specific drug	Non steroidal inflammatory drugs(NSAID), paracetamol
Nausea and vomiting	**Eto/Pto, PAS,** R H,, Z, E, FQ	Re-hydration
		Metoclopromide
		Divide dose (AM & PM) as long as supervised

Olfactory hallucination	**Eto/Pto**	reassurance
Peripheral Neuropathy	**INH, Cs**, S, Km, Eto/Pto, FQ	Increase pyridoxine to maximum daily dose (200 mg/day) Tricyclic antidepressants such as amitriptyline
Pain at injection site	S, Km, **Am**, Cm	Cold compress
Photophobia	**Eto/Pto**	Reassurance
Vertigo/dizziness	**S, Km,** Cm, Eto/Pto	Betahistine, Cinnarizine

Annex 12: Moderate to Severe Adverse Reactions

Moderate – Severe Adverse Reactions	Suspected Agents	Suggested Management
Acute renal failure	**S, Km, Am,** Cm	Discontinue suspect drug
		Consider using Cm if an aminoglycoside had been the prior injectable in the regimen
		Consider dosing 2/3 times a week if drug is essential to regimen and patient can tolerate (close monitoring of creatinine)
		Adjust the dose according to creatinine clearance.
Bartter-like syndrome (decrease in serum K^+, mag^{2+} and ca^{2+})	**Cm,** Km, Am, S	Check electrolytes (K, Mg, Ca)
		Replace electrolytes as needed
Generalized hypersensitivity (Stevens-Johnson Syndrome)	Any drug	Withdrawal of the drugs and refer to specialist
Hearing loss	**S, Km, Am**, Cm, Clr	Document hearing loss and compare with baseline audiometry if available
		change parenteral treatment to Cm if appropriate (no resistance confirmed or suspected)
		Increase frequency and/or lower dose of suspected agent if it can be done without compromising regimen
		Discontinue suspected agent if this can be done without compromising the regimen
Hepatitis/jaundice	**Z, H, R**, Eto/ Pto, PAS, E, FQ	Discontinue therapy pending resolution of hepatitis
		Eliminate other potential causes of hepatitis
		Consider suspending most likely agent permanently. Reintroduce remaining drugs, one at a time with the most hepatotoxic agents first, monitoring liver function
Hypothyroidism	**PAS, Eto/Pto**	Initiate thyroxine therapy

Intractable vomiting	**Eto/Pto, PAS**, H, E,Z	Assess for dehydration, initiate rehydration if indicated
		Divide the dose (AM and PM) as long as it is supervised
		Discontinue suspected agent if this can be done without compromising the regimen
Optic neuritis	**E**	Discontinue drug and refer to ophthalmologist
Psychosis/psychotic symptoms (violent/ suicidal tendencies)	**Cs, H**	Discontinue suspected agent for a short period of time (1-4 weeks) while psychotic symptoms are brought under control.
		Antipsychotic treatment, referral to psychiatrist
		Lower the dose of suspected agent if this can be done without compromising regimen
Seizures	**Cs,** H, FQ	Discontinue suspected agents pending resolution of seizures
		Anticonvulsant therapy (phenytoin, valproic acid)
		Discontinue suspected agent if this can be done without compromising regimen

Annex 13: Drug Resistant TB Side-Effect Monitoring Form

Continuation phase																										
Adverse effect (indicate grading*)	Month **																							Management	Outcome
Abdominal pain																									
Constipation																									
Decreased hearing																									
Depression																									
Diarrhea																									
Dizziness																									
Fatigue																									
Fever																									
Headache																									
Joint pain																									
Nausea																									
Psychosis																									
Rash																									
Sink colourization																									
Tinnitus																									
Tremors																									
Vision changes																									
Vomiting																									
Other (list)																									

* Grading: 1 = mild; requiring no intervention 2 = moderate; requiring palliative intervention 3 = severe; requiring change in treatment

** Indicate in the first column the month of treatment that continuation phase started

INTENSIVE PHASE

Adverse effect (indicate grading*)	Week																						Management	Outcome
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24		
Abdominal pain																										
Constipation																										
Decreased hearing																										
Depression																										
Diarrhea																										
Dizziness																										
Fatigue																										
Fever																										
Headache																										
Joint pain																										
Nausea																										
Psychosis																										
Rash																										
Sink colourization																										
Tiinitus																										
Tremors																										
Vision changes																										
Vomiting																										
Other (list)																										

* Grading: 1 = mild; requiring no intervention 2 = moderate; requiring palliative intervention 3 = severe; requiring change in treatment

Annex 14: Anti-tuberculosis medication challenge

Example of anti-TB medication challenge				
Drug	**Day 1 (mg)**	**Day 2 (mg)**	**Day 3 (mg)**	**Day 4**
Isoniazid	25	50	100	5 mg/kg
Rifampicin	50	100	150	10mg/Kg
Pyrazinamide	125	250	500	25-30mg/kg
Ethambutol	100	200	400	20 - 30mg/kg
Streptomycin, Kanamycin, Capreomycin, Amikacin	125	250	500	15-20mg/kg
Ofloxacin	100	200	400	800mg
Ethionamide, Prothionamide	6.25	125	250	15mg/kg
Cycloserine	62.5	125	250	15mg/kg
PAS	100am	500am	2000am	150mg/kg
	200pm	1000pm	2000pm	

Annex 15: Adherence support and Preparation for the initial phase of MDR-TB treatment

Action	Description
1. Check for patient understanding on drug resistant TB?	• Explain the patient causes of MDR TB that it occurs when the patient with TB do not take anti-TB drugs regularly • Can be transmitted to family and friends • Can be transmitted easily to the people with HIV
2. Explain to the patient the duration of MDR TB treatment and possible side effects	• Describe to the patient that MDR TB treatment lasts for two years and that the initial six months (at a minimum) of treatment will be by hospitalization to ensure daily DOT. Explain that there is no other treatment for MDR TB • Also patient should know that those side effects are manageable and clinical team at the hospital should know immediately about the side effects
3. Ask if the patient is willing to undergo two years treatment with a minimum of six months hospitalization and is ready to receive DOTS?	• Agree with patient on drugs DOTS adherence and for the first six months will be accompanied with injections which will be given at Kibongot'o MDR TB hospital, the Programme will stop treatment if the patient does not take drugs regularly

Annex 16: Adherence support and Preparation for the continuation phase of MDR-TB treatment

Action	Description
1. Evaluate patients home condition for continuation of drugs at home	• Inquire about adequate family support at home (psycho-social, financial). • Explore if the patient can obtain adequate nutritional support to continue with second line medication while at home. • Identify previous history drug or alcohol abuse and mental illness
2. Demonstrate ability of the patient to keep appointment	• Ask the patient past experiences on other medications appointments and follow up • Deduce if there is history of drugs abscondment
3. Many patients have problem in taking medications on an ambulatory basis	• Ask the patient what trouble is he/she has when taking drugs, determine when is most difficult time for the patient when taking pills, how many pills is he/she taking daily
4. Who will observe the patient treatment?	• Explain to the patient that their treatment will be observed by health worker with support from the DTLC
5. Discuss with treatment supporter to find solutions	• Train supporter how to be emphatic and supportive • To do home visit if adherence is a problem • Refer if depression or anxiety is a problem
6. Arrange follow ups	• Make sure that the patient and treatment supporter understand the follow- up plan and how to contact the clinical team if there is problem
7. How taking of medication is be integrated in patient's work and home routines?	• Describe to the patient that during his/her medication period they will be provided with food packages and transportation if needed. Those in the remote areas are advised to move closer to the clinic for specific period of time

Annex 17: MDR TB drug order form

MINISTRY OF HEALTH AND SOCIAL WELFARE
NATIONAL TB AND LEPROSY PROGRAMME
MDR TB Drug Requisition Form **FORM 20**

Region_____
District_____
Requesting Facility_____ Date Requested_____
Period order will cover (circle) **Q1** **Q2** **Q3** **Q4** **Year**_____
Number of patients_____

SN	**Description** (specify preparation of drug	**Expiry dates**	**Quartley Use**	**Buffer**	**Quantity Needed**	**On-hand**	**Quantity Requested**	**Units per Container**	**Number of Containers Sent**
			(a)	*(b)*	*(c=a+b)*	*(d)*	*(e=c-d)*		
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									

Prepared by; Name_____ **Title – DTLC**_____ **Date & Signature**_____

Approved by; Name_____ **Title – RTLC**_____ **Date & Signature**_____

Annex 18: District DR TB Register

MDR-TB Suspect Register

REGISTER OF MDR-TB SUSPECTS

Year: **Facility:**

Date	MDR-TB Suspect Number (Current Registration)	Name of MDR-TB Suspect	Age		Complete Address and phone number	Result of HIV test*	Date First Sputum Collected	Date Sputum sent to Laboratory	Date results received	Results of Sputum Examinations			DST Results	Outcome / Action Taken
			M	F						1	2	3		

*(Pos) Positive; (Neg) Negative; (I) Discordant/Inconclusive; (ND) Not Done/unknown. Documented evidence of HIV test performed during or before TB treatment is reported here.

Annex 19: MDR TB Identity Patient Card

Ministry of Health and Social Welfare
National Tuberculosis and Leprosy Programme

FORM 12

MDR-TB PATIENT IDENTITY CARD (front side)

MDR-TB Treatment Unit:			**MDR TB Reg. Number:**			**Date of registration:**		
Patient name:						**Age**	M	F
Address:					**Telephone number:**			
Employment/profession			**Tribe:**			**Village Secretary cell #:**		
Previous TB treatment history:	Number of previous treatments with first-line TB drugs (≥ 4 weeks):							
	Number of previous treatments with second-line TB drugs (≥ 4 weeks):							

Period TB drugs were taken (month/years)			**Diagnostic category (tick)**			
Rifampicin (R)			New patient, never treated for TB, or treated for less than 4 weeks			
Isoniazid (H)						
Pyrazinamide (Z)			Previously treated with first-line drugs more than 4 weeks			
Ethambutol (E)						
Streptomycin (S)			Previously treated with second-line drugs more than 4 weeks			
Ofloxacin (Ofx)						
Amikacin (Am)						
Capreomycin (Cm)						
Cycloserin (Cs)						
Ethionamide (Et)						
p-aminosalicylic Acis (PAS)						

Pulmonary TB		**Extra-Pulmonary TB**				**Body weight** (kgs)	

Initial sputum-smear results (neg, positive and grading, not done, no data)	**Date**	**Lab #**	**Result**	**Date**	**Lab #**	**Result**
Initial Culture results (Negative/positive *M.tb*/contaminated/not done/pending)						
Initial Drug Sensitivity Test: (Date collected, laboratory number, date result) (Res, Sens, not done, pending)						

Close contacts:

(left inner side)

Medical History:
(Adverse reactions and allergies to non-TB medications; last menstrual period; method of contraception; pregnancy history)

Other complicating conditions:
(Diabetes, renal insufficiency, hepatitis, drug or alcohol abuse, psychiatric disorders, depression etc.)

Other drugs that the patient is currently taking:

Physical examination:
(General physical condition, blood pressure, length, BMI, full physical examination, urine analysis, liver /kidney function)

X-ray findings:

TREATMENT (right inner side)

Date treatment started				
	Initial phase	**Dose**	**Continuation phase**	**Dose**
Standard second-line	Pyrazinamide		Pyrazinamide	
	Amikacin		Ofloxacin	
	Ofloxacin		Ethionamide	
	Ethionamide		Cycloserine	
	Cycloserine			
Specific regimen (DST result)	Isoniazid			
	Rifampicin			
	Ethambutol			
	Pyrazinamide			
	Streptomycin			
	Amikacin			
	Capreomycin			
	Moxifloxacin			
	Levofloxacin			
Additional treatment	Cotrimoxazole		Cotrimoxazole	
	Pyridoxine		Pyridoxine	
Anti-Retroviral Treatment				
Other medicines				

MONITORING (Treatment duration in months)	**Sputum-smear**		**Culture** (always 2 specimens)		**DST (See Guidelines)**	**Body weight (Kg)**
	1	2	1	2		
Pre-treatment						
1						
2						
3						
4						
5						
6						
8						
10						
12						
14						
16						
18						
20						
22						
24						
End of treatment						

INTENSIVE PHASE OF TUBERCULOSIS CHEMOTHERAPY

Month/ day	✓*for date of DOT.*																													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

CONTINUATION PHASE OF TUBERCULOSIS CHEMOTHERAPY

Month/ day	✓*for date of DOT. X for date medicines are collected. Draw a horizontal line for dates that TB medicines are taken as DOT.*																													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Treatment Outcome:

☐ Cured ☐ Completed ☐ Died ☐ Failed ☐ Defaulted ☐ Transfer out

Date: _____

Annex 20: MDR TB Treatment Card

Ministry of Health and Social Welfare
National Tuberculosis Control Programme

FORM 13

Name: _____

MDR-TB registration number: _____

Date of MDR-TB registration: ___ / ___ / ___

Prior TB registration number: _____

Date of prior TB registration: ___ / ___ / ___

Address: _____

Address (Next of kin): _____

Telephone: _____

Country/District: _____

Treatment centre: _____

Sex		Age	Date of birth	
M	F			
Initial weight (kg)			**Height** (cm)	
Site (mark one):	PTB	EPTB	Both	
If EPTB, describe site:				

MDR TB Treatment Card

	Registration group	Select 1 only
1	New	
2	Relapse of first line drugs	
3	Treatment after default of first line drugs	
4	After failure of first line drugs (Category I failure)	
5	After failure of first line drugs (Category II failure)	
6	Retreatment after default of second line drugs	
7	Retreatment after relapse of second line drugs	
8	Retreatment after failure of second line drugs	
9	Transfer in (from another Category IV treatment site)	
10	Other (previously treated without known outcome)	

Previous tuberculosis treatment episodes

No.	Start date (if unknown, put year)	Regimen (write regimen in drug abbreviations)	Outcome

Classifications of previous drug use:

Used second- line drugs previously? ❑Yes ❑No

If yes, specify: _____

_____

Drug abbreviations:

First-line drugs
H= Isoniazid
R= Rifampicin
E= Ethambutol
Z= Pyrazinamide
S= Streptomycin

Second-line drugs
Am= Amikacin
Cm= Capreomycin
Ofx= Ofloxacin
Lfx= Levofloxacin
Cs = Cycloserine
Eto= Ethionamide
PAS= p-aminosalicylic acid

Quarterly Treatment Review panel meetings: dates and decisions:

Date	Issue and Decision	Next date

Rvsd March 2011

HIV Information (Fill for all patients)
HIV testing done: ☐ Y ☐N ☐Unknown
Date of test: ___/___/___ Results:
CD4 Cell Count: Date: ___/___/___
Started on ART: ☐ Y ☐ N Date: ___/___/___
Started on CPT: ☐ Y ☐ N Date: ___/___/___

ART = antitretroviral therapy;
CPT = co-trimoxazole preventive therapy

Antiretroviral Flow Sheet

Regimen	Start date	Stop date	Reason for stop/change

Reasons for interruption of medications:	1 = Failure 2 = Tuberculosis/ Interaction	3 = Adverse effects 4 = Pregnancy	5 = Stock out 6 = Dose change	7 = Patient refusal 8 = PMTCT ended	9 = Other (specify)
Abbreviations:	NRTI 3TC = Lamivudine D4T = Stavudine AZT = ZDV=	NRTI ABC = Abacavir DDI = Didanosine TDF = Tenofovir	NNRTI NVP = Nevirapine EFV = Efavirenz	PI LOP/R = Lopinavir/ ritonavir	PI NFV = Nelfinavir R = Ritonavir

Weight Monitoring

Month	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Date																									
Weight																									

Laboratory Monitoring

Date																									
ALT/ SGPT																									
AST/ SGOT																									
Creatinine																									
K																									
TSH																									
Hemoglobin																									
WB count																									
CD4																									
Lipase																									
HIV test																									
Pregnancy test																									

Patient name:_____ MDR TB Registration No. _____

Drug-susceptibility testing (DST) results (notation method for DST: R = resistant, S = susceptible, C = contaminated)

Date*	INH	RMP	EMB	PZA	SM	Am	Km	Cm	Ofx	Lfx	PAS	Eto	Cs		

Bacteriology

Month	Date	Specimen Number	Smear Result	Specimen Number	Culture Result
Prior**					
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					

Chest x-ray*

Date	Result
At diagnosis	
Mo. 6	
Mo. 12	
Mo. 18	
Mo. 24	
End of Treatment	

*Please note key findings of chest X-ray performed at diagnosis, during treatment, and at the end of treatment

**Refers to specimen obtained prior to MDR-TB Treatment start

Patient name:_____ MDR TB Registration No. _____

Medical Diagnosis other than tuberculosis

Date	**Type** (i.e. diabetes, hypertension, cardiomyopathy, HIV, opportunistic infections)

Adverse Effects

Date	**Type** (i.e. neuropathy, hepatitis, rash, etc.)	**Suspected drug**	**Intervention**

Vestibular Exam: (monthly while patient on injectable agent)

	DATE:														
Vestibular	Romberg														
	Heel-to-toe														
	Point-to-point														

(Indicate pass or fail for each)

Patient name:_____ MDR TB Registration No. _____

Treatment Regimen (date treatment started and dosage [mg], change of dosage, and cessation of drugs

Date	H	R	Z	E	S	Am	Cm	Ofx/Lfx	Eto	PAS	Cs		

Administration of drugs (one line per month) INTENSIVE PHASE OF TREATMENT

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Mark in the boxes: X = Directly observed (in hospital or by DOT Nurse)
→ = (Draw a line) Observed by treatment supporter
N = Not supervised
= Drugs not taken

Date of Discharge from inpatient care to District level care: ___/___/____

Patient name:_____ MDR TB Registration No. _____

Administration of drugs (continued) CONTINUATION PHASE OF TREATMENT

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

Mark in the boxes: X = Directly observed (in hospital or by DOT Nurse)
→ = (Draw a line) Observed by treatment supporter
N = Not supervised
= Drugs not taken

Comments:

_____
_____
_____
_____
_____
_____
_____

Treatment Outcome:

Outcome	Mark one	Date
Cured		
Completed		
Died		
Failed		
Defaulted		
Transferred out		

Name of treating clinician/DTLC: _____ **Signature:** _____ **Date:** ___ / ___ / ___

Annex 21: MDR-TB Register

MDR-TB Register

TB Treatment Registration Group	
1	**New**
2	**Relapse** of **first line** drugs
3	Treatment after **default** of **first line** drugs
4	After **failure** of first line drugs (**New patient regimen**)
5	After **failure** of first line drugs (**Retreatment regimen**)
6	Retreatment after **default** of **second line** drugs
7	Retreatment after **relapse** of **second line** drugs
8	Retreatment after **failure** of **second line** drugs
9	**Transfer in** (from another Cat. IV treatment site
10	**Other** (previously treated without known outcome)

MDR-TB Number*	Date of MDR-TB Treatment Start	Full Name	Sex (M/F)	Age	Address	District TB Register number (for last TB episode) and Date	Disease Site (P/EP)	Registration Group (see above)	DST Results			Type of Resistance (MDR/XDR/ Poly-Res)
									Date of Sample	Date of Result	Resistance to (list drugs)	
	/ /								/ /	/ /		
						/ /			/ /	/ /		
	/ /								/ /	/ /		
						/ /			/ /	/ /		
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	/ /								/ /	/ /		
						/ /			/ /	/ /		

* District Number/KKS/Year of Registration/Serial number of pt.

MDR-TB Register (page 2)

Drug Abbreviations					
First-line drugs		Second-line drugs			
H	Isoniazid	Km	Kanamycin	Gati	Gatifloxacin
R	Rifampin	Cm	Capreomycin	Pto	Prothionamide
E	Ethambutol	Ofx	Ofloxacin	Eto	Ethionamide
Z	Pyrazinamide	Lfx	Levofloxin	CS	Cycloserine
S	Streptomycin	Moxi	Moxifloxacin	PAS	p-aminosalycilic acid

Notation Method for Recording Smear Results	
No AFB	0
1-9 AFB per 100 HPF	Scanty (and report number of AFB)
10-99 AFB per 100 HPF	+
1-10 AFB per HPF	++
>10 AFB per HPF	+++

Notation Method for Recording Culture Results	
No growth reported	0
Fewer than 10 colonies	Report number of colonies
10-100 colonies	+
More than 100 colonies	++
Innumerable or confluent growth	+++

		Smear (S) and Culture (C) Results During Treatment																															
MDR-TB Number	MDR-TB Regimen	Baseline		Mo 1		Mo 2		Mo 3		Mo 4		Mo 5		Mo 6		Mo 7		Mo 8		Mo 9		Mo 10		Mo 11		Mo 12		Mo 13		Mo 14		Mo 15	
		S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C
		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y	

MDR-TB Register (page 3)

Treatment Outcomes	
C	Cure
TC	Treatment complete
F	Failed
D	Died
Def	Defaulted
TO	Transferred out

Notation Method for Recording Smear Results	
No AFB	0
1-9 AFB per 100 HPF	Scanty (and report number of AFB)
10-99 AFB per 100 HPF	+
1-10 AFB per HPF	++
>10 AFB per HPF	+++
Notation Method for Recording Culture Results	
No growth reported	0
Fewer than 10 colonies	Report number of colonies
10-100 colonies	+
More than 100 colonies	++
Innumerable or confluent growth	+++

MDR-TB Number	Smear (S) and Culture (C) Results During Treatment																						Treatment Outcome (see above)	TB/HIV Activities				Comments
	Mo 16		Mo 17		Mo 18		Mo 19		Mo 20		Mo 21		Mo 22		Mo 23		Mo 24		Mo 25		Mo 26			Testing Done	HIV Result	ART (Y/N)	CPT (Y/N)	
	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	Date	Y/N Date	(Circle result)	Start date	Start date	
	d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y		d/m/y							
																							/ /	/ /	Pos – Neg	/ /	/ /	
																							/ /	/ /	Pos – Neg	/ /	/ /	
																							/ /	/ /	Pos – Neg	/ /	/ /	
																							/ /	/ /	Pos – Neg	/ /	/ /	
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																							/ /	/ /	Pos – Neg	/ /	/ /	
																							/ /	/ /	Pos – Neg	/ /	/ /	

Annex 22: Monthly Follow Up Programme

FORM 17

Ministry of Health and Social Welfare
National Tuberculosis and Leprosy Programme
DRUG RESISTANT TB MONTHLY TREATMENT FOLLOW-UP FORM

Surname: _____ First Name _____
Age _____ (years) Sex ___ (M/F) MDR-TB Reg. No. _____
Hospital File No.: _____ Location _____ Treatment Mo. _____

TB Symptoms

Improved	Not improved/ worsened
☐	☐ Cough
☐	☐ Bloody sputum (haemoptysis)
☐	☐ Fever/night sweats
☐	☐ Shortness of breath
☐	☐ Weight loss

Side Effects

- ☐ Nausea/vomiting
- ☐ Fatigue
- ☐ Visual problems (recent change)
- ☐ Headache
- ☐ Confusion
- ☐ Rash
- ☐ Ringing in ears
- ☐ Deafness
- ☐ Tingling in hands/legs/feet
- ☐ Jaundice (yellow eyes, skin)
- ☐ Others _____

Adverse Events

- ☐ Hypokalemia
- ☐ Psychosis
- ☐ Depression
- ☐ Nephrotoxicity
- ☐ Ototoxicity
- ☐ Peripheral neuropathy
- ☐ Rash
- ☐ Hepatotoxicity
- ☐ Other _____

Adherence Assessment

Any medication missed in the past month? ☐ YES ☐ NO
Type and doses of medication missed (**to be identified by the health personnel**) _____
_____
Reason for missing the above medications:

1. Side effects
2. Forgot
3. Alcohol abuse
4. Others _____

Has the patient visited the health facility daily during the past month? ☐ Yes ☐ No

If no, does the treatment supporter, supervised every daily dose? ☐ Yes ☐ No

Describe the relationship with the treatment supporter

Physical Exam **Functional Status**

Wt _____ (kg) ☐ Functional

Ht/Lng ____ (cm) ☐ Ambulatory

BP ___ / ____ ☐ Bedridden

Temp _____ (C) RR _____ /min

N AN

☐ ☐ Head, ears, eyes, nose, throat _____
☐ ☐ Lymph nodes _____
☐ ☐ Heart _____
☐ ☐ Lungs _____
☐ ☐ Abdomen _____
☐ ☐ Skin _____
☐ ☐ Urogenital _____
☐ ☐ Musculoskeletal _____
☐ ☐ Neurological _____
☐ ☐ Others _____

Lab results (blood tests, sputum smear /culture, etc.)

SPECIAL CONDITIONS

HIV Information (Fill for all patients)
HIV testing done: ☐ Y ☐N ☐Unknown
Date of test: ___/___/___ Results:
CD4 Cell Count: Date: ___/___/___
Started on ART: ☐ Y ☐ N Date: ___/___/___
Started on CPT: ☐ Y ☐ N Date: ___/___/___

Note details of condition in Comments section below

Pregnancy	
Breastfeeding	
Liver disorders	
Renal insufficiency	
Contraception	
Psychiatric disorders/ Epilepsy	
Diabetes mellitus	
Substance abuse	
Other (please indicate)	

INVESTIGATIONS ORDERED THIS MONTH

	Exam or Test	**Date**
☐	Sputum smear	____/____/____
☐	Sputum culture	____/____/____
☐	Chest X – ray	____/____/____
☐	DST (one/two)	____/____/____
☐	RFT (serum creatinine)	____/____/____
☐	LFT (ASAT, ALAT, bilirubin)	____/____/____
☐	TSH	____/____/____
☐	FBP	____/____/____
☐	Serum electrolytes (potassium, magnesium, sodium)	____/____/____
☐	HIV rapid tests	____/____/____
☐	CD 4 counts	____/____/____
☐	Other (specify test and date)_____ _____	

OTHER COMMENTS: _____

_____

_____

_____

Annexure 23: Laboratory TB Register for culture/DST

Ministry of Health and Social Welfare
National Tuberculosis and Leprosy Programme

FORM 15

Laboratory Register for culture and DST (left side of register)

Laboratory serial number	Laboratory MDR TB number	Patient Name	Sex M/F	Date of birth	Patient Address (if new)	Referring Health Facility	Type of specimen received	Date of specimen collection	Date specimen received	Date specimen processed	Reason for examination		Smear result	Result of culture (Week)								
											Diagnosis*	Follow-up**		1	2	3	4	5	6	7	8	9

*New patient or patient starting a re-treatment regimen
**Patient on TB treatment. Indicate months of treatment at which follow-up examination is performed

National Tuberculosis & Leprosy Programme

Laboratory Register for culture and DST (right side of register)

Confirmatory test for M.tb (positive of negative)	Culture sent for DST Y/N ☐ Yes ☐ No	Name of person reporting culture result	Signature	Date results reported	Date results issued	DST Results***										Name of person reporting DST result	Signature	Comments
						INH	RIF	EMB	Sm	Am	Cm	Lfx	Mxf					
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	
	☐ Yes ☐ No																	

***Report DST results as s = susceptible, r = resistant, c = contaminated

Annex 24: DR TB referral/Transfer form

FORM 16

MINISTRY OF HEALTH AND SOCIAL WELFARE
NATIONAL TUBERCULOSIS AND LEPROSY PROGRAMME

DRUG RESISTANCE TUBERCULOSIS REFERRAL/TRANSFER FORM

(Complete top part in triplicate)

Tick and comment to indicate the reason for this referral or transfer:

☐ Referral to register and begin TB treatment ☐ Referral for _____ _____ _____ ☐ Transfer (registered patient is moving)

Name/address of referring/transferring facility_____
District_____Region_____

Name/address of facility to which patient is referred/transferred _____
_____District_____Region_____

Name of the Patient (Three Names)_____ Age ____

Sex: M ☐ F ☐ Tel/Mobile No: - _____

Address (if moving, future address) _____

_____

Name and address of contact person for patient_____

Mobile No: -

Name and address of Area Leader/Village Secretary _____

_____Mob No: - _____

Diagnosis*_____

District TB No/MDR TB No: -.* _____ Date treatment started*_____

Category of treatment:*

☐ New case, smear-positive
☐ Re-treatment
☐ New case, smear-negative or extrapulmonary
☐ Chronic or MDR-TB

Drug-susceptibility testing (DST) results (notation method for DST: r = resistant, s = susceptible, c = contaminated)

Date*	INH	RMP	EMB	SM

Drugs patient is receiving by Names _____

_____

Remarks (e.g. side-effects observed) _____

_____

_____

Name _____Signature _____

Position _____ Date of referral/transfer_____

**Complete if known. If this is a referral for diagnosis, these items may be unknown.*

For use by facility to which patient has been referred or transferred:

Name of facility _____

District _____ Date _____

Name of patient _____District TB No/MDR TB No_____

The above patient reported at this facility on _____(date)

Name_____Signature_____

Position_____

Send this part back to referring/transferring facility as soon as patient has reported

NB:

1st Copy: - For the Receiving facility

2nd Copy: - For the patient

3rd Copy: - For the Referring facility

Annex 25: Six Month Interim Outcome Assessment of confirmed MDR-TB cases

Ministry of Health and Social Welfare
National Tuberculosis and Leprosy Programme

FORM 18

Six month interim outcome assessment of confirmed MDR-TB cases
(To be filled out 9 months after treatment start)

Name of Unit:_____

Date filled in: _____

Quarter treatment was started: _____

Date of the report: _____

Category started on treatment	Bacteriological results at 5 and 6 months of treatment			No longer on treatment		
	Negative (all smears and cultures negative during month 5 and 6, and at least a smear and culture done each month)	Positive (any smear or culture is positive during month 5 and 6)	Culture and smear unknown (Consider unknown if a culture or smear results is not done for either month 5 or 6)	Died	Defaulted	Transferred Out
New						
Relapse of first line drugs						
Treatment after default of first line drugs						
After failure of first line drugs for new patients' standardized regimen						
After failure of first line drugs retreatment regimen						
Retreatment after default of second line regimen						
Retreatment after relapse of second line regimen						
Retreatment after failure of second line regimen						
Transfer in (from another MDR TB treatment site)						
Other (previously treated without known outcome						

Annex 26: Quarterly Report on MDR TB Detection and MDR TB Treatment Start

Ministry of Health and Social Welfare
National Tuberculosis and Leprosy Programme

FORM 19

Quarterly report on MDR-TB detection and treatment start

Name of area _____	Name of area coordinator _____
Patients identified during _____ quarter of year _____	Date _____

1 - Number of patients detected with MDR-TB/XDR-TB in the lab (by date of result of MDR-TB/XDR-TB in labortory register) during the quarter

MDR-TB ☐ **XDR-TB** ☐

2 - Number of MDR-TB patients who started MDR TB treatment during the quarter

	New	Relapse of first line drugs	Treatment after default of first line drugs	After failure of first line drugs for new patients' standardized regimen	After failure of first line drugs retreatment regimen	Retreatment after default of second line regimen	Retreatment after relapse of second line regimen	Retreatment after failure of second line regimen	Transfer in (from another MDR TB treatment site)	Other (previously treated without known outcome	Total
Confirmed cases											
Suspected cases											

1st quarter: 1st January - 31 March
2nd quarter: 1er April - 30 June
3rd quarter: 1er July - 30 September
4th quarter: 1er October - 31 December

Signature _____

Annex 27: Annual report of treatment result of confirmed MDR TB patients

Ministry of Health and Social Welfare
National Tuberculosis and Leprosy Programme

FORM 14

Annual report of treatment result of confirmed MDR-TB patients starting second line treatment
(To be filled in 24 and 36 months past the closing date of year of treatment)

Year of treatment start: _____

Patient group	Cured	Treatment completed	Failed	Defaulted	Died	Transferred out	Still on treatment	Total
New								
Relapse of first line drugs								
Treatment after default of first line drugs								
After failure of first line drugs for new patients' standardized regimen								
After failure of first line drugs retreatment regimen								
Retreatment after default of second line regimen								
Retreatment after relapse of second line regimen								
Retreatment after failure of second line regimen								
Transfer in (from another MDR TB treatment site)								
Other (previously treated without known outcome								
Total								

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7. The United Republic of Tanzania, Ministry of Health and Social Welfare, 2006. Manual of the National Tuberculosis and Leprosy Programme 5th Edition
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