Ministry of Health

PROGRAMMATIC MANAGEMENT

OF

DRUG RESISTANT TURBERCULOSIS (PMDT)-KENYA

NATIONAL TUBERCULOSIS, LEPROSY & LUNG DISEASE UNIT

June 2014

Foreword

Tuberculosis (TB) remains a major cause of morbidity and mortality in Kenya with the emergence of resistance to anti-tuberculosis drugs, and particularly of multidrug-resistant TB (MDR-TB), being a major public health problem. New cases of MDR-TB continue to emerge every year due to inappropriate or absence of updated treatment guidelines and noncompliance of the treatment guidelines among other causes of drug resistant TB in various places. Various health facilities in the country have established centres for treatment of multidrug resistant TB (MDR TB) in every region where up to 558 MDR TB patients have been enrolled for treatment by the end 2012.

These guidelines therefore offer updated recommendations for Programmatic Management of Drug resistant TB (PMDT). The updated guidelines take into particular account a number of considerations and important developments and recent evidence for the diagnosis e.g. Xpert MTB/RIF and management of MDR-TB in different settings. This is in order to avail culture and drug susceptibility testing for all patients in whom DR-TB is considered possible. The guidelines therefore replaces the second edition; "*the guidelines for the programmatic management of drug resistance TB produced in March 2010".*

Previous experiences in treating DR-TB guided the therapeutic recommendations contained in these guidelines. In addition, these guidelines provide standards for registering, monitoring and reporting the treatment outcomes of patients with DR-TB. This uniform information management system will allow systematic, consistent data collection and analysis, which will play an important role in shaping PMDT in Kenya. These revised guidelines focus on care for DR-TB patients, in the hope that the occurrence of many new cases can be prevented through sound TB control practices. The DOTS strategy remains the cornerstone of TB control and the most effective tool for preventing the onset and dissemination of drug resistance. Without the essential elements of TB control fully in place, management of MDR-TB will undoubtedly fail in the long term, as one cannot control it if the tap is not turned off. These guidelines therefore are designed to be used by TB control program officers, medical practitioners and other personnel involved in TB control in Kenya in addition to other TB training materials to enable comprehensive care to TB patients including MDR TB patients.

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List of abbreviations

AFB	-	Acid Fast Bacilli
AIDS	–	Acquired Immunodeficiency Syndrome.
ART	–	Antiretroviral Therapy
CBOs	-	Community Based Organizations.
CDC	–	Centres for Disease Control and Prevention.
CDR	–	Case Detection Rate
CHEW	-	Community Health Extension Worker
CNR	–	Case Notification Rate
CRL	–	Central Reference Laboratory
CTLC`	–	CountyTuberculosis and Leprosy Coordinator
NTLD -UNIT	–	National Tuberculosis, Leprosy and Lung Disease Unit
DMOH	–	District Medical Officer of Health
DOTS	–	Directly Observed Therapy Short course.
DST	-	Drug Susceptibility Testing
DTC	–	Diagnostic Testing and Counselling
SCTLC	–	Sub county Tuberculosis and Leprosy Coordinator
EPTB	–	Extra-Pulmonary Tuberculosis
HIV	–	Human Immunodeficiency Virus.
INH	–	Isoniazid
IPC	–	Infection Prevention and Control
KAPTLD	–	Kenya Association for Prevention of Tuberculosis & Lung Disease
KEMRI	–	Kenya Medical Research Institute.
KNH	–	Kenyatta National Hospital.
MDRTB	–	Multi-Drug Resistant Tuberculosis
MOH	–	Ministry of Health
NASCOP	–	National Aids & Sexually transmitted infections Coordinating Program
NGOs	–	Non Governmental Organizations
NRL	–	National Reference Laboratory
NSN	–	New Smear Negative
NSP	–	New Smear Positive
OPD	–	Out Patient Department
PPM	–	Private Public Mix
PTB	–	Pulmonary Tuberculosis
PMDT	–	Programmatic Management of Drug Resistant Tuberculosis
R	–	Rifampicin
SCC	–	Short Course Chemotherapy
SRL	–	Supranational Reference Laboratory
TB	-	Tuberculosis.
UV	–	Ultraviolet light
WHO	–	World Health Organization
XDRTB	–	Extensively Drug Resistant Tuberculosis
ZN	-	Ziehl-Neelsen

Introduction

There were about 650 000 cases of MDR-TB present in the world in 2010. It is estimated that about 9% of these cases had XDR-TB. Annually, about 440 000 fall ill with MDR-TB and 150 000 die due to this form of tuberculosis. In 2012, WHO estimated 450,000 MDR TB cases of whom 170,000 died

Kenya is one of the 22 high burden TB countries that collectively contribute about 80% of the world's TB burden. TB in Kenya is primarily driven by HIV and poverty with the urban-slum population making the greatest contribution. The TB case notification rose from 57/100,000 in 1985 to 329/100,000 in 2008, but has now declined to 264/100,000 in 2011

In Kenya, treatment period for TB has reduced from 18 months to 12, then 8, and now 6 months The TB Short Course Chemotherapy (SCC) was initiated in the country in 1993 and covered the whole country in 1997.

In 2012 there were 99,179 TB cases in the country of whom 9, 879 (9.6%) were previously treated. WHO estimates in 2012 that 2.5% of the new smear positive cases and 10% of previously treated patients have MDR TB leading to a total of 2,780 cases of MDR TB.

Since 2002 surveillance of MDR TB has been strengthened and conducted for all retreatment cases of TB. Over the years, the proportion of retreatment patients submitting sputum specimens to the CRL has improved and in 2011, up to 83 % of all retreatment cases submitted sputum for culture and DST. From 2006 to 2013, the CRL has documented a total of 1191 MDR TB cases of which 285 patients were notified in 2013. Over 150 patients have been cured, and 210 treated successfully (cured inclusive). Kenya achieved a treatment success rate of 80% in MDR TB for the 2011 cohort.

Chapter 1 Political commitment and coordination

1.1 General considerations

Sustained political commitment and leadership are the foundation for any sound programme to control TB. The legal and regulatory context defines the potential as well as the structure and policies of the National Tuberculosis, Leprosy and Lung Disease- Unit(NTLD -UNIT). Political commitment is expressed through adequate financial support and appropriate infrastructure, including facilities and trained human resources. Political commitment is also demonstrated through regulatory and legal support, policy guidance and leadership at the national level, Coordination among the different components of public and private health programmes and organizations is essential for successful programme implementation. Sufficient training and retention of medical, public health personnel depend on long-term government planning and support.

1.2 Political commitment

Political commitment must be expressed at all stages of the health intervention process, from planning and implementation to monitoring and evaluation. Political support needs to be garnered from sources including government ministries and regional departments responsible for TB control, non-governmental organizations and the private sector, the pharmaceutical industry, academic and research institutions, professional medical societies and the donor community. This commitment takes the form of leadership, financial and human resources, training, legal and regulatory documents, infrastructure and coordination of all stakeholders involved in all aspects of the framework for control of drug-resistant TB.

1.3 Sufficient economic support

The NTLD -UNIT budget must be sufficient to develop and retain an adequate workforce with interest and expertise in drug-resistant TB without weakening the workforce of the national programme as a whole. The financial resources needed to support the framework should be provided. Efforts should be made to limit barriers including financial barriers to patients accessing appropriate care for drug resistance TB.

1.4 Regulatory and operational documents

Programmatic management of drug resistant tuberculosis control programme in Kenya is integrated into the national TB control Programme. To improve access, scale-up follows a decentralized model. Follow up is either community based through clinics or home based. Patients are hospitalized only when necessary. To appropriately care for DRTB patients, isolation wards are required in all level 4, 5, 6 and other facilities guided by need to provide critical care to those who require admission or have severe side effects especially in children and pregnant women. Treatment is provided through well trained and supported health **care** workers and community health **care** workers through the DOTs plus strategy.

The following are examples of the use of regulatory and operational measures:

- Legislation need to be drafted to ensure proper registration, availability, quality, safety and distribution of both first-line and second-line drugs.
- There are TB/HIV committees at all levels. These committees should also address the DRTB issues.
- There should be DRTB clinical management teams at county and sub-county levels to review and evaluate new DRTB patient for initiation of treatment, review the progress of those patients on treatment and recommend appropriate action.
- Roles and responsibilities of different partners should be articulated clearly to avoid duplication, ambiguity in implementation plans, targets and area of operations to maximize benefit. Stewardship of this process is given by the Ministry of Health/NTLD -UNIT.

1.5 Coordination

Coordination includes the contributions of all the key stakeholders, organizations and other partners.

• The NTLD -UNIT is the central coordinating body for the activities described in the strategic framework. Commitment of the necessary resources, particularly for a strong central management team, ensures that these elements are in place, from the procurement of second-line drugs to the appropriate implementation and monitoring of the DOTs lus programme. As

needed, the national programme may build partnerships with all relevant healthcare providers and development partners.

• ***The NTLD -UNIT recognizes the involvement and communication with community leaders*** can greatly facilitate implementation of treatment and respond to needs that cannot be met by medical services alone. Community health education, involvement and organization around TB issues, can encourage a feeling of community ownership of TB control programmes and reduce stigma and discrimination.

• ***Coordination with prisons.***

Transmission in prisons is an important source of spread of drug-resistant TB in some countries, and infection control measures can reduce incidence substantially. In many cases, inmates are released from prison before they finish treatment. Close coordination and communication between NTLD -UNIT and prison authorities, advance planning, targeted social support and specific procedures for transferring care will help ensure that patients complete treatment after release from prison.

• ***Coordination with agencies dealing with mobile populations*** (Nomads, refugees, street families, migrants, internally displaced people)

Close coordination and communication between NTLD -UNIT, development partners, civil societies and the concerned authorities, will help ensure patients complete treatment.

• ***All health-care providers*** (both public and private).

In some countries, private practitioners manage most cases of drug-resistant TB. In these settings, it is important to involve the private sector in the design and technical aspects of the programme.

- ***Many PPM programmes have demonstrated effective and mutually beneficial cooperation.***

In PPM systems, move in both directions. For example, private providers can be compensated fairly through negotiated systems of reimbursement, and the public health system may provide clinic- or community- based DOT as well as registering patients and

their treatment outcomes. Similar PPMs can be established for treatment of drug-resistant TB, but they require exceptional coordination.

1.6 DR TB Management Clinical teams

Clinical teams will be established at the county and district levels and they will be responsible for managing DR TB in those regions.

Composition

- COUNTY TLC
- Clinician (Physician/M.O)
- District (Sub county) TLC
- Pharmacist
- DOT Nurse
- Social worker
- Public health officer
- Lab technologist
- Nutritionist.
- Community Health Extension Worker (CHEW)

The Sub County TLC (SCTLC)will be the focal person to convene the monthly meetings with 3 or more members. Partners managing DR TB should send a representative to the clinical team meetings.

The Sub County TLC (SCTLC)is also expected to review all DR TB patients during the routine monthly supervision.

Roles

- Overall responsibility of managing DR TB in their regions.
- Reviewing DST and culture results of DR TB suspects and patients on treatment.
- Recommend initiation of DR TB treatment.
- Carry out follow up of DR TB patients on treatment
- Reviewing complex cases as need arises e.g. adverse drug effects, co-morbidities and recommending appropriate interventions.

- Co-ordinate referrals of DR TB patients to and from their counties.
- Ensuring adequate and consistent commodity supply in their regions.

1.7 Multi-drug resistant tuberculosis and DOTS-Plus

Special considerations for DOTS-Plus

DOTS-Plus is more complex than the basic DOTS strategy. For DOTS-Plus to be successful, special attention is needed for the following:

- Quality-assured laboratory capacity (smear, culture and DST);
- Treatment design;
- Adherence to difficult-to-take regimens for long periods;
- Side-effect management;
- Drug procurement;
- Recording and reporting; and
- Human and financial resource constraints.

The method of case finding is designed taking into consideration the resources and technical capacity available to the NTLD -UNIT at this time. Also the DOTS-Plus treatment regimen for MDR-TB has been tailored to the Kenyan setting. Many health care providers have little or no experience with second-line drugs and their side effects, especially in combinations of 4 to 6 at a time. The framework presented in this document is designed to address the challenges faced by NTLD -UNIT in relation to MDR-TB in Kenya.

1.7.1 Five components of DOTS-Plus

1. **Sustained political and administrative commitment**

- A well-functioning DOTS programme
- Long term investment of staff and resources
- Coordination efforts between community, local governments, and International agencies
- Addressing the factors leading to the emergence of MDR-TB

2. **Diagnosis of MDR-TB through quality-assured culture and Drug susceptibility testing**

- Proper triage of patients for Culture & DST testing and management under DOTS-Plus
- Co-ordination with National and Supra-National Reference Laboratories

3. **Appropriate treatment strategies that utilize second-line drugs under proper management conditions**

- Rational standardized treatment design (evidence-based)
- Directly observed therapy (DOT) ensuring long-term adherence
- Monitoring and management of adverse drug reactions
- Adequate human resources**.**

4. **Uninterrupted supply of quality assured anti-TB drugs.**

5. **Recording and reporting system designed for DOTS-Plus programmes that enable performance monitoring and evaluation of treatment outcome**

Chapter 2 Case finding strategies for MDR TB

2.1 Operational definitions

2.1.1 Revised case definitions

Presumptive TB refers to a patient who presents with symptoms or signs suggestive of TB (previously known as a DR *TB suspect*).***A bacteriologically confirmed TB* case** is one from whom a biological specimen is positive by smear microscopy, culture or any WHO-approved rapid diagnostics (such as Xpert MTB/RIF). All such cases should be notified, regardless of whether TB treatment has started.

A clinically diagnosed TB case is one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or histology results and extra pulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Bacteriologically confirmed or clinically diagnosed cases of TB are also classified according to:

- anatomical site of disease;
- history of previous treatment;
- drug resistance;
- HIV status.

2.1.2. Classification based on anatomical site of disease

Pulmonary tuberculosis (PTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Military TB is classified as PTB because there are lesions in the lungs. Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or Tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extra pulmonary TB. A patient with both pulmonary and extra pulmonary TB should be classified as a case of PTB.

Extra pulmonary tuberculosis (EPTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

2.1.3. Classification based on history of previous TB treatment (patient registration group)

New patients have never been treated for TB or have taken anti-TB drugs for less than 1 month.
Previously treated patients have received 1 month or more of anti-TB drugs in the past. They are further classified by the outcome of their most recent course of treatment as follows;

1. **Relapse patients** have previously been treated for TB, were declared *cured* or *treatment completed* at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by re-infection).

2. **Treatment after failure patients** are those who have previously been treated for TB and whose *treatment failed* at the end of their most recent course of treatment.

3. **Treatment after loss to follow-up patients** -these are patients who have previously been treated for TB and were declared *lost to follow-up* at the end of their most recent course of treatment. (These were previously known as *treatment after default* patients.)

4. **Other previously treated patients** are those who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

5. **Patients with unknown previous TB treatment history** do not fit into any of the categories listed above.

6. New and relapse cases of TB are **incident** TB cases.

It can also be classified according to previous treatment as follows:
There are 2 classifications:

1: Previous treatment history:

(a) No previous treatment

(b) Previous treatment with first line drugs

(c) Previous treatment with second line drugs

2: Previous treatment outcome

(a) New case, no previous outcome

(b) Relapse – this is correct just as you have it

(c) After failure – this is correct, but you need to define treatment failure more specifically

(d) Loss to follow-up should be divided into two, making a distinction between default and transfer

2.1.4. Classification based on HIV status

HIV-positive TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care, such as enrolment in the pre-ART register or in the ART register once ART has been started.

HIV-negative TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis. Any HIV-negative TB patient subsequently found to be HIV-positive should be reclassified accordingly.

HIV status unknown TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrolment in HIV care. If the patient's HIV status is subsequently determined, he or she should be reclassified accordingly.

2.1.5. Classification based on drug resistance

Cases are classified in categories based on drug susceptibility testing (DST) of clinical isolates confirmed to be *M. tuberculosis*:

1. ***Monoresistance:*** resistance to one first-line anti-TB drug only.
2. **Polydrug resistance (PDR TB):** resistance to more than one first-line anti-TB drug (other than both isoniazid and Rifampicin).
3. ***Multidrug resistance (MDR TB):*** resistance to at least both isoniazid and Rifampicin.
4. ***Extensive drug resistance (XDR TB):*** resistance to any Fluoroquinolone and to at least one of three second-line injectable drugs (Capreomycin, Kanamycin and Amikacin), in addition to multidrug resistance.
5. ***Rifampicin resistance (RR TB):*** resistance to Rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to Rifampicin, whether Monoresistance, multidrug resistance, Polydrug resistance or extensive drug resistance.
6. **Pre–XDR** TB was **defined** as TB with resistance to isoniazid and Rifampin and either a Fluoroquinolone or second-line injectable agent but not both
7. Presumptive drug resistant TB cases: these are patients without bacteriological confirmation but are highly suspected to have drug resistant TB. These include presumptive MDR TB, Presumptive XDR TB and presumptive Rifampicin resist cases

2.2. Treatment outcome definitions

The new treatment outcome definitions make a clear distinction between two types of patients:

- Patients treated for drug-susceptible TB
- Patients treated for drug-resistant TB using second-line treatment.

The two groups are mutually exclusive. Any patient found to have drug-resistant TB and placed on second-line treatment is recorded as transfred to MDR TB register in the drug-susceptible TB outcome cohort. This means that management of the standard TB register and of the second-line TB treatment register needs to be coordinated to ensure proper accounting of the outcomes of treatment.

2.2.2. Outcomes for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment

Outcome	Definition
Cured	Treatment completed with three or more consecutive negative cultures taken at least 30 days apart after the intensive phase
Treatment completed	Treatment completed BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: • lack of conversion by the end of the intensive phase, *or* • bacteriological reversion in the continuation phase after conversion to negative, *or* • evidence of additional acquired resistance to Fluoroquinolone or second-line injectable drugs, *or* • Adverse drug reactions (ADRs).
Died	A patient who dies for any reason during the course of treatment.
Loss to follow up	A patient whose treatment was interrupted for 2 consecutive months or more.
Transferred out (TO)	A patient who initiated treatment in one facility and is transferred to another to continue treatment for whom treatment outcome is unknown
Not evaluated	A patient for whom no treatment outcome is assigned and "still on treatment"
Treatment success	The sum of *cured* and *treatment completed*

Note:

For ***Treatment failed,*** lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of intensive phase of 8 months.

Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

Reversion (to positive): culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining *Treatment failed*, reversion is considered only when it occurs in the continuation phase.

2.3 Classification of category IV TB patients;

Category IV patient: This is any form of TB requiring 2nd line drugs which includes XDR, PDR, and MDR etc.)

Before enrolling a patient, for second line drugs determine whether s/he has previously received anti-tuberculosis treatment and if so, record the dates of treatment and the treatment outcome. Also record whether the patient ever previously received second-line drugs.

- **New (N)**. Patients who have never received anti-tuberculosis treatment, or who have received anti-tuberculosis treatment for less than one month. (Note: patients who had DST at the start or within one month of a WHO Category I regimen and are then switched to a Category IV regimen because of resistance are placed in this group, even if they received more than one month of Category I treatment).

- **Relapse (R)**. Patients previously treated for tuberculosis that has been declared cured or treatment completed, and then diagnosed with MDR-TB.

- **Return after loss to follow up.** Patients who return to treatment with confirmed MDR-TB after interruption of treatment for two months or more.

- **After failure of Category I treatment (FFT)**. Patients who return after having failed the first treatment.

- **After failure of Category II treatment (FRT)**. Patients who return after having failed the re-treatment.

- **Transfer in (TI)**. Patients who have been transferred from another register for treatment of drug-resistant TB to continue Category IV 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.

- **New extra pulmonary**. Patients who have never received anti-tuberculosis treatment, or who have received anti-tuberculosis treatment for less than one month with tuberculosis of organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

2.4 Causes of Drug Resistant TB

The main cause of drug resistant TB is a mycobacterial characteristic. Mycobacteria's genetic machinery is programmed to mutate at a certain rate and still keep on growing, enabling them to survive otherwise effective anti-TB drugs. Other causes include:

- Health care providers: Inadequate regimen
  - Inappropriate guidelines
  - Noncompliance with guidelines
  - Absence of guidelines
  - Poor training
  - No monitoring of treatment
  - Poorly organized or funded TB control programmes

- Drugs: Inadequate supply or quality
  - Poor quality
  - Unavailability of certain drugs (stock outs or delivery disruptions)
  - Poor storage conditions
  - Wrong dose or combinations

- Patients: Inadequate drug intake

- Poor adherence (or poor DOT)
- Lack of information
- Lack of money(no treatment available free of charge)
- Lack of transportation
- Adverse effects
- Social barriers
- Malabsorption
- Substance dependency disorder

2.5 Case finding strategies

The program will enrol patients from the high risk groups for MDR TB. The diagnostic tool for MDR TB is DST and this will be used selectively for the patients highly suspected to be having MDR TB.

All health care workers should send sputum specimen from all the suspected DRTB cases and to the nearest DST centre (this includes GeneXpert). The sample collected should reach the lab within 3 days others wise it should be refrigerated. Spillage should be avoided. The sample should be well labelled and accompanied by a fully and accurately filled GeneXpert culture request form.

The DST centres have the capacity to carry out rapid molecular testing using GeneXpert or LPA and the results obtained within 24-48 hours. The results will then be communicated by phone, email, and the hard copy sent by courier or any other available method

Chapter 3 Diagnosis of DR TB

DR TB should be suspected in a patient who has had previous exposure to anti TB drugs e.g. re-treatment cases and clinically when a patient has a persistently positive acid-fast bacilli smear or culture or clinical progression of tuberculosis while on standard therapy. DR TB may also be suspected epidemiologically when a patient is known to have had contact to a person with MDR TB.

The only way to confirm the diagnosis of DRTB is to perform drug-susceptibility testing (DST). Performing DST in all suspected patients before treatment using a rapid test that detects resistance Rifampicin and Isoniazid or Rifampicin alone is the best strategy for averting deaths and preventing acquired DR-TB.

3.1 Selecting patients to undergo drug-sensitivity testing

- In Kenya, patients in whom DR TB is suspected should have their sputum sent for GeneXpert as the first test. Any sample found to have TB should be followed by a culture and susceptibility testing. Any patient with Rifampicin reistance of is MDR TB should then undergo a secondline DST.
- The following is a list of suspected patients for whom GeneXpert, culture and DST should be performed based on the GeneXpert algorithm (MDR TB Surveillance algorithm).
    - Patients who remain or turn positive after 2 months of TB treatment.
    - Patients previously treated for TB (relapses, loss to follow up, failures)
    - Patients who have a contact with known MDR TB
    - Patients who had contact with anyone who died of TB.
    - Hospital and health care workers with symptoms of TB.
    - Refugees with signs of TB
    - TB patients from countries with poorly operating program or no program
    - Patients who develop TB while on IPT

3.2 Samples for DST

- Pulmonary

Sputum, Bronchoalveolar Lavage Fluids, Bronchial Washings & Brushes

- Extra-Pulmonary

Fluids (Synovial, Pleural, Peritoneal, Paracentesis, Pericardial, Ascites, dialysis fluid, Laryngeal Swabs & Aspirates, Stool, Urine, Tissue, Lymph Nodes, Bone, Biopsies, etc. etc. etc.

Blood (whole blood in Heparin), Bone Marrow, CSF (2-3 ml), Gastric wash/ lavage (Na Carbonate to neutralize if <1 hr.)

Gene Xpert can be used for the above samples

3.3 Specimen Collection, Transport and Referral

Collection of sputum specimens should be done in the early morning in an open space away from people or in sputum collection booths. The specimen should be put into a sterile falcon tubes (or any other appropriate sterile collection) bottle, which should be tightly screwed and protected from sun light (UV light) by placing it in a dark thick envelop or appropriate transportation containers as shown below in Figure 1. The recommended packaging is to put the specimen container (primary container) in secondary and tertiary containers.

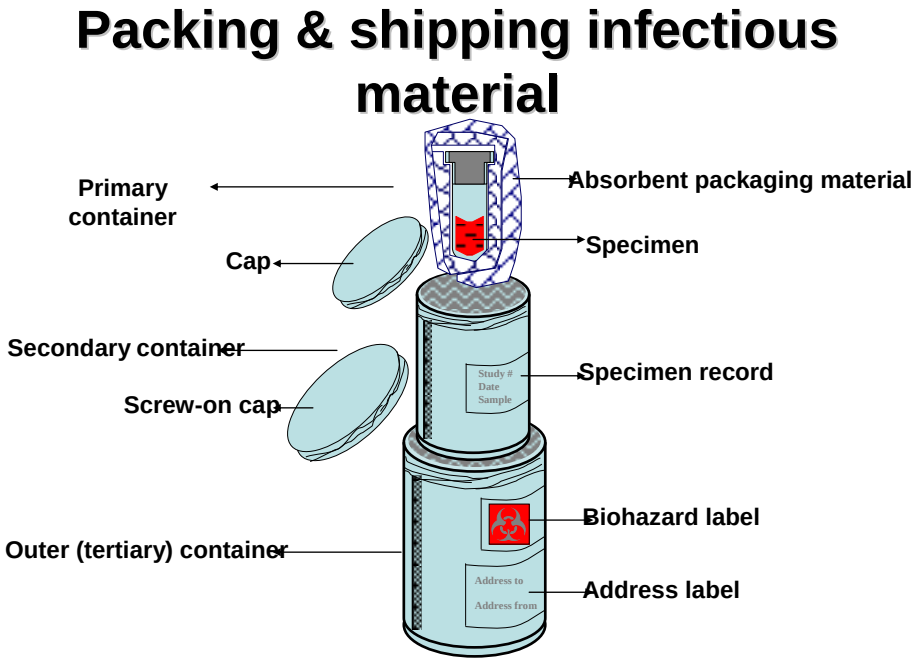


Figure 1: Packing of samples

Sputum culture and DST is done in the TB Central Reference Laboratory and other decentralizes culture laboratories.

3.3.1 Materials:

- A sterile rigid wide-mouthed screw-capped 25 -50ml sputum/Sterile Falcon Tube container made of strong transparent plastic
- Marker pens
- Gloves
- Lab coats/gowns
- Request forms
- JIK/5% phenol
- Heavy duty transport plastic box with lid for transporting sputum specimens to the referral lab
- Cetylpyridinium chloride
- Sodium Chloride (NaCl)
- Distilled water/filtered rain water

3.3.2 Sputum Collection

- Make collection convenient and efficient for both patient and lab worker
- Sputum specimens should never be collected in the laboratory or enclosed room
- Sputum specimens should therefore be collected in the open air, as far away as possible from other people
- Health workers should wear laboratory coats/gowns and gloves when handling specimens
- Clearly demonstrate and instruct patients on proper collection of specimen
    - suitable wide-mouth containers should be used
    - how to open and close the sputum containers
    - the need for collecting real sputum, not saliva
    - how to produce good sputum (i.e., by repeated deep inhalation and exhalation of breath followed by cough from as deep inside the chest as possible)
    - how to avoid contamination of the exterior of the container (i.e., by carefully spitting and closing the container)
    - how to collect and safely deliver the morning sputum Good quality
    - specimen should be 3-5 mL, thick and mucoid
- After collecting the specimens, remove gloves and wash hands with soap and water
- Disinfect spills with disinfectants (i.e. JIK/5% phenol)
- The SUB COUNTY TLC (SCTLC)• /DMLT will label specimen container on the side (not on the lid), with the name of the patient, date and time of collection and complete the request form
- Store specimen for processing or package specimen as per local guidelines

3.3.3 Specimen Transport

- Diagnostic specimens must be packed to withstand leakages of contents, shocks, pressure changes and other conditions incident to ordinary handling practices.
- Package sputum specimens in a double container in a plastic/biohazard bags and place in a vertical position to avoid leaking in a transport box (? cool box)
- Securely fasten the lid of the box
- Keep request forms separately in a plastic bag or preferably in biohazard bag.

- Prepare an accompanying list, which identifies the specimens and the patient from whom the specimens were collected, with each transport box.

3.3.4 Specimen Referral

For centres without microscopy consider the following:

- Patient referral
- Specimen referral
- Smear referral

Follow the local guidelines or consult with referral laboratory

3.4 When sputum should be collected for XPERT MTB/RIF/, Culture & DST?

Contacts

- Immediately a history of contact with a DRTB patient is elicited
- One found to have TB symptoms during contact tracing of a DR TB patient
- Before initiation of CAT 1 treatment

New Smear positive

- Before initiation of CAT 1 treatment if:
  - A contact to drug resistant TB case or someone with chronic cough
  - A Refugee
  - HIV positive
  - Patient on IPT who develops TB

  At month 2, 3, 4, 5 of treatment if still smear positive

New Smear Negative

- A contact
- HIV positive

Relapse

- Prior to initiation of retreatment regimen

Retreatment case

- Prior to initiation of retreatment regimen
- At month 2 of treatment or after if the sputum prior to treatment was not taken

NB: Children who can produce sputum will however be subjected to Xpert MTB/RIF for diagnosis of TB and if they are contacts, they should be screened for Rifampicin resistance.

HIV positive with TB symptoms after screening with TBICF/IPT tool*[1] prior to TB treatment initiation

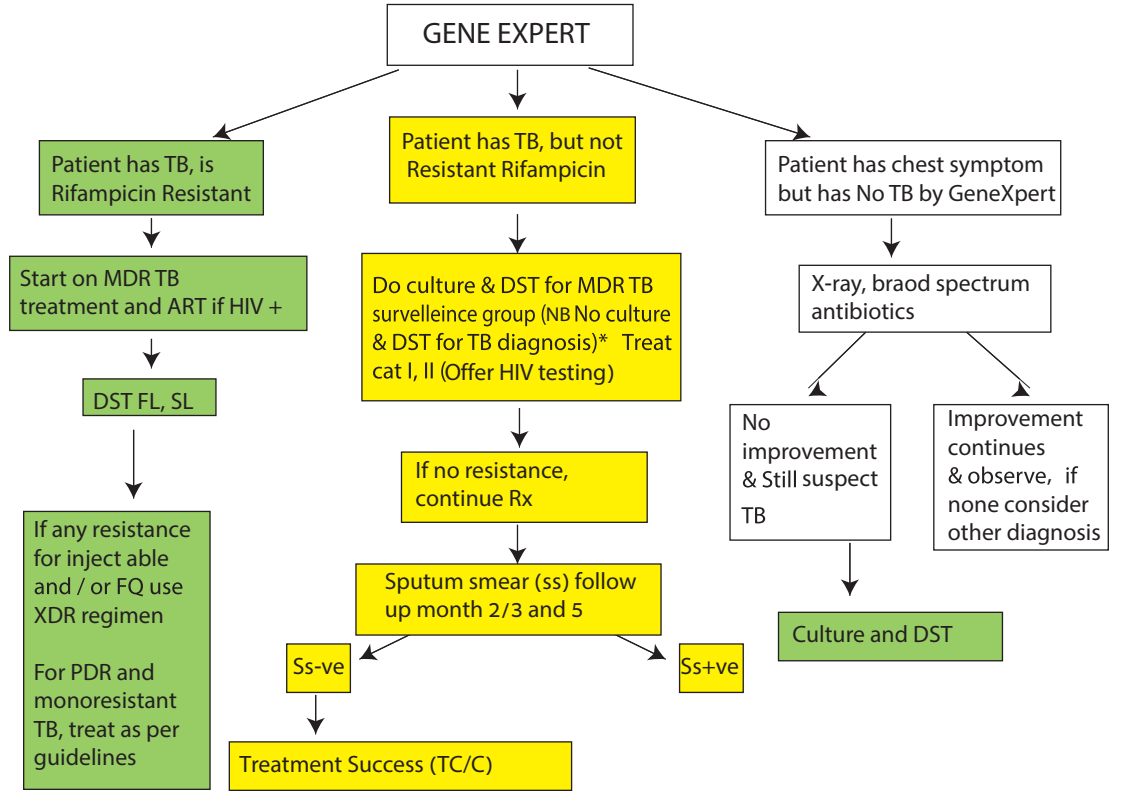
Children under 15 years with TB symptoms * - prior to initiation of TB treatment

Figure 2 DR TB Diagnosis and surveillance algorithm

MINISTRY OF HEALTH

National Tuberculosis, Leprosy and Lung Disease Unit (NTLD)

GENE EXPERT ALGORITHM



Indicators for GeneXpert

MDR TB Surveilleince

All treatment cases: a) Failures b) Relapses C)Return after default
DR TB contacts
Smear positive Refugees
Smear positive after months 3 of treatment

TB Diagnosis*

HIV positive Smear negative, Diagnosis of TB in children

3.5. Organization and development of the laboratory network

The laboratory network has a pyramidal structure based on a large number of Level I laboratories accessible to all TB suspects and patients, a moderate number of Level II laboratories located in mid-sized population centres and health facilities and a few (or even a single) apex Level III laboratories at the county, regional or national level.

In the public sector CRL, Moi Teaching and Referral Hospital, KEMRI and HomaBay carry out both culture and DST while in the private sector several hospitals have the capacity to do culture and DST. All these laboratories are supervised by the CRL.

3.5.1. Regional Labs

Selected laboratories from all regions will be upgraded to perform cultures and DST.

Samples will be referred to these laboratories from sites performing GeneXpert and LPA testing.

3.5.2. Quality Assurance

Diagnostic TB microscopy laboratories have been strengthened to provide quality work by participating in both internal quality control and external quality assurance (IQC & EQA)
All labs performing cultures do internal quality control by including H37RV in their routine cultures. CRL oversees External Quality Assurance (EQA) activities of the labs performing cultures. Links between National Reference Laboratories (NRL) and Supra reference labs (SRL) have been strengthened to ensure quality of culture and DST laboratory services and validation of DST for both first line and second line drugs.

3.6 Diagnosis of DRTB in children

- Clinical features and chest radiography do not distinguish DS from DR/MDR TB.
- DR TB is a microbiological diagnosis - Only confirmed if MDR *M. tuberculosis* strain is isolated from a child (Often difficult):
- Obtain specimens from all possible sources for GeneXpert, culture and susceptibility testing.
- Known contact with an adult MDR PTB case: Child contact probable MDR TB

- If the child is a contact of
  - ✓ An adult with infectious DR tuberculosis; or
  - ✓ A source case who is a retreatment case (especially treatment after failure) with unknown drug susceptibility, or who is a contact of DR-TB
- if the child, while adhering to treatment *:*
  - ✓ responds unsatisfactorily or deteriorates, or
  - ✓ relapses shortly after completing or
  - ✓ If the community in which the child resides (or had resided) has a high prevalence of drug-resistant tuberculosis.

Chapter 4 Infection prevention and control

4.1. Prevention

MDRTB development can be prevented by implementing a high quality DOTS plus program but if MDRTB cases occur despite this, there is need to contain such cases through proper and adequate treatment. Detailed infection control measures should be put in place wherever DR-TB patients are treated. The DRTB patients should not be mixed with other patients, more so HIV infected patient population.

4.2. Components of TB infection control in the health facility

4.2.1. Administrative Controls

These are the most effective and least expensive measures and thus are of high priority in resource limited settings. They comprise policies and procedures intended to promptly identify infectious TB patients (smear positive) by same day sputum examination and initiation of treatment of infectious cases to reduce exposure to close contacts.

TB infection control policies and procedures include:

- The establishment of an infection control committee
- Appointment of an **infection control officer**
- Formulation of an **infection control plan** which should be made known to all health care providers in the facility
- **Physical separation of patients** suspected or known to have TB including those with DRTB from other patients especially those patients who are immuno-compromised. (Isolation wards / rooms / one section of the waiting bay or ward) and

The **triaging of patients** with chronic cough (two or more weeks) should be done in the outpatient department to hasten TB screening. In patients with cough should be screened for TB. Patients who have had TB in the past (i.e., high risk of MDR) should wait in a different location than new TB cases with no risk factors for MDR TB.

- Diagnostic tools for TB (request forms, sputum mugs) should be freely available in all departments.

Table 1 Steps to prevent TB transmission in HIV

Five steps for Patient Management to Prevent transmission of TB in HIV Care Settings	
Step	Action
1	**Screen for TB in all confirmed or suspected HIV patients**
2	**Educate on cough etiquette**
3	**Separate patients suspected of having TB**
4	**Investigate for TB or Refer**
5	**Provide HIV care services**

Key interventions for the prevention against hospital transmission of tuberculosis

1. Cough for 2 weeks or more may indicate PTB
2. Contacts of Smear positive PTB patients must be diagnosed immediately
3. It is safer to diagnose PTB in OPD than in the wards
4. Sputum specimen must be collected as soon as possible, within 24 hrs.
5. Sputum smear results must be communicated to the responsible clinician as quickly as possible.
6. Windows in the wards where PTB suspects or patients are managed should be left open during the day.
7. PTB suspects must be taught cough etiquette (to cover their mouth when they cough).
8. PTB patients should wear masks when going to theatre
9. X-ray examinations for PTB suspects and patients should be scheduled for those times when the X-ray department is not busy.

4.2.2. Environmental /Engineering controls

These measures reduce transmission of TB in the hospital by reducing the concentration of infectious droplet nuclei in the air. They include natural and or mechanical ventilation; use of high efficiency particulate air filtration **should not replace administrative controls.**

1. Ventilation

Natural ventilation is the least expensive environmental measure. Transmission is less outdoors and therefore TB suspects and patients should be encouraged to spend most of the day time outdoors. Special comfortable sheds which maximize on natural ventilation and sunlight should be promoted for outpatient departments with a high burden of TB suspects and patients.

Adequate ventilation inside health facilities should be a priority. The use of extraction fans, which work properly, to improve ventilation, may be used in facilities with large number of DRTB patients are cared for.

Ventilation may be supplemented by upper room Ultraviolet Germicidal Irradiation (UVGI) which may also be used in ventilation ducts or in fan driven air sterilizing devices mounted on ceilings, walls or portable units that can be moved from room to room. **These measures are however expensive and are not be routinely available in Kenya.**

4.2.3 Personal respiratory protection

The usual surgical masks are relatively loose fitting and are made of paper or cloth. They are not adequate for prevention of TB infection but can be used by the DRTB patients. Particulate respirators (e.g. the N-95 mask) on the other hand are designed to protect the wearer from tiny (1-5 µm) airborne infectious droplets. These respirators should fit well individual wearers. Health care workers, patients, visitors and care givers should wear masks at all times during consultations or when at DRTB care zones

4.2.4. Care of the health worker

- HIV infection predisposes individuals to getting tuberculosis. It is advised that health care workers who are HIV positive or who suspect they may be HIV positive should not work in high risk TB areas. All health care workers should be encouraged to know their HIV status.
- HCWs need to be educated on DRTB and TB IPC.
- All staff working in TB clinics should be provided with respirators i.e. N95 masks.
- Staff in health facilities are encouraged to go for periodic TB screening and HIV testing.

4.2.5. Laboratory Considerations

The laboratory should process sputum samples as quickly as possible. It is preferable that a same day sputum smear microscopy service is established in every hospital to allow for a rapid turn around of sputum smear results. Results of smear positive cases must be communicated as quickly as possible to the clinicians managing the patient. In particular, staff must ensure that smear positive results from **"in patients"** are forwarded to the wards as soon as the results are known.

4.2.6. Other High Risk areas

1. The x-ray department

It is preferable to schedule radiological procedures for suspected or confirmed infectious TB at a time when the x-ray department is not busy with other patients. Radiology departments should be encouraged to provide separate waiting areas for TB patients and suspects.

2. Minor Theatre

All TB patients who come for chest drains, biopsies and other TB related procedures should wear surgical masks while in the minor theatre.

Staff working in the minor theatre should use respirators while handling TB patients.

4.3. Role of the TB / Infection Control Officer

Health facilities should appoint one or more health care workers as the TB coordinating officer. This officer(s) should coordinate infection control measures (including those for TB control) in the health facility including triage, diagnosis, treatment, separation / isolation, case recording and reporting, recommending and installation of environmental measures and to ensure that the logistics, required for infection control in the health facility are working optimally.

4.4. Prevention and control of TB transmission within the community

Awareness on reduction of TB transmission in the community should be enhanced through early identification of TB suspects and referral for follow-up in the health care setting.

Health education should be given to patients, family and community on the signs and symptoms of TB disease and the need to support patients on treatment so that they complete their regimens effectively to avoid various drug resistances.

The DRTB patients should be advised to spend as much time as possible outdoors, sleep in a separate bedroom at home, to wear the ordinary masks when receiving visitors, to practice cough etiquette, use sputum mug and dispose of the mugs in pit latrines. Where sputum mugs are not available, locally available containers with fitting lids should be used.

Due to HIV TB co infection the community should be encouraged to go for HIV counselling and testing. Contacts of DRTB patients should also be screened for TB and HIV.

4.5. Infection control measures in congregate settings

There are special settings in the community that are of high risk and call for special attention as far as TB infection, prevention and control is concerned. Structures and buildings in congregate settings should comply with national norms and regulations for public buildings, and should meet the design criteria for sufficient ventilation. These places include;

- Prisons and remand cells
- Informal settlements (slums)
- Refugee and internally displaced persons (IDP) camps
- Learning institutions (schools, colleges)
- Security forces training camps (military, GSU, police national youth service etc.)
- Public transportation
  - Matatus, buses and trains
  - Air transport

TB is spread more readily in congregate settings such as prisons, remands, informal settlement and public transport. This is because of the long duration of potential exposure, crowded environment, poor ventilation, and limited access to health care services.

4.5.1. Prisons and remand cells

All inmates on admission should be screened for TB. The prison and remand cell should follow and implement TB infection control guidelines. There is need for active advocacy and sensitization of the relevant ministry and departments for the implementation of TB infection control guidelines in prisons.

4.5.2. Informal settlements (slums and refugee camps)

To reduce TB transmission in the informal settlement: - there is need to have adequate sensitization, advocacy on proper ventilation of existing structures/ housing, practice cough etiquette. The implementation of community TB infection control guidelines should be emphasized. Screening, contact tracing and defaulter tracking should be highly emphasized in such settings.

4.5.3. Learning institutions and security forces training camps

Learning institutions and training camps should embrace TB infection prevention and control guidelines. TB infection prevention and control should be incorporated in the school health program. Learning institutions and training camps should adopt and own TB environmental measures and UVGI.

4.5.4. Public transportation

TB infection control guidelines should be implemented in public transport sectors. There should be adequate ventilation by opening windows on both sides of the vehicles or applying mechanized ventilation. Advocacy and sensitization with different ministries and the community is required for this to succeed. Airline services should implement TB Infection control guidelines. Transportation of suspected MDR-TB Patients from one facility to another should be by well ventilated means of transport with personal respiratory protective devices.

Chapter 5 Treatment of Drug Resistant Tuberculosis

Any patient with chronic or DR-TB requiring treatment with second-line drugs falls under WHO treatment category IV and will require specialized regimens (termed "Category IV regimens" in these guidelines)

5.1 Classes of anti TB drugs used in management of DR-TB

5.1.1. Drugs used for treatment of drug-resistant tuberculosis

The drugs used are classified into 5 groups based on their efficacy, experience of use and drug class. These groups are shown in the table below.

Table 2. Drugs for treatment of tuberculosis

First-line	**Second-line**			**Third-line**
Oral	**Injectable**	**Quinolone**	**Other 2nd-line**	**Other agents**
Rifampicin	Streptomycin	Levofloxacin	Prothionamide	AMX/CLV
Isoniazid	Kanamycin	Ofloxacin	Cycloserine	Clofazimine
Ethambutol	Amikacin	Moxifloxacin	Terizidone	Clarithromycin
Pyrazinamide	Capreomycin		PAS	Linezolid

5.2. Treatment strategies For MDR-TB

Considerations When Designing a Treatment Strategy

MDR treatment requires a combination of drugs from various groups as listed in the table 2 above. The decision on which drugs are to be used to treat the DRTB and on which the Kenya Standardised regimen was constructed is based on;

- the available national anti-tuberculosis drug resistance survey data,
- the extent of use of anti-tuberculosis drugs in the country,
- prevalence of drug resistance in the different categories of tuberculosis patients,
- the availability of 2nd line of anti-tuberculosis drugs and
- the frequency of their use in the country

5.3. Kenya MDR TB Regimen

5.3.1. Treatment of MDR-TB in Kenya

NTLD- Unit will make every effort to ensure that access to prompt treatment for MDR-TB is available. While awaiting treatment, thorough IPC measures should be taken. Malnourished patients should receive nutritional therapy, to retard disease progression. Active contact tracing should be initiated as soon as the DR-TB diagnosis is made

In Kenya the treatment for MDR-TB is generally based on a **standardized regimen.** However **individualized regimen** is used in some special situation based on individual resistance pattern of the infecting strain. In the event this is required, the decision should be made by a medical doctor in consultation with the TB coordinators and the PMDT team.

Standardized regimen is as the follows:

8 Km-Pto-Lfx-Cs-Z / 12 Pto-Lfx-Cs-Z

- The number shown before each phase stands for the duration of time in months and is the minimum recommended time the phase should last.

PAS can be substituted for PTO or Cs in case there is intolerance, contra-indication (including pregnancy) or resistance to any of them.

5.3.2. Surgical management

In specific cases surgery can be used as additional management of MDR-TB especially in cases of lung fibrosis but there has to adequate healthy lung tissue remaining, i.e., when the disease is localized to one lobe or to one lung or in some cases of EP DR-TB, e.g., TB of the spine.

5.3.3. Duration of Treatment

The duration of treatment is guided by smear and culture conversion. The minimum recommended duration of treatment is 20 months or 18 months after culture conversion. The treatment consists of two phases as follows;

I). Intensive Phase

This lasts for a minimum of 8 months, and should continue 4 months after sputum conversion or at least 3 consecutive negative culture results. The following drugs are recommended:

a) Inj. Kanamycin [Km]
b) Tabs Prothionamide [PTO]
c) Tabs Levofloxacin [Lfx]
d) Tabs Cycloserine [Cs]
e) Tabs Pyrazinamide [Z]

The regimen being **– *8Km-Pto-Lfx-Cs-Z***

ii). Continuation Phase –

This lasts for 12 months and uses the following drugs:

a) Tabs Prothionamide [PTO]
b) Tabs Levofloxacin [Lfx]
c) Tabs Cycloserine [Cs]
d) Tabs Pyrazinamide [Z]

The regimen being 12Pto-Lfx-Cs-Z

5.3.6. Extra-pulmonary MDR-TB Treatment

The treatment strategy is the same as in patients with pulmonary MDR-TB. Monitoring by the clinical team should be done on a monthly basis. If patient is able to give sputum, it is recommended to perform sputum follow-up as well.

5.4. Treatment of Extensively Drug-Resistant Tuberculosis (XDR-TB)

XDR-TB is a public health emergency that requires prompt diagnosis and treatment, appropriate isolation, and aggressive contact tracing. While cure rates for XDR-TB are lower than for MDR-TB, XDR-TB is a curable disease.

All XDR-TB patients should receive an individualized treatment regimen. The regimen should include an injectable agent, a higher generation Fluoroquinolone, and drugs from Groups 1, 4 and 5 to which the isolate is known or suspected to be susceptible. An effective regimen should contain at least five effective drugs. The use of new drugs such as Bedaquiline should only be used after the National MDR TB clinical team has agreed on it and minutes of the same availed.

While treatment should be individualized, the following empiric regimen is recommended in cases where first and second line DST is not yet available:

- Intensive phase: 12 months of CM-Mfx-PAS-Cfz-Amx/Clv
- Continuation phase: 18 months of Mfx-PAS-Cfz-Amx/Clv

Include Groups 1 and 4 drugs thought to be effective (strain still susceptible). Clofazimine can be used for the duration of the regimen if extensive disease is present and if the drug is tolerated.

NB :Patients with Streptomycin TB monoresistance should be treated using first line medicine

*Patient with RR Resistance are **NOT** all MDR TB BUT should be treated using the MDR TB regimen apart from XDR TB and Pre XDR TB whose regimen are individualised.*

5.5 Patients diagnosed with mono and poly-drug resistant TB

Pattern of drug resistance	Regimen	Duration of treatment
H (± S)	R/Z/E/LFX	9 months
H, E, Z (± S)	3Km-Lfx-R-Z/ 15 -Lfx-R—Z**	18 months
H and Z	3Km-Lfx-R-Z/ 15 -Lfx-R—Z**	18 months
H and E	3Km-Lfx-R-Z/ 15 -Lfx-R--Z**	18 months
R	8 Km-Pto-Lfx-Cs-Z / 12 Pto-Lfx-Cs-Z*	20 months
R and E (± S)	8Km-Pto-Lfx-Cs-Z/* 12 Pto-Lfx-Cs-Z	20months
R and Z (± S)	8Km-Pto-Lfx-Cs-Z/ 12 Pto-Lfx-Cs-Z*	20 months

5.6. Treatment for contacts of MDR-TB patients

Active contact tracing is a cornerstone of DR-TB control. All household and other close contacts of an MDR or XDR patient should receive prompt and thorough screening including clinical evaluation for signs and symptoms of TB disease. If signs and symptoms are present, a chest X-ray should be performed and sputum sample collected. Young children and HIV-positive contacts should receive a chest X-ray even if they are asymptomatic.

Close monitoring of all household and other close contacts of MDR TB patients is needed. If active TB develops in a contact of a known DR-TB patient, culture and DST should be done as soon as possible. In areas where rapid DST testing is not immediately available, the contact patient should receive empiric second-line treatment based on the index case DST. The regimen may be adjusted when DST results are available. The patient should be started on an empiric

MDR regimen and another sample collected for DST. If Isoniazid is still sensitive it should be introduced and Cycloserine withdrawn. Consider a patient's previous drug history between the time of sample collection and results being received before starting the patient on the recommended regimen.

5.7. Special situations

5.7.1. Management of MDR-TB patients in prison

The same guidelines have to be used in terms of treatment regimens. Treatment centres on site are needed. Special nutritional support has to be added. Infection control in prisons should include policies that an MDR-TB patient cannot share a cell with other prisoners. A separate isolation ward is needed.

Contact tracing in prison includes theoretically all other prisoners. All prisoners who are symptomatic should undergo sputum smears, cultures, DST and CXR.

5.7.2. Management of MDR-TB patients in refugee camps

The same guidelines have to be used in terms of treatment regimens. Onsite treatment has to be made available. Entire treatment should be coordinated by NTLD -UNIT. Should the camp close, NTLD -UNIT, IOM/UNHCR shall ensure continuation of treatment.

5.7.3 Cross border patients

There is a need to establish cross border initiatives to facilitate treatment of patients that seek treatment in a neighbouring country. MDR TB among the refugee populations will be managed in the refugee camps as per the guideline

5.8. Management of MDR-TB patients who are HIV co-infected

When a patient is newly diagnosed with both HIV and MDR-TB, the MDR-TB regimen should be started first. Cotrimoxazole and fluconazole prophylaxis if needed should be started together with the start of the MDR regimen. ARVs should be initiated 2-8 weeks after starting DR-TB treatment irrespective of the CD4 count. For patients receiving Rifampicin (i.e., Polydrug resistance), nevirapine should be avoided. The preferred regimens are AZT/3TC/EFV or

ABC/3TC/EFV. If TDF is given in the intensive phase of MDRTB treatment, monitor regularly Creatinine levels due to potential additive nephrotoxic side effects with the injectable.

5.9 Treatment delivery and adherence

5.9.1. Patient care

All centres managing MDRTB should have in place an MDR TB clinical management team. The DR-TB management team should discuss new patients prior to treatment initiation, and meet regularly to discuss challenges during treatment. Such challenges may include side effects, pregnancy, poor adherence, psychosocial barriers and other issues. The management committee should visit the home before initiation treatment.

All the doses for second line should be observed by the health care worker and confirmed as swallowed by asking the patient a question. Adequate staffing is recommended to ensure success of the program.

MDR-TB patients should be monitored closely for clinical and bacteriological progress and any emergence of adverse drug effects and appropriate actions taken.

Patient and family support should include food, transport, non-TB drugs, and investigations. The social support should be provided directly to the patients in order to ensure the money reaches the ones who need it. All MDR- TB patients, their families and communities require health education, including stigma reduction.

5.9.2. Treatment delivery and adherence

Treatment of MDR-TB should aim to ensure maximum adherence. The prevention of non – adherence and default from treatment should be emphasized, as it's more important than default retrieval measures. It is important to understand that many patients with MDR-B may have been non-adherent to previous treatment and could become non-adherent to current treatment if not strongly supported. To prevent non adherence and default from treatment the following measures are essential:

1. Education/ counselling of patients

All patients with MDR-TB and their families should receive education and counselling about MDRTB, its treatment, duration, potential adverse drug effects and the need for adherence to treatment throughout the period of treatment. This can be done by health care workers (clinicians, nurses), lay health care workers, community health care workers and current or former TB patients. Interpersonal Communication, the most effective way of communication, should be used to educate patients and their families complimented with use of IEC materials including pamphlets and brochures in various languages.

2. Assessment for risk factors for non-adherence

All patient must be assessed for risk factors for non-adherence to treatment, including poor social circumstances (e.g. severe poverty or homelessness), drug and alcohol abuse, nutritional barriers (lack of food), non-facilitatory work schedules, drug adverse effects, denial of disease state and other adherence barriers including distances from health delivery points. Any identified factor(s) that may impact on adherence should be addressed. This may include the provision of incentives and enablers including food, shelter, transport, and psychological support (counselling and peer support.)

5.9.3. Treatment delivery settings

During the initial phase of MDR-TB treatment, therapy will mostly be delivered in a hospital/clinic setting (the MDR-TB treatment centre) because of the need for daily injections. However it is possible to deliver the same treatment at home through community nurses, a treatment delivery mechanism that may reduce the risk of hospital transmission of MDR-TB and which may be inexpensive for the health care system and the patients.

In ideal setting patients who are smear or culture positive MDR-TB should be managed in an isolation facility, meeting all infection prevention and control measures as per WHO recommendations. Patients who have converted can be managed on ambulatory basis or through home based care.

In case of shortage of beds in, the isolation facility, priority should be given to patients who develop drug side effects/adverse reactions.

PDR patients who need hospitalization should be isolated separate from the MDR TB - patients. XDR-TB patients **SHOULD NOT** is mixed with MDR, PDR, or other TB patients.

5.9.4. Direct Observation of Therapy (DOT):

All doses of MDR-TB medicines will be directly observed by HCW (DOTS-plus). *The choice of DOT observer should be agreed with the patient and or his/her family. The DOT observer may be a health care worker, a workmate, a family member or a community volunteer who should make every effort to accord the patient respect and dignity and maintain confidentiality. DOT providers/observer should receive appropriate training on DR-TB treatment and side effects, TB infection prevention control, and the importance of adherence.*

5.9.5. Default Retrieval

A clinic attendance register should be maintained in every centre treating MDR-TB patients. This will facilitate the identification of treatment defaulters. Every effort should be made to trace patients who default from treatment. The skills of social workers, community health care workers and volunteers should be used to assist with defaulter tracing.

5.10 Patient Monitoring

5.10.1 Initial evaluation and monitoring of treatment

Pre-treatment screening and evaluation is done to ensure a baseline for this treatment and to identify patients who are at risk of increased incidence of side effects

Table 4 Monitoring and evaluation

Monitoring Evaluation	Recommended frequency
Evaluation by Clinical team	At baseline, monthly until conversion, then every 2-3 months
Screening for side effects by DOTworker	At every DOT encounter
Weight	At baseline and monthly
Sputum smear and cultures	Baseline,, then monthly smears and cultures till end of treatment
DST 1st and 2nd line	Baseline and at 6 months. DST should also be done anytime there is a positive culture in a previously culture negative case 2nd line DST should be done for all MDR TB patients
CXR	At baseline then 6 monthly
Hemogram	At baseline then at month 3 and 6, then 6 monthly (or when necessary)
Serum Creatinine	At baseline then monthly while on injectable drug (and when necessary)
Serum potassium, Magnesium	At baseline, then one week, then monthly while on the injectable agent (or when necessary)
Serum calcium & magnesium	At baseline then monthly while on the injectable agent (or when necessary)
TSH	At baseline then 3 and 6 months, then 6 monthly if on Ethionamide/ Prothionamide / PAS Monitor clinically monthly for hypothyroidism
ALT	At baseline then 1-3 monthly if on Pyrazinamide
HIV screening	At baseline and if clinically indicated
Pregnancy test	At baseline for women of child bearing age; repeat if indicated. Family planning methods should be offered to all woman of reproductive age undergoing DR-TB treatment.
Audiometry	At baseline then monthly while on Injectable

Table 5: Laboratory and Clinical Follow up for patients on treatment for MDR TB and HIV

Month	Baseline	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21
Clinical review	X	Every 2 weeks	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**
Audiometry	X	X	X	X	X	X	X	X	X							
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Smear	X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly till treatment completion		
Culture	X	X	X	X	X	X	X	X	X	X	X	X	X	Monthly till treatment completion		
DST	X						SLD DST									
LFTs (AST, ALT, Bilirubin)	X	X	X	X			X			X			X	X	X	
Creatinine Potassium, Magnesium	X	X	X	X	X	X	X	X	X							
Full Hemogram	X			X			X						X		X	
CD4	X						X						X		X	
CXR	X						X						X		X	
TSH	X		X				X						X			

Key:

- SLD DST: Second line DST; it should be done at the beginning of treatment. It should also be carried out if a culture negative patient turns positive.
- Liver function and renal function tests may be done at any time as clinically indicated
- Patient's height should be taken at baseline in adults and monthly in children. BMI should be calculated monthly
- Hemogram (HB) in a patient on Zidovudine (AZT) should be carried out at baseline, 4, 8 and 12 months

5.10.2. Sputum conversion while on second line treatment

Sputum conversion is when sputum for a patient who was smear / culture positive is found to be negative by the same procedure/s. It is a guideline on when to stop intensive phase and stop isolation. Intensive phase in MDRTB treatment will last up at least 8 months and until three consecutive negative cultures taken 30 days apart are obtained. This is equivalent to 4 months after culture conversion. Also both smear and culture results are used to monitor patients' progress throughout treatment and as indicators of program performance

5.11. Management of patients failing MDR-TB treatment

While treating MDRTB some unfavourable outcomes are anticipated, including treatment failures and the presence of extensively drug resistant TB (XDRTB). When this happens**,** the following steps are recommended:

1. Review the treatment card and assess adherence to determine if the patient is receiving all the right drugs and doses.
2. Review the treatment regimen in relation to medical history to determine if the patient may have been re-infected during the course of treatment.
3. Review all DST reports to determine the adequacy of the regiment and consider an alternative regimen where possible.

5.11.1. Signs indicating Treatment failure:

- Persistent cultures and positive smears past 6 months of treatment
- Progressive extensive and bilateral lung damage confirmed on X-Ray with no option for surgery.
- Worsening patient's condition usually including weight loss and respiratory insufficiency

Caution:

Please note that occasionally patients have a positive smear with negative cultures. It is important to appreciate that it may be caused by the presence of dead bacilli and hence does not necessarily indicate treatment failure. Such cases should be discussed with the DR-TB clinical management team.

In patients with repeated negative culture and smear results and no corresponding clinical and radiological improvement, then consider other diseases other than MDR-TB.

5.11.2. Suspending Therapy:

Treatment should be suspended when it is confirmed that all the drugs have been administered and there is no possibility of adding other drugs or carrying out any surgical intervention. At this point, supportive care regimen is considered. The 2 most important considerations to suspend therapy and consider supportive care are:

- Patient's quality of life: continued use of the failing regimen can cause additional suffering without any benefits
- Public health concern**:** Continuing with the failing regimen can amplify resistance in the patient's strain and hence subsequent infection in the public.

This decision to suspend treatment should be made by the MDR-TB management team.

Prepare the supportive care plan for the patient after consensus with the patient and the family members. This may include pain relief, management of respiratory insufficiency, nutritional support, and regular medical visits-particularly psychosocial support, home nursing care, prevention and infection control measures as these patients normally remain infectious for a long time.

Chapter 6 Treatment under special conditions

6.1. Treatment of Drug Resistant TB in Special Conditions and Situations

Drug resistant TB may coexist with any number of medical problems and thereby present clinical challenges in the management of both diseases. These challenges include increased risk of drug toxicity, alterations in drug metabolism or pharmacokinetics that requires dose adjustment, multiple drug therapies leading to drug-drug interactions etc. These co-morbid conditions often require high level of clinical expertise and therefore early cross referrals with relevant clinicians with this expertise where feasible is highly recommended. Some common clinical conditions that may co-exist with TB include pregnancy, breastfeeding, contraceptives, drug resistant TB in Children, diabetes mellitus, renal insufficiency, liver disorders, seizure disorders, psychiatric disorders, drug and other substance abuse and HIV infection and use of anti-retroviral drugs.

6.1.1. MDR-TB in Pregnancy

All female patients with MDR-TB and of child bearing age should be screened for pregnancy prior to initiating treatment. An appropriate birth control method for all non-pregnant female patients should be provided during treatment.

Pregnant patients should be carefully evaluated, taking into consideration gestational age and severity of the drug-resistant TB. The risks and benefits of treatment should be carefully considered, with the primary goal of smear conversion to protect the health of the mother and child, both before and after birth. The following are some general guidelines;

- Start treatment of drug resistance in second trimester or sooner if condition of patient is severe. Since the majority of teratogenic effects occur in the first trimester, therapy may be delayed until the second trimester. The decision to postpone the start of treatment should be agreed by both patient and doctor after analysis of the risks and benefits

- Avoid injectable agents. For the most part, aminoglycosides should not be used in the regimens of pregnant patients and can be particularly toxic to the developing foetal ear. Capreomycin may carry the same risk of ototoxicity but is the injectable drug of choice if an injectable agent cannot be avoided.

- Avoid Ethionamide. Ethionamide/Prothionamide can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies. If possible, Ethionamide should be avoided in pregnant patients. PAS can be used as an alternative.

Caution: Medications that induce hepatic enzymes, e.g., Rifampicin, protease inhibitors, some second-line MDRTB drugs, reduce the effectiveness of intradermal implanted contraceptives. Patients should be counselled to use alternative methods, e.g., condoms, Depo-Provera, while taking these medications to avoid accidental pregnancy.

6.1.2. Breastfeeding

Breastfeeding mothers should receive full treatment. Small quantities of the drugs will be passed into the milk. Because the impact of this to the foetus is unknown, it is recommended that where feasible infant formula feeds should be substituted for breast milk. For sputum smear positive mothers the care of the infant should, where feasible, be left to the family. Infant-mother contact should take place in sunny (ideally outdoors) and well-ventilated areas. The mother should be provided with an N-95 respirator if close infant – mother contact cannot be avoided. In the absence of an N-95 mask, the mother should be provided with a surgical mask until she converts.

6.1.3. Children

Children present particular challenges for DR-TB management. At least 50% of children with active TB may be smear and culture negative, making confirmation of MDR or XDR diagnosis difficult. Every effort should be made to confirm drug resistant TB by culture and DST in children. In children too young to produce sputum, early morning gastric aspirate samples may be obtained for smear and culture.

Children with active TB who are household contacts of a confirmed MDR-TB or XDR-TB patient should be considered to have DR-TB, even if smear and culture are negative. In children for whom DST results are not available, the DST pattern may be assumed to be similar to that of the adult contact. Empiric treatment for DR-TB should be initiated promptly, using a regimen based on the resistance pattern of the source case. In culture-negative children with DR-TB, clinical criteria can be used to determine response to therapy and the duration of the intensive and continuation phases. The DR-TB management committee should be actively involved in such cases.

The regimen used to treat childhood drug resistant TB is similar to that used in adults. The benefit of Fluoroquinolone far outweighs the risk, and should be part of every DR-TB regimen. Drug dosages should be based on body weight and based on the higher end of recommended range. Weight should be measured monthly, and dose adjustments need to be made as the child's weight changes.

6.1.4. Diabetes mellitus

Diabetes must be managed closely during treatment for drug resistant TB. Renal function should be monitored closely during treatment for drug resistant TB. The Creatinine and potassium levels should be monitored weekly in the first month and monthly thereafter.

6.1.5. Renal insufficiency

Great care should be taken in the administration of second-line drugs in patients with renal insufficiency, and the dose and/or the interval between dosing should be adjusted for patients with a renal clearance of < 30 ml/ min or on haemodialysis. Table 5 below show the necessary Adjustment of ant tuberculosis medication in renal insufficiency

Table 6 Dosing of selected ant tuberculosis drugs in renal failure

Drug	**Frequency**	**Recommended dose and frequency for patients with Creatinine clearance < 30 ml/min or for patients receiving haemodialysis**
Isoniazid	No change	300mg once daily or 900mg 3* wk.
Rifampicin	No change	600 mg once daily
Pyrazinamide	Yes	25-35 mg/kg/dose 3 * wk.
Ethambutol	Yes	15-25 mg/kg 3* wk.
Ofloxacin	Yes	600-800mg/dose 3 * wk.
Levofloxacin	Yes	750-1000mg/dose 3 * week
Moxifloxacin	No change	400mg once daily
Cycloserine	Yes	250mg OD or 500mg 3* wk.
Prothionamide	No change	15-20mg/kg/day
Para Aminosalicilic acid	No change	4g/dose twice daily
Capreomycin	Yes	12-15 mg/kg/dose 2 or 3 * wk.
Kanamycin	Yes	12-15 mg/kg/dose 2 or 3 * wk.
Amikacin	Yes	12-15 mg/kg/dose 2 or 3 * wk.
Clofazimine	No change	200-300mg daily
Amoxicillin/Clavulanate	Yes	1g based on amoxicillin component daily

6.1.6. Liver disorders

Pyrazinamide is the most hepatotoxicity of the three first-line drugs: Rifampicin, isoniazid and pyrazinamide. Among the second-line drugs, Ethionamide, Prothionamide and PAS can also be hepatotoxicity, although less so than any of the first-line drugs. Hepatitis occurs rarely with the flouroquinolones.

Patients with a history of liver disease can receive the usual drug-resistant TB chemotherapy regimens provided there is no clinical evidence of chronic liver disease, hepatitis virus carriage, past history of acute hepatitis or excessive alcohol consumption. However, hepatotoxicity reactions to ant tuberculosis drugs may be more common in these patients and should be anticipated.

In general, patients with chronic liver disease should not receive Pyrazinamide. All other drugs can be used, but close monitoring of liver enzymes is advised. If significant aggravation of liver inflammation occurs, the drugs responsible may have to be stopped. If liver enzymes are elevated but less than 5 times normal, continue anti-TB therapy but follow liver function tests each week. However, if liver enzymes greater than 5 times normal stop all anti-TB medications and repeat liver function tests weekly. Re- introduced the treatment once the LFTs are normal.

Uncommonly, a patient with TB may have concurrent acute hepatitis that is unrelated to TB or anti tuberculosis treatment. In this case, clinical judgement is necessary. In some cases, it is possible to defer ant tuberculosis treatment until the acute hepatitis has been resolved. In other cases when it is necessary to treat drug-resistant TB during acute hepatitis, the combination of four non-hepatotoxicity drugs is the safest option.

6.1.7. Seizure disorders

Cycloserine may be given as long as seizure disorder is controlled. Alternative to Cycloserine will be PAS in Kenya. Ensure pre-existing seizure disorder is under control before initiating treatment for drug resistant TB. This may require dose adjustment of the current treatment for the seizure disorder. Examine the drug regimen and modify treatment where feasible for patients who develop seizures during treatment. Such seizures are often due to drug adverse effects.

6.1.8. Psychiatric disorders

Provide psychiatric assessment prior to initiating treatment in patients with existing psychiatric disorders. Provide appropriate psychiatric treatment for patients who develop psychiatric problems while on treatment for drug resistant TB. Consider substituting PAS for Cycloserine in such patients.

6.1.9. Substance dependence

Usually substance abuse is not a contraindication to treatment with anti-TB drugs but appropriate treatment should be offered for the addiction.

Ensure strict DOT for such patients who are at high risk of abandoning treatment

Health care workers should be aware that Cycloserine side effects may be more common in patients dependent on alcohol and other substances.

6.1.10. HIV infection and MDRTB

In Kenya the national co-infection rate is 39% but it varies from one region to another (0% IN NEP and highest in Nyanza North at 50%). The drug management of HIV infected MDRTB patients are challenging especially as regards to pill burden, drug – drug interactions and adverse effects.

The pursuance of recommended TB/HIV interventions as outlined in the NLTP's policy document on TB/HIV collaborative activities is paramount when developing strategies for care and prevention of drug resistant TB in HIV infected persons.

Health care workers need to be aware of the pharmacokinetic interactions between Rifamycins e.g. Rifampicin and protease inhibitors in cases of treatment of mono and poly resistant TB but not MDRTB.

Also health care workers need to be aware that the Fluoroquinolone absorption may be decreased by non-enteric coated didanosine which contains aluminium / magnesium antacid, therefore the administration of didanosine should be given six hours before or two hours after the Fluoroquinolone

When treating HIV infected patients for MDRTB health care workers should look out for increased drug adverse effects e.g. increased risk of peripheral neuropathy when Stavudine is co-administered with aminoglycosides, increased risk of cutaneous hypersensitivity reactions by all the drugs; increased risk of neuron-psychiatric syndromes with co-administration of Efavirenz and Cycloserine; increased risk of renal impairment by aminoglycosides and adverse gastrointestinal effects by all the drugs

6.1.11 Contacts of MDR-TB patients

Close contacts should be identified through active contact tracing and evaluated for active tuberculosis. If the contact appears to have active TB, the health care worker should organize for his/her evaluation including sputum smears; culture, DST and CXR and HIV counselling and testing.

MDR-TB should be suspected in children with active TB and having a close contact of an MDR-TB adult or an adult suspected to have died of MDR-TB or if they have bacteriological proven tuberculosis that is not responding to 1st line TB treatment.

Symptomatic paediatric household contacts should be offered screening tests for TB. If smear/culture is positive, start on treatment as per the second line treatment regimen with adjusted drug doses for weight. Adjust the treatment based on the DST results.

- Currently, **WHO does not recommend** any use of 2nd line drugs for chemoprophylaxis in MDR-TB contacts.

Chapter 7 Nutrition in MDR TB

Tuberculosis affects the metabolism of important nutrients such as protein and some micronutrients. Malnutrition on the other hand limits cell mediated immunity and increases susceptibility to infection .This leads to nutritional stress and weight loss, thereby lowering the body's ability to fight infections (weakening immune functions) and nutritional status.

Table 7.0 Clinical presentation of TB and nutritional implications

Sign/symptom	Nutritional impact
Cough lasting 2 weeks or more	An increased energy demand.
Fever and night sweats	Increased Calorie requirement (10% extra calorie per every 1°C rise in body temperature) and dehydration
Loss of appetite	Inadequate nutrient intake hence poor nutritional status.
Weight loss	Poor health and nutritional status predisposing the clients to frequent, prolonged and severe infections due to impaired immunity
Blood in the sputum	Increased energy demand and loss of blood/iron predisposing the clients to anaemia and other infections.
Oozing matted lymph nodes or enlarged lymph nodes	Increased protein and micronutrients requirement for tissue repair.
Breathlessness and fatigue – pleural effusion, pericarditis	Increased energy need.

7.1 Nutrition requirements in DR TB

Foods from the seven basic food groups (water, cereals and starch, vegetables, fruits, animal protein, plant protein, fats and oils and sugars and sweets). Food choices should meet nutrient requirements, promote health, support active lives and reduce risks of nutrition related conditions. A normal diet consists of three (3) main meals and may include various snacks depending on individual needs. The following principals must be followed:

- **a.** Adequacy in all nutrients
- **b.** Balance of foods and nutrients in the diet
- **c.** Nutrient dense
- **d.** Energy dense
- **e.** Moderation in the diet
- **f.** Variety in food choice

Nutrient deficiencies may develop because of inadequate intake, impaired absorption, increased demand, or increased excretion. Excessive intakes of some nutrients may promote deficiencies of others through impaired absorption, increased demand, or increased excretion. Therefore the day's meal must provide;

7.2 Energy

Protein: to help in repair of damaged/torn tissues in the nitrogen breakdown, growth and development and continue maintaining metabolisms (hormones and enzymes), drug absorption, at least 3-4gms protein for children and 1.2- 1.5gms for adults must be available either from consumption of animal and plant foods with emphasis on eggs, milk and milk products ,fish, soybean and other legumes available in the local markets or through medical nutrition recommended products for enteral or parental feeding depending on the condition.

Carbohydrates; Many a times the patients will have lost a lot of energy due to the prolonged coughs and needs 36-40gms /kg body weight/day. The carbohydrates will come from many staple foods available locally e.g. grains, roots and tubers, bananas and sugar. If a patient cannot be able to feed normally then it should be given in form of enteral or parental feeding depending on the condition.

Lipids; These provide the body with energy, cushion organs and aid in digestions.

Fats and oils provide all that is needed .Oils are better. The diets should contain only 25 – 30% of the daily energy requirement.

7.12Micronutrients:

Vitamins and minerals: the bodies needs them in small amounts and are very essential. Of importance is Vitamin A, C, D. Zinc, iron, calcium and selenium because of the part they play in immune restoration. These micronutrients are destroyed in TB and need to be replenished through diet. Emphasis on consumption of dark green leafy vegetables, dark red and yellow fruits should be laid. However since Vitamin A deficiency prevalent is high in Kenya patients should be supplemented as per National Vitamin A schedule – Disease target 100000i.u for children>6<11months,200000i.u to>1yr including adults every 6 months.

A good multivitamin and mineral supplement, providing 50%-150% of the recommended daily intake, is advisable since it will be most unlikely that a person with TB will be able to meet the increased requirements for vitamins and minerals with diet alone (due to a poor appetite).

Multiple micronutrients providing 1 Recommended Nutrient Intake (RNI) should be provided.

Table 8 Normal diet food guide

Food group	**Major nutrients**	**Servings per adult**	**Servings per child**	**One serving equivalent 1 cup/glass = 250 ml**
Water		8		
General starchy foods bread, cereals and other grains	Carbohydrates • Vitamin (B1) • Iron, • Niacin	6-11	6	• 1slice bread, • ½ cup cooked cereals, pastas or rice, ¾ to 1cup • potatoes, green bananas, • 2 small 3 inch pancakes. • 1cup ready to eat cereals
Milk and milk products	• Calcium •Riboflavin (*Vit B2)* • Vitamin B12, • Proteins, • fats	2-4	2	• 1 cup : o fresh milk, o fermented milk or o yoghurt
Meat or substitutes	• Protein, • Niacin, • iron • thiamine (Vit B1) • B6, • B12, • Zn, • Mg,	2-3	2	• 1oz. Or approximately 30g (6 small pieces meat. • Thigh of chicken • Portion of fish, • 1 egg, • ½ cup cooked dry beans or •2 tablespoon peanut butter
Vegetables	Vitamin A • Vitamin C • Vitamin K+, • fibre, • folate • potassium,	3-5	3	• ½ Cup cooked vegetables • 1 cup raw vegetables, • ½ cup fresh cooked legumes, • ¾ cup vegetable juice

	• Magnesium			
Fruits	• Vitamin A • Vitamin C • Vitamin K+ • Fibre	2-4	2	• ¾ Cup 100% fresh fruit juice, • ½ cup fresh diced fruit. • ¼ cup dried fruit. • One medium apple, banana, orange, 1 melon wedge
Fats and sugars	• Vitamins A, D, E, K, • Fats, • Carbohydrates	Sparingly	Sparingly	• Vegetable oil • Margarine, • Butter, • Cream, salad dressings, • Mayonnaise • Sweets, • Sugar

HIGH PROTEIN-HIGH CALORIE DIET

This diet is tailored to provide higher amounts of calorie and protein than usual diet. It is prescribed where tissue regeneration is required. Its purpose is to help heal wounds, maintain or increase weight, promote growth, decrease respiratory complications, resist or fight infections and support the immune system. For a high protein diet, adequate energy from carbohydrates and fats must be supplied.

Purpose

The diet is designed to maintain a positive nitrogen balance, promote normal osmotic pressure, promote body tissue repair, prevent excessive muscle atrophy in chronic disease states and build or repair worn out tissues of severely malnourished individuals. This diet can also be used to meet increased energy and protein demands during illness, during certain periods like pregnancy and lactation. Table 32 below shows indication for and characteristics of the diet.

7.3 Nutritional Care and Management

The general objectives in Nutritional Care and management of TB patients are to;

1. Maintain good nutrition status
2. Prevent and control body wasting and weakness
3. Correct nutritional deficiencies which may have occurred during the disease.
4. Modify diets to improve the body's ability to metabolize nutrients during TB disease
5. Accelerate healing process.

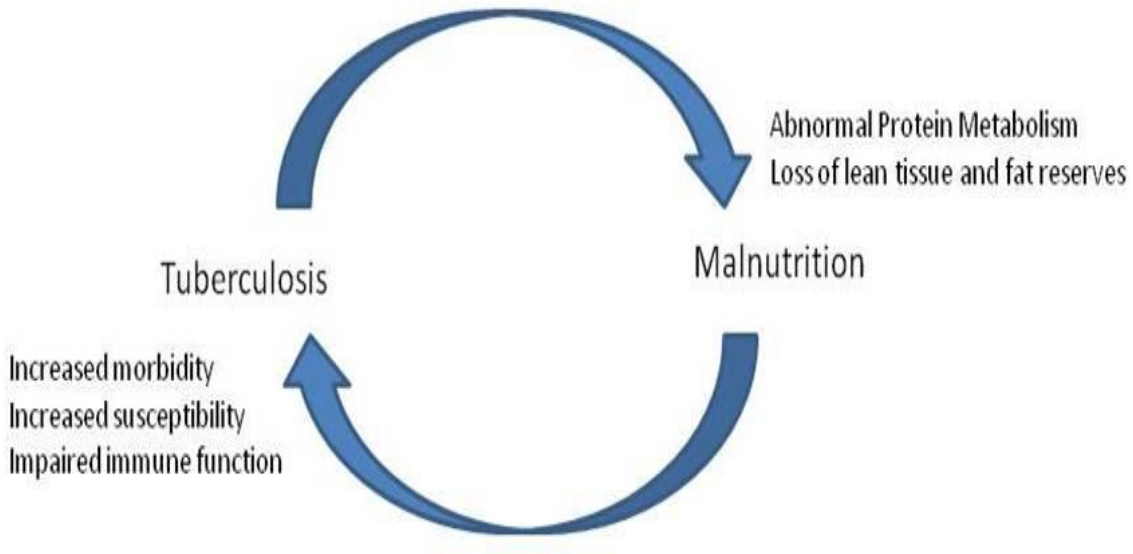
Table 9

Immediate causes	Disease (Tuberculosis) Inadequate food intake
Inadequate food intake and disease create a vicious circle .Tuberculosis and HIV worsens the situation. Malnutrition- infection complex	
Underlying causes →	**Insufficient house hold food security** **Inadequate maternal and child care** **Insufficient health services** **poor hygiene and sanitation**

Effects of DR TB on Nutrition

1. Increase in basal metabolic rate (BMR)
2. Increase in energy expenditure depleting the adipose and glycogen stores
3. Reduced absorption of minerals, vitamins, proteins and increase in nitrogen breakdown leading to low immunity.
4. Reduced food intake and depletion of body stores.
5. Mal-absorption leading to malnutrition and wasting

Figure 2 Interactions between TB and Malnutrition

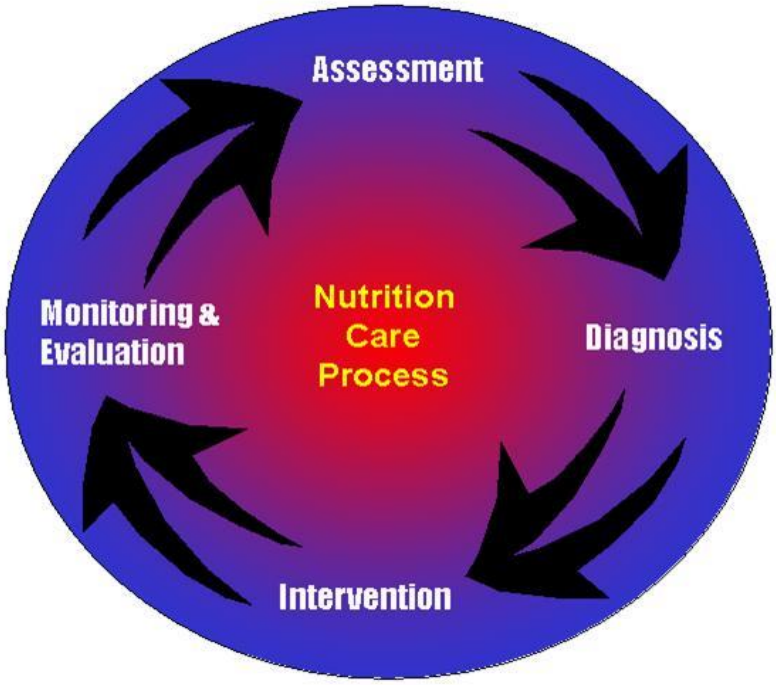


7.3.1 Nutrition care and support for DRTB patients

Nutrition care process is a standardized systematic approach to providing high quality nutrition care benefitting the patients in the following ways:-

1. Individualization of nutrition care
2. Identification of patients nutritional needs.
3. Monitoring and follow up of the nutrition status of the patients and provision of quality evidence based interventions

Figure 3 Nutrition care process consists of 4 distinct and connected steps.



Step 1. Nutrition Assessment

All patients should have their nutrition status **assessed**

A- Anthropometry,

B- Biochemical,

C- Clinical,

D- Dietary,

E- economic

F- Functional assessments emphasis on anthropometry, biochemical and clinical indicators in the Main DR-TB register.

Step 2. Nutrition Diagnosis

Basically to identify patients with nutritional problems, classify them according to severity.

Indicator	Severe acute under nutrition	Moderate acute under nutrition	Mild acute under nutrition
Children 6 months to 59 months			
Weight for height / Length Z scores	< - 3 Z score	Between – 3 to < -2 Z score	Between -2 to < -1 Z score
Weight for height / Length % of median	< 70% W/H	Between 70 – 80 % W/H	Between 80 – 90%
MUAC	< 11 cm (under 5s)	11 –13 cm (under 5 s)	
Bilateral pitting Oedema	Oedema (+) present	Oedema absent	Oedema absent
Children 5 – 9 years			
BMI for age Z scores	< - 3 Z score	Between – 3 to < -2 Z score	Between -2 to < -1 Z score
MUAC	< 13.5 cm	Between 13.5 – 14.5 cm	
Bilateral pitting Oedema	Oedema (+) present	Oedema absent	Oedema absent
Adolescents 10 – 17 years			
BMI for Age Z score	< - 3 Z score	Between -3 and -2 Z score	Between -2 to < -1 Z score
MUAC	<16 cm	Between 16 – 18.5cm	
Bilateral pitting Oedema	Oedema (+) present	Oedema absent	Oedema absent
Adults 18 years and above			
BMI	< 16 cm	Between 16 – 17 kg/m^2	Between 17 – 18.5 kg/m^2
MUAC	- <16 cm - 16-18.5cm plus one of the following: 1. Inability to stand 2. Apparent dehydration	16 - 18.5cm with no relevant clinical signs. Few relevant social criteria	
Oedema	Oedema (+) present	Oedema absent	
Pregnant or postpartum women			
MUAC	< 22 cm	Between 22 - 23 cm	Between 23 – 24 cm
Oedema	Oedema (+) present	Oedema absent	

Step 3. Intervention

Should be targeted at aetiology, if not aetiology, then signs and symptoms. Plan, identify and implement the planned intervention. Prepare a **food drug-plan** with the client (or Care givers). There are four categories of nutrition interventions:

a) **Food and/or nutrient delivery (ND)**

- Meals and snacks
- Enteral/parenteral nutrition
- Medical food supplements
- Vitamin and mineral supplement
- Bioactive substance supplement
- Feeding assistance
- Feeding environment (ND-5)
- Nutrition-related medication management (ND-6)

b) Nutrition education (E)

- Initial/brief nutrition education (E-1)E.g. survival skills on discharge
- Comprehensive nutrition education (E-2)
- Purpose
- Recommended modifications
- Result interpretation

Note: Education is appropriate for food and nutrition-related knowledge deficit. If the client knows the content, more education probably won't help

c) Nutrition counselling (C)

- Theory or approach
- Strategies
- Phase

d) Coordination of nutrition care (RC)

- Coordination of other care during nutrition care (RC-1)
- Team meeting
- Referral to other departments
- Collaboration with other providers
- Referral to community agencies/programs
- Discharge and transfer of nutrition care to new setting/provider
- Collaboration
- Referral to community agencies/programs

Step 4. Nutrition Monitoring and Evaluation

- Continuous monitoring and follow up of patients on treatment is vital. Carry out a follow-up plan (set target timelines, return date, referrals to specialized nutrition clinics e.g. Diabetic
- Monitor progress and determine if goals are met:- Weekly weight for severely undernourished adults, daily for children
- Identifies patient/client outcomes relevant to the nutrition diagnosis and intervention plans and goals
- Measure and compare to client's previous status, nutrition goals, or reference standards

7.4 MDR TB drugs and nutrition recommendations

The absorption of many TB drugs is adversely affected by food and some medications.

Table 11.. Tuberculosis drugs and food recommendations.

DRUG NAME	FOOD GUIDE	FOODS TO AVOID	POSSIBLE SIDE EFFECTS	POTENTIAL DRUG NUTRIENT INTERACTION
Ethambutol	May be taken with food	Alcohol		There are no restrictions on foods, beverages,
Streptomycin	Increase fluid intake		Taste changes of food, nausea	
Pyrazinamide	May be taken with food			
Ethionamide	Take with or after meals (Supplement with vitamin B6)	Alcohol	Abdominal discomforts, nausea	
Ofloxacin	Take 2 hrs. before or after supplements	Antacids, milk products	Review	
Kanamycin	Can be taken without regard to food			
Capreomycin	Increase fluid intake			Take with foods high in potassium (bananas, avocados)
Para-amino-salicylique acid (PAS)	Take with or immediately after food.	Alcohol		Increase fluid intake
Cycloserine	Supplement B6	Alcohol		Affects absorption of pyridoxine
Prothionamide				

Chapter 8 Management of drugs side effects

8.1. Basics of drug side effects

Recent experience in MDRTB treatment programs suggests that chances of cure are significantly improved when maximal doses of multiple second-line drugs are used while rapidly and aggressively treating side effects to improve tolerance.

Permanent dose reduction or definitive elimination of a drug from the regimen is a serious step and should be considered only after all other possibilities have been exhausted, used as a last resort, i.e., in cases of significant organ dysfunction or intractable symptom intolerance. Ideally, any drug eliminated should be replaced with an equally effective drug so as not to compromise the overall effectiveness of the regimen. Often, if side effects cannot be completely eliminated, patients may be asked to tolerate symptoms until they subside.

It is often difficult to ascertain whether a given side effect is due to a single medication or the result of several drugs given simultaneously. If after following the various treatment schemes given below the patient remains intolerably symptomatic, a dose reduction or elimination of one of the drugs may be necessary. This can be done in a systematic manner by reducing the dose of the most likely offending drug for one week to see whether the symptoms diminish or disappear; if symptoms persist, the drug is returned to its original dose and the same process repeated for the other drugs in the regimen, until all potentially responsible drugs have been tested. Systematic dose reduction of multiple drugs simultaneously would be the next option. The nurse should record side effects (annex 1) and report the event to the managing clinician at the earliest appropriate time. A proper form can help the nurse to check out side effects. The best time to check side effects is usually at the first DOT in the morning. Only the clinical team should do dose changes or eliminate a specific drug.

8.2. Management of specific adverse reactions

8.2.1. Nausea and vomiting

Suspected agents: PAS, Eto/Pto, Clofazimine, H, E, Z.

Nausea and vomiting are frequent during the first few weeks of therapy and usually cease with supportive therapy. Nausea and vomiting are reversible upon discontinuation of the suspected agent.

1st Phase:

- Check signs of dehydration (thirst, dry mouth, sunken eyes, low blood pressure, orthostatic, and weakness) and serum concentration of electrolytes.

- Check out other causes such as hepatitis (jaundice or icterus, pruritus, right-sided abdominal pain)

- Adjust administration of medications:

-administer ETO or Clofazimine in three separate doses

-administer medication associated with nausea at night with short-acting benzodiazepine;

-administer PAS one hour after taking other anti-TB medications.

2nd Phase:

- Administer anti-emetics: start with metoclopramide 10 mg by mouth given 30 minutes before morning and/or afternoon dose of anti-TB drugs, to a maximum of 15 mg twice daily.

Notes: Avoid metoclopramide and prochlorperazine if neurological problems develop.

Anti-emetics include: prochlorperazine (available in drops and very effective before

dose of DR TB drugs), diphenhydramine, lorazepam, dimenhydranate,

metoclopramide, promethazine, chlorpromazine (very effective if given at night)

3rd Phase:

- If ineffective, start promethazine 25 mg with diphenhydramine 25 mg (or other antihistamine) by mouth 30 minutes prior to anti-TB drugs or prior to meals, up to 3 times daily. If necessary, the dose may be increased to promethazine 50 mg (with diphenhydramine 25 mg) 3 times daily to control symptoms. Promethazine is very useful at night for nausea and for sleeping

NB: Side effects of promethazine include sedation, dry mouth, urinary retention, and, rarely, tardive dyskinesia or confusion in the elderly. Diphenhydramine is used to minimize these side effects.

- Chlorpromazine drops (10-25 mg, available in 25mg/5ml) can be given 4-6 hourly.

Ideally given 30 minutes before DR TB drugs are given (liquid form is best absorbed and works in 30 –60 minutes)

- If the patient cannot take drugs orally, give promethazine 25-50 mg intramuscularly according the schedule given above or promethazine 25mg per rectum.

4th Phase:

- If persistent vomiting results in dehydration, give 500-1,000 ml of 0.9% NaCl or Ringer's solution intravenously as needed.

- Consider ondansetron 8mg BD for 3 days, then 8 mg OD when necessary.

5th Phase:

- If taking ETO, reduce to 750 mg OD

- If taking Clofazimine, reduce to 200 mg OD Note: Cfz can cause the clinical picture of acute abdomen

- If absolutely necessary, stop all anti-TB drugs until symptoms resolve.

8.2.2. Gastritis.

Suspected agents: PAS, Lfx, Ofx, Mfx, ETO, H, E, and Z.

For dyspepsia, belching, hyperacidity, and epigastric pain, start with aluminium hydroxide 2-4 tablets given by mouth up to 4 times daily, at least 2 hours before or after anti-TB medications.

If symptoms persist: refractory symptoms may in some cases be treated with omeprazole 20 mg once a day by mouth.

If this treatment is not successful, medically re-evaluate while considering other aetiologies .

Note: dosing of antacids should be timed so as not to interfere with the absorption of anti- TB drugs, i.e., at least 2 hours apart from anti-TB drugs.

8.2.3. Dermatitis

Suspected agents: all are possible - most likely agent is Thioacetazone, especially in HIV infected patients.

Rule out other likely causes (i.e., scabies, allergic reaction to non-TB medications).

Treatment of localized rash or mild generalized rash, give diphenhydramine 25 mg (or other antihistamine) by mouth as needed up to 3-4 times daily. If itching is severe, 1% topical hydrocortisone may be applied directly to lesions.

If rash is severe or if bullous or exfoliative lesions appear, all anti-TB medications must be stopped immediately. A parenteral corticosteroid (i.e., dexamethasone 2-4 mg 4 times daily intravenously or intramuscularly) may be necessary in severe cases. After rash has resolved, anti-TB drugs should be added back one at a time 1-2 days apart in gradually increasing doses, in the following order: H - R - Z – Pto / Eto -Flouroquinolones- Cs - E - PAS – injectable.

If the rash recurs after resumption of one of these agents, then discontinuation of that agent may be required and another agent should be substituted. If the rash was particularly severe, reintroduce the anti-TB medications starting with one-tenth of the original dose and increase the dose more slowly.

Note: if a rash appears while the patient is on T, this drug should be stopped immediately and prednisone administered at a dose of 1 mg/kg. T should never be given again in such cases.

8.2.4. Seizures.

Suspected agents: Cs, H, and Ofx, Lfx and Mfx

Prior history of seizures is not a contraindication to the use of the above agents if the seizures are well controlled on anti-convulsive therapy. Seizures are not a permanent sequel of treatment with any of the above agents.

Seizures should be controlled in patients with active uncontrolled seizures before starting treatment. Risks and benefits should be discussed with patients. Seizures that appear for the first time during TB treatment are likely to be caused by a TB drug. Pyridoxine should be given to all patients on Cycloserine to reduce neurological side effects (50 mg for every 250 mg of Cycloserine to a maximum of 200 mg/day). If patient experiences a seizure for the first time during therapy suspend the Cs for a short period and initiate therapy for seizures and the reintroduce the Cycloserine if it is essential to the regime (usually it is). It can be restarted at a lesser dose but the usual dose should be achieved as soon as possible.

If actively fitting:

Place the patient in the lateral decubitus position, remove objects nearby that can cause danger for the patient, protect the tongue with a soft object too large to be swallowed, observe until patient stops seizing,

Ensure airway is protected.

Give diazepam 5 mg intravenously or intramuscularly immediately, followed by a loading dose of phenytoin (typically 20 mg/kg intravenously, or orally). Diazepam may be repeated once in 10 minutes if seizures do not cease.

Monitor the patient carefully for signs of respiratory depression.

If the seizure has already stopped at the time of initial evaluation and the patient is post-ictal, do not give diazepam but give phenytoin loading dose as described above.

In both instances, begin phenytoin maintenance dose of 300 mg/day (3-5 mg/kg/day) once the loading dose has been administered.

If seizures recur, phenytoin may be increased to a maximum of 500 mg/day or a second agent (valproic acid, phenobarbital) may be added.

Increase pyridoxine to 300 mg/day in all cases.

Note: caution with diazepam which may depress respiratory function.

Initiate antiepileptic treatment for the remainder of MDR-TB therapy:

o Phenytoin (3-5 mg/kg/day), 300 mg/day –100mg 3 times a day

Note: Potential adverse effects: ataxia, in coordination, confusion, skin rash, cerebella dysfunction, hepatotoxicity, gingival hyperplasia, lymphadenopathy and hirsutism increased level by H.

If seizures recur, phenytoin may be increased to a maximum of 500 mg/day or a second agent (valproic acid, phenobarbital) may be added.

o Valproic acid (750-1250 mg/day). Start with 500mg and increase by 250mg.

Note: Potential adverse effects: ataxia, sedation, tremor, hepatotoxicity, bone marrow suppression, GI upset and weight gain

o Carbamazepine (600-1200 mg/day)

Note: Potential adverse effects: ataxia, dizziness, diplopia, vertigo, GI upset, hepatotoxicity; skin rash

o Phenobarbital (60-120 mg/day)

Note: Potential adverse effects: sedation, ataxia, confusion, dizziness, decreased libido, depression, skin rash. Enhances metabolism of other drugs, including H.

Always rule out other causes of seizure: previous history of seizure or epilepsy, meningitis, encephalitis, history of substance or alcohol abuse, metabolic disturbances (hypoglycaemia,

hyper- or hyponatremia, hyper- or hypocalcaemia), cerebrovascular accident, malignancy or other space-occupying lesion.

Check electrolytes.

Neurological consultation.

Note: Even if there is an underlying condition (e.g. history of previous stroke, epilepsy,

Substance abuse), aggravating triggers should be considered.

Note: sub-therapeutic levels of anti-seizure drugs can be caused by drug-drug interactions between anti-seizure drugs and anti-TB drugs, especially H and R

8.2.5. Psychosis.

Suspected agents: Cs, flouroquinolones and H.

Psychotic symptoms refer to a constellation of symptoms that indicates a disintegration of personality or a loss of contact with reality. Patients tend to present with hallucinations or delusions. The causes of psychotic symptoms in patients with DR TB may be related to socio-economic circumstances and/or underlying psychiatric disease.

Prior history of psychiatric disease is not a contraindication to the use of the above agents, though psychiatric side effects are more likely. Some patients may need anti-psychotic medication throughout the duration of anti-TB therapy, though side effects are generally reversible upon discontinuation of treatment.

For acute psychosis: If the patient is at risk of harming himself/herself or others: urgent hospitalization is advised.

Give haloperidol 1 mg orally or intramuscularly, or chlorpromazine 25mg orally or IM.

If no improvement after 20 minutes, give 2mg and if no improvement after 20 minutes give

4 mg.

A benzodiazepine may be given concomitantly provided if there is no evidence of respiratory compromise.

If good response, start haloperidol 2-4 mg orally once daily and increase pyridoxine to 300 mg/day. Haloperidol may be increased by 2 mg per day to control symptoms, to a maximum dose of 10 mg orally per day. Adjunctive agents that may be useful include clonazepam if haloperidol is not fully effective, and diphenhydramine to control the extra pyramidal side effects of haloperidol.

Risperidone can be used instead of haloperidol:

Start with 0.5mg to 5mg twice or three times per day. The usual dose is 2-10 mg per day. Risperidone is as effective and causes less extra-pyramidal effects than haloperidol.

Rule out other causes of psychosis, including illicit drugs, alcohol withdrawal.

It may be necessary to stop anti-TB therapy temporarily (1-4 weeks) while symptoms are brought under control. Consider reducing the dose of the offending agent or replacing it if the strength of the overall regimen is not compromised. The most common causative drug will be Cycloserine. Cycloserine should therefore be introduced from a low dose of 250mg per day. Observe for 3 days, if no occurrence of symptoms, increase the dose to 250mg BD and monitor for 3 more days. Increase the dose then to 500mg morning and 250mg nocte. In the event that the symptoms recur, reduce back to the lower dose. If regimen is compromised consider replacing Cycloserine with PAS. Psychotic symptoms stop once the offending drug is withdrawn.

Note: Haloperidol has anticholinergic as well as ant dopaminergic effects. If patient develops symptoms of neuroleptic syndrome, must discontinue haloperidol immediately. If patients develop dystonia, Parkinsonism, or Extra Pyramidal Symptoms, administer with diphenhydramine 25 mg PO QD or biperiden or benzotropine.

An anxiolytic is useful.

8.2.6. Peripheral neuropathy.

Suspected agents: S, Km, Cm, H, FQ, Cs, and E (rarely PTO / Eto).

Patients with co-morbid disease such as diabetes or alcoholism are more likely to develop neuropathy, but such conditions are not a contraindication to use of the above agents.

Neuropathy is generally *not* reversible upon discontinuation of anti-TB therapy, but only a small minority of patients requires long-term treatment to control symptoms.

Increase pyridoxine to 200mg/day in patients on second-line drug therapy, 50 mg/day for those on first-line therapy.

If the patient is on Km and is known to be susceptible to Cm, consider changing the parenteral agent to Cm.

Physical therapy focusing on the affected regions may be of benefit.

If the above measures are ineffective, begin nortriptyline or amitriptyline (tricyclic antidepressant-TCA) 25 mg orally at bedtime, increasing the dose by 25 mg each week to a maximum of 100-150 mg until symptoms are controlled.

Peripheral neuropathy can have several forms; TCA typically work with chronic constant pain, can be supplemented by NSAIDS; 'shooting' pain responds well to carbamazepine and valproate

If no improvement, start carbamazepine 200mg BID and increase to 600mg BID. Consider use of phenytoin.

If not controlled, ask for a neurological consultation and decrease dose of responsible medication: Cs to 750mg and Km/Am 750mg if Cm not available. Then resume normal dose once pain controlled.

8.2.7. Drug-induced hepatitis.

Suspected agents: Z, H, R, PTO / ETO, and PAS.

Consider checking for presence of hepatitis B surface antigen etc. Liver function tests are checked if patient has symptoms of hepatitis (i.e., anorexia, nausea, vomiting, abdominal pain,

jaundice) or as part of regular monthly screening. Any signs of hepatitis (including nausea, severe vomiting, scleral icterus, jaundice, dark urine, pale stool) merit immediate evaluation of liver function tests.

If liver enzymes elevated but less than 5 times normal, continue anti-TB therapy but follow liver function tests each week.

If liver enzymes greater than 5 times normal, stop all anti-TB medications and repeat liver function tests weekly.

If liver enzymes continue to worsen, then progressive drug-induced hepatitis or an unrelated cause must be suspected.

If liver enzymes plateau or revert to normal and symptoms resolve, one may restart anti-TB drugs sequentially beginning with the agents least likely to be hepatotoxicity: Injectable – Cycloserine - Fluoroquinolone–- Eto/Pto -Z. The following agents can then be resumed one at a time in the sequence indicated, over a period of one week, while checking liver enzymes at the end of each week:. The offending agent can generally be identified in this manner and discontinued or replaced.

8.2.8. Arthralgia's.

Suspected agents: Z, flouroquinolone**s** (rarely PTO / ETO, Cs, Cm and aminoglycosides).

Arthralgias generally diminish over time even without treatment. Serum uric acid levels may be elevated, but this is of little clinical relevance and anti-hyperuricemic therapy is of no proven benefit in these patients. H can rarely induce a systemic lupus erythematous.

Begin therapy with anti-inflammatory agents (indomethacin 50 mg by mouth twice a day or ibuprofen 400-800 mg by mouth 3 times a day). Paracetamol 500-1,000 mg by mouth 2- 4 times per day may also help bring relief when given together with an anti-inflammatory drug.

Physical therapy is often beneficial. Narcotic analgesics are rarely needed.

If symptoms fail to resolve, consider lowering the dose of the suspected agent provided this does not significantly compromise the effectiveness of the treatment regimen.

8.2.9. Diarrhoea.

Suspected agents: PAS, PTO / ETO.

Since many patients use the term diarrhoea to describe bowel movements that are more frequent or loose than normal, it is important to note whether the stool is truly watery and more than three or four times a day.

For mild diarrhoea, treat with loperamide 4 mg by mouth initially followed by 2 mg after each loose stool to a maximum of 10 mg per 24 hours. Encourage fluid intake.

For severe diarrhoea, particularly if accompanied by bloody stools, severe abdominal pain, or fever greater than 38.5 °C, consider other causes such as acute bacterial enteritis, or pseudo-membranous colitis related to flouroquinolones. Such patients may need hospitalization and IV fluid replacement.

8.2.10. Hypothyroidism.

Suspected agents: PAS, PTO / ETO (particularly when given in combination).

Symptoms include fatigue, weakness, cold intolerance, decreased appetite, and constipation, loss of energy, depression, and inability to concentrate. Physical signs include enlarged thyroid, dry skin, coarse hair, and weight gain. Check TSH level if suggestive symptoms or signs are present. If TSH level is greater than 10, then symptomatic hypothyroidism is likely and therapy should be given.

Hypothyroidism is reversible upon discontinuation of PAS and/or Eto/Pto, i.e., the TSH level normalizes after 2-3 months.

Levothyroxine therapy should be initiated at a dose of 50µg daily (or 25µ g daily for patients older than 65 years), increasing the dose by 25 µg and checking a TSH level every 4 weeks until a normal level is attained.

Thereafter TSH should be checked every 4 months until the patient's course of anti-TB therapy has been completed. If TSH testing is not available, discontinue levothyroxine after two to three months and follow symptoms

If symptoms do not improve, lower PTO dose by 250 mg or decrease PAS to 4 gm. twice daily. Discontinue the drug(s) if above measures are ineffective and equally effective agents can be substituted.

Note: do not give levothyroxine at same time as antacids or phenytoin, as these impair GI absorption.

8.2.11. Renal failure.

Suspected agents: aminoglycosides, Cm.

Diminished urine production (< 0.5 ml/kg/hour or < 30 ml/hour), oedema or anasarca, malaise, nausea, increased difficulty breathing can be related to acute renal failure.

Co-morbid conditions such as diabetes or chronic renal failure are not a contraindication to treatment with the above agents, though greater caution must be exercised in such circumstances. Renal impairment may be permanent following treatment with the above agents.

Suspend the nephrotoxic agent.

Rule out other causes of renal failure (e.g. diabetes, dehydration, congestive heart failure, urinary obstruction, urinary tract infection, prostatic hypertrophy)

Follow serum creatinine and electrolytes closely.

If renal function stabilizes or improves, resume the parenteral agent, switching to Cm if an aminoglycoside was being used previously. Reduce the frequency of the injectable. Give the injectable, Cycloserine and Pyrazinamide 3 times a week and monitor creatinine and electrolytes levels monthly.

8.2.12. Electrolyte loss.

Suspected agents: Cm, aminoglycosides, PAS, (rarely PTO / ETO)

Although often asymptomatic, low serum potassium and magnesium may present as fatigue, myalgia, cramps, paraesthesia, lower extremity weakness, behaviour or mood changes, somnolence, and confusion. More severe disturbances can lead to tetany, paralysis, and life-

threatening cardiac arrhythmias. For this reason, frequent electrolyte surveillance is recommended in patients with significant GI losses and in all patients receiving parenteral therapy.

Electrolyte wasting is more often associated with Capreomycin than other injectable agents. The magnitude of total body depletion of potassium (K+) and magnesium (Mg++) may be far lower than that which is reflected in serum levels. Hypokalaemia (defined as serum potassium less than 3.5meq/L) and hypomagnesaemia (defined as serum magnesium less than 1.5 meq/L)* are not uncommon in patients receiving MDR TB therapy and are caused by the following:

- Direct renal tubular effect of aminoglycosides and Capreomycin.
- Vomiting and diarrhoea.

Once hypomagnesaemia or hypokalaemia is diagnosed, the following actions should be taken:

- Underlying causes such as vomiting and diarrhoea should be treated.
- Arrhythmogenic medications (such as digoxin, tricyclic antidepressants) should be discontinued if possible.
- An electrocardiogram should be performed in patients with significant electrolyte disturbances; if the QT segment is prolonged, any drugs contributing to QT prolongation – including certain flouroquinolones, haloperidol, fluconazole, and cisapride – should be held.

Treatment of hypokalaemia and hypomagnesaemia:

- May be administered orally if electrolyte disturbance is not severe.
- Replacement may be needed during the whole course of the use of the aminoglycoside or capreomycin.
- Hypokalaemia will be refractory to treatment unless hypomagnesaemia is also treated.

Normal renal function should be confirmed prior to instituting repletion, although even patients with renal failure should receive repletion in smaller doses. Both electrolytes can be supplemented in IV or oral form. When possible, potassium depletion should be corrected orally

by increased dietary uptake or supplementation with potassium salts. Intravenous treatment is required for patients with gastrointestinal disorders or severe potassium deficiency.

Potassium-sparing diuretics (spironolactone, triamterene, or amiloride) may be used as adjuvant therapy in severe renal potassium losses secondary to aminoglycosides and capreomycin.

Great caution must be used when potassium-sparing diuretics are given in conjunction with potassium supplements, as hyperkalaemia may result.

Of note is that hypomagnesaemia often causes hypokalaemia and hypocalcaemia. Hypokalaemia (and hypocalcaemia) may be refractory to treatment if hypomagnesaemia is present and not

addressed. Since serum magnesium levels are not always reflective of total body magnesium content, empiric magnesium replacement is often needed in hypokalaemia even if the serum magnesium levels are within normal range.

Potassium

Oral Potassium replacement

Serum K^+(mmol/l)	***Dose of Slow-K(mg)***
3.3 - 3.5	1200mg tds (6tabs = 48mEq,per day)
2.9 – 3.2	1800mg tds (9tabs = 72mEq, per day)
2.5 – 2.8	2400mg tds (12tabs = 96mEq, per day)
≤ 2.4	3000mg tds (15tabs = 120mEq, per day)

Oral potassium supplementation

- KCl tablets may be diluted in water or take as pills.
- The dose may be split and give two or three times per day.
- Supplement diet with banana, orange/tomato/avocado/grapefruit juice.

IV Supplementation

• Should NOT exceed more than 20 meq/hr. of KCl.

• Normal preparation is 40 meq in 1 litre of NaCl 0.9%; maximum preparation is 60 meq/L.

Table 12 Frequency and replacement table for potassium

Potassium level meq/L	Dose KCl in meq	Frequency of monitoring (sooner if patient has vomiting / diarrhoeal)
Above 3.7	None	Monthly
3.4-3.6	20-40	
3.0-3.3	60	
2.7-2.9	80	
2.4-2.6	80-120	
2.0-2.3	60 IV and 80 P.O every 6-24 hrs.	Hourly after infusion until serum K^+ is > 2.8 meq/L
< 2	60 IV and 100 P.O every 6 hours	Hourly after infusion until serum K^+ is > 2.8 meq/L. Consider withholding injectable until > 2.4

Magnesium

Oral Supplementation

• Presentations:

- Magnesium gluconate
- Magnesium oxide

• Different preparations have different amounts of elemental magnesium. The following table gives the tablet dosage amount; we assume that a 400 mg tablet will contain 240 mg elemental magnesium.

If the preparations you are using have less elemental magnesium, you may have to increase the tablet dosage.

• Quantities greater than 2000 mg are often more easily given IV or IM.

IV Supplementation

• Maximum concentration: 5 g or 40 meq MgSO4 in 1 litre of NaCl 0.9% or dextrose 5%

• Do NOT exceed 150 mg per minute.

• If not emergency:

  • 2 g in 100 ml administered over 1–2 hours

  • 4 g in 250 ml administered over 2–4 hours

Intramuscular Supplementation

• 1 g (or up to 250 mg/kg) of MgSO4 without dilution IM every 6 hours.

• No advantage over IV magnesium.

• Indicated if supplementation cannot be received PO or IV.

Table 13 Frequency and replacement table for magnesium

Magnesium level meq/L	Total daily dose mg	Frequency of monitoring
>1.5	None	Monthly
1.1-1.4	1000-1200	Monthly
0.8-1.0	2000 (consider IM)	1-2 weeks1-6 days
<0.8	3000-6000MG (Give IV or IM)	

Calcium

Symptomatic hypocalcaemia should be treated on an emergency basis with 2 grams of calcium gluconate (180 mg elemental calcium or 20 ml 10% calcium gluconate) IV over 10 minutes, followed by infusion of 6 grams calcium gluconate in 500 ml D5W over 4–6 hrs. The IV infusion should be tapered. The initial oral dose during the transition from IV to oral therapy is 1–2 g elemental calcium three times a day.

• For long-term therapy the typical dose is 0.5–1.0 g PO TID.

• Hypomagnesaemia must be treated if present.

• Total serum calcium levels need to be adjusted for low albumin (ionized levels of calcium do not need to be adjusted). The total serum calcium can be corrected by adding 0.8 mg/dL for every 1 g/dL decrease of serum albumin below 4 g/dL. By doing this calculation one can determine if true hypocalcaemia is present:

Table 14 Frequency and replacement table for calcium

Calcium level (Total calcium adjusted for low albumin)	Dose of calcium	Frequency of Monitoring
>8.5 mg/dL	None	
7.5-8.4	500mg TID	Monthly
7.0-7.4	100mg TID	1-2 weeks
<7.0	Consider IV and tapper to 1000mg TID	1-4 days

Use of potassium-sparing diuretics in the treatment of hypokalaemia and hypomagnesaemia

• Certain diuretics decrease renal loss of K and Mg:

- Amiloride 5–10 mg per day

- Spironolactone 25–50 mg per day

• Often diuretics use must continue with K and Mg supplement but in lesser quantity.

• Side effects of potassium-sparing diuretics: increased urination, dehydration, gynecomastia (not seen with amiloride), and gastric intolerance.

Additional points

• Always treat vomiting and diarrhoea which may contribute to electrolyte abnormalities.

• Capreomycin causes electrolyte abnormalities more frequently than other injectable. Consider changing CM to AMK or KM if the strain is susceptible.

• Continue electrolyte monitoring and replacement until injectable course is completed.

• If electrolyte abnormalities do not correct once the injectable is suspended suspect another cause.

8.2.13. Optic neuritis.

Suspected agent: mainly E (rarely Cs, PTO / ETO provoke visual disturbances)

A rare side effect and usually reversible after discontinuation of E. Loss of red-green

Colour distinction is usually the first sign.

Stop E (permanently).

8.2.14. Hearing loss.

Suspected agents: mainly S, Km, and Cm, (rarely PTO / ETO).

If a patient has had prior treatment with aminoglycosides then he or she may start the new regimen with established hearing loss, which could worsen with further therapy. Hearing loss is generally not reversible upon discontinuation of therapy. Audiometry for baseline and/or follow-up testing is required.

Change parenteral agent to Cm if currently on aminoglycoside. Consider reducing the dose or discontinuing the agent provided this does not compromise the effectiveness of the regimen.

8.2.15. Depression.

Suspected agents: Cs, flouroquinolones, and H.

Patients receiving anti-TB therapy are subject to a variety of factors (prolonged sickness, separation from family, difficult living conditions, etc.), which should not be underestimated as contributors to depression. Depressive symptoms may fluctuate during therapy. Prior history of depression may increase the risk of developing depression during treatment but is not a contraindication to use of any of the above agents.

Address socio-economic conditions if possible. Promote:

- Supportive counselling by medical and paramedical (i.e., health educators, social workers) staff.
- Intensive psychological therapy with counselling to patient and family.
- Emotional support from the family and health promoter.
- Group therapy or informal support groups

Always give pyridoxine 50mg per 250mg of Cs.

If necessary, initiate antidepressant medication (i.e., amitriptyline or fluoxetine) according to usual prescribed doses. Consider lowering the dose or discontinuing a suspected anti-TB agent provided this does not compromise the effectiveness of the regimen.

Note: when the regimen contains H: avoid serotoninergic (fluoxetine) and clomipramine; treat by amitriptyline.

Table 15 Adverse effects of MDR-TB/ART co-treatment

Signs or symptoms	**Response**
Abdominal pain	May be caused by several drugs. The patient should take drugs with food (except for ddI or IDV). Treat symptomatically
Nausea, vomiting	May be caused by many drugs. If due to ARV, they will often improve in a few weeks. If due to Ethionamide or PAS, nausea or vomiting may be chronic. Check for other causes of vomiting
Diarrhoea	If due to ART, the diarrhoea will improve in a few weeks. If it is due to PAS, it may be chronic If the patient is dehydrated, re-hydrate with ORS or an IV line. Examine, and treat for other possible causes of diarrhoea
Fatigue	Consider hypokalaemia or renal failure as a cause. Check creatinine, potassium Consider anaemia as a cause and check haemoglobin. Consider hypothyroidism due to Ethionamide and PAS and check TSH
Depression, anxiety, nightmares,	These may be due to EFZ or Cycloserine/Terizidone. If they are due to EFZ, symptoms will usually last less than three weeks. Mild depression can be managed with amitriptyline at night. Call for advice or refer if the patient has severe depression or is suicidal or psychotic.

	Serious symptoms may improve with a decreased dose of Cycloserine/Terizidone
Itching of skin, skin rash	If these symptoms are mild, give an antihistamine and monitor closely. If the patient has recently started NVP and is not responding to antihistamine, consider changing NVP for EFZ If the itching is generalized, or there is skin peeling, mucosal involvement, or other symptoms (fever, jaundice, etc.) stop all drugs (including CTX). This is very serious. Drugs will need to be reintroduced carefully when the rash has been resolved. Call for advice
Jaundice (yellow skin or eyes)	Check the patient's liver function tests (AST, ALT, and bilirubin) and stop all drugs. The jaundice may be due to EFZ, NVP, pyrazinamide or Ethionamide or other drugs. Call for advice on how to restart drugs
Pallor: anaemia	Measure the patient's haemoglobin. Anaemia may be a sign of an undiagnosed OI. AZT may cause anaemia, often in the first four to six weeks. If the patient has severe pallor or very low haemoglobin (<8 g/dl; <7 g/dl in a pregnant woman), stop AZT/substitute d4T. Refer/consult
Neuropathy (burning sensation in feet)	This may be due to ddI, d4T, Cycloserine/Terizidone, isoniazid, injectable or other drugs. Stop Stavudine and replace with Zidovudine. If patient shows no improvement, start amitriptyline or carbamazepine and call for advice
Muscle cramps, muscle spasms	The patient may have electrolyte wasting. Check potassium immediately; replace low potassium with bananas or potassium supplements
Headache	Give patient Paracetamol. Assess for meningitis. If patient is on AZT or EFZ, reassure him/her that this is common and usually self-limited. If headaches are chronic, they may be due to Cycloserine
Renal failure (swelling, decreased urine, hypertension)	Check creatinine. Stop injectable and call for advice
Hypothyroidism (fatigue, slowing)	Due to Ethionamide and PAS. Do not stop any Medications. Give thyroxin 50-100 mcg/day and recheck.

	The thyroid will return to normal once MDR-TB treatment is over
Blue/black nails	Reassure. It is normal with AZT
Gradual hearing loss *(confirm that this is not due to ear wax)*	May be due to injectable. Refer or consult
Dizziness, lack of balance	May be due to injectable. Refer or consult
Changes in fat distribution	Due to d4T or ddI. Discuss this carefully with your patient—can she/he accept it?

Chapter 9. Monitoring & Evaluation

9.1 Case recording and reporting

The national TB control program collects information on patients to monitor response to treatment and program performance. Efforts have been made to ensure the information collected is of high quality, accurate and timely for planning purposes.

The patients and health care workers should recognize the importance of collecting the patient data and storing this information in confidential standard files. This information should only be released to authorized personnel or when the patient gives consent for the information to be shared.

A patient appointment card will be in custody of the patient. S/he will be responsible for keeping it safe and producing it at all times when required by the health care worker serving him/her for information retrieval and updating. This card will carry the summary information of the patient and will serve as a primary source of patient information. It will be used to monitor progress and clinic attendance including daily ticking of supervision of treatment. The facility register and the patient record card will be kept in the health facility and, together with the laboratory register, forms the core patient records. The data are used by the clinicians to make decisions that will affect the management of the patients. A facility MDR TB register will collate all the information on patients with MDR TB within the facility Reporting of treatment outcomes will be based on these tools (cohort analysis).

Definitions based on site of disease and history of previous anti-tuberculosis treatment

Patients with tuberculosis involving the lung parenchyma are considered to have pulmonary TB. Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or Tuberculous pleural effusion, without radiographic abnormalities in the lungs, therefore constitute a case of extra pulmonary TB, acknowledging the lung fields may be obscured by large pleural effusions. A patient with both pulmonary and extra pulmonary TB should be classified as a pulmonary case because of the potential for transmission. The categories for case registration include **New, Relapse(either after after first-line treatment, or retreatment), Return after loss to follow**

up (either from first-line treatment or from retreatment), After failure of first-line treatment, After failure of retreatment treatment and Transfer in.

- **New.** Patients who have never received anti-tuberculosis treatment, or who have received anti-tuberculosis treatment for less than one month. (Note: patients who had DST at the start of a WHO Category I regimen and are then switched to a Category IV regimen because of resistance are placed in this group, even if they received more than one month of Category I treatment).
- **Relapse.** Patients previously treated for tuberculosis that has been declared cured or treatment completed, and then diagnosed with MDR-TB. This includes relapse after completion of category 1 or 2.
- **Return after loss to follow up.** Patients who return to treatment with confirmed MDR-TB after interruption of treatment for two months or more. This includes those who have defaulted category 1 or retreatment regimen.
- **After failure of Category I treatment.** Patients who return after having failed the first treatment.
- **After failure of Category II treatment.** Patients who return after having failed the re-treatment.
- **Transfer in.** Patients who have been transferred from another register for treatment of drug-resistant TB to continue Category IV 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.
- **New extra pulmonary.** Patients who have never received anti-tuberculosis treatment, or who have received anti-tuberculosis treatment for less than one month with tuberculosis of organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.
- **Other.** Patients who do not fit the above definition. This group includes previously treated pulmonary patients without known outcome status and all previously treated extra pulmonary patients.
- **Total.** The sum of Pulmonary, New extra pulmonary and Other.

9.2. Treatment outcome definitions for Category IV treatment

.Outcomes for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment

Outcome	Definition
Cured	Treatment completed with three or more consecutive negative cultures taken at least 30 days apart after the intensive phase
Treatment completed	Treatment completed BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: • lack of conversion by the end of the intensive phase, *or* • bacteriological reversion in the continuation phase after conversion to negative, *or* • evidence of additional acquired resistance to Fluoroquinolone or second-line injectable drugs, *or* • Adverse drug reactions (ADRs).
Died	A patient who dies for any reason during the course of treatment.
Loss to follow up	A patient whose treatment was interrupted for 2 consecutive months or more.
Transferred out (TO)	A patient who initiated treatment in one facility and is transferred to another to continue treatment for whom treatment outcome is unknown
Not evaluated	A patient for whom no treatment outcome is assigned and "still on treatment"
Treatment success	The sum of *cured* and *treatment completed*

Note:

For *Treatment failed*, lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of intensive phase of 8 months.

Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

Reversion (to positive): culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining *Treatment failed*, reversion is considered only when it occurs in the continuation phase.

9.3 Category IV recording and reporting system

This section describes the information system for Category IV 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 Category IV treatment. Tools are also introduced to track screening and enrolment efforts.

9.4 Category IV recording and reporting system

- A standardized method of recording and reporting should be implemented in DR-TB control programmes.
- DR-TB treatment cards should have an expanded section for information on patients with HIV.

The information system and performance indicators allow NTP managers at different levels to monitor overall programme performance. This includes:

- patients started on treatment and treatment outcomes
- follow trends in the number of cases notified
- plan drug supply
- Provide the basis for programme and policy developments.

9.4.1 Main forms/registers and flow of information

All patients diagnosed and treated for MDRTB should be registered and treatment outcomes recorded in the MDRTB facility registers that every facility/clinician treating MDRTB should have. This is essential for monitoring and evaluation of TB control activities. Before being registered for initiation of treatment the patient will be screened to ensure suitability for

treatment and possibility to treat without introducing the risk of XDRTB. This is because all failures of this treatment will be likely candidates of MDRTB.

The following tools will be used for reporting and recording

9.4.2 Category IV Patient Log book

Once the decision to start a patient on Category IV treatment is made, the health staff in the treatment unit should enter the patient in the Category IV Register. The staff should complete the Category IV **Patient Log book** when the patient is actually starting treatment. This card is a key instrument for DOT workers who administer drugs to patients on a daily basis. The card should be updated daily by ticking off the supervised administration of drugs. The card represents the primary source of information to complete and update the Category IV Register. The card, or a copy of the card, must always follow the patient (e.g. from a specialized hospital to an ambulatory facility). A copy of the card may be used as a notification form and later also to report the final outcome of treatment.

The **DR TB Patient Treatment log book** was an improvement of the patient treatment card. This was to act as the patient file with more details of history, examination, and follow up. It also has lab follow up test results and side effects monitoring. The consent in the patient log book ensures that health care workers remember to get consent from every patient. Patient contacts are also recorded in the last page of the leg book for ease of reference and follow up. The treatment log book contains the following sections:

- **Basic demographic and clinical information**. Records name, address, sex, age, weight and site of disease
- **Category IV registration number.** This is a new unique identification number assigned when the patient is entered in the Category IV Register.
- **Date of Category IV registration.** Provides registration date in the Category IV Register
- **Previous district TB registration number and date of registration.**
- **Type of TB**
- **Past Medical History**- record other chronic illness, other lung diseases and any medication that the patient could have.
- **Registration group according to result of previous ant tuberculosis treatment.**

- **HIV testing information.** DTC should be offered to all patients and the date of testing and results recorded here. If HIV-infected, indicate whether patient is on ART and/or CPT.
- **Previous TB treatment episodes.** Lists and describes any previous ant tuberculosis treatment and outcomes. Start with the earliest treatment and label it number 1. Use the drug abbreviations given on the front of the treatment card. Also note here the outcome of any previous treatment.
- **Previous use of second-line ant tuberculosis drugs.** Documents use of any of the second-line drugs listed at the front of the chart for ant tuberculosis treatment for more than one month.
- **TB Symptoms** – Tick the symptoms that the patient presents with
- **Social History**- enter the reproductive history of the patient especially in women such as last menstrual date, parity, and contraceptive use
- **Physical exam and lab result findings should be entered in the various areas**
- Baseline laboratory investigations are entered next.
- The Body Mass Index Chart- fill the baseline height for adults and monthly length/height in children. Record monthly weight and BMI for all.
- Consent form: The consent form should be signed by all patients of second line anti TB drugs
- **Meetings of MDR TB team.** This section provides a space to record major decisions by the team.
- **DST results.** Record the date of sputum collection and results of all DST performed. These should be filled for culture, HAIN results and GeneXpert
- **DR TB REGIMEN –** fill the date treatment is started, the dosage (mg), change of dosage and cessation of drugs
- **Monitoring of smear and culture.** Record date of sputum collection, sample number in the laboratory register and result of smear and culture accordingly Month "0" is the time of specimen collection at the start of the Category IV regimen. The specimen used for MDR TB diagnosis is recorded in the category called "prior" in the patient log book or register.

- **Regimen.** Record the initial Category IV regimen and later changes. Use one line for each date for each drug(s) that is changed. If drug dosage is progressively increased (e.g. starting 250 mg of Ethionamide daily and increasing by 250 mg over 2–3 days until the full dose is reached), record this in the patient's medical record (not on the treatment card).
- **Record of daily observed administration of drugs.** This is constructed with one line per month to facilitate assessment of adherence. Mark one box for each day the entire treatment is administered. Additionally, if dosing is twice daily, one slash mark could be made for the A.M. dose and a second, intersecting mark could be made for the P.M. dose; if both are received, the box would contain an "x".
- **Monthly laboratory and Clinical follow up-** record an finding – lab result and clinical- in the chart
- **Recommended Contraceptive (for females)** – record the contraceptive that patient is on (NB- *all female patient of reproductive age should be on contraceptive while on treatment to avoid pregnancy*)
- **Daily Observation drug intake** – enter O for directly observed, N for not supervised and X for drugs not taken. This is a page per month till end of treatment.
- **Outcome of treatment.** Record the outcome of treatment when the final bacteriology results become available in the first page of the logbook
- **MDR TB side effect monitoring** – indicate the grade of an side effect the patient develops management and outcome
- **Clinical notes** – all notes made by a clinician should be entered in the clinical notes section
- **Household contacts** – list all of them by name, age, sex, telephone number and outcome. Transfer this same list to the MSR TB suspect/contact register.

9.4.3 The Category IV Register

This is the record of all patients who start Category IV treatment. This register allows quick assessment of the implementation of Category IV, facilitating quarterly reporting and analysis of treatment start and outcomes. Any patient with mono- or poly resistance should stay in the DR-TB programme should not be crossed out of the Category IV Register.

The District Tuberculosis Register is the traditional register used by DOTS programmes in which all TB patients are first registered. Any patient who is switched to a Category IV regimen should have the outcome category "Change to Category IV" entered in the District Tuberculosis Register.

The following information is recorded in the Category IV Register as it is in the patient treatment card

- **Category IV registration number.**
- **Date of Category IV registration.**
- **Name, sex, date of birth, address**
- **District TB registration number.** All patients should have been entered in a District Tuberculosis Register. A patient who for any reason has never been registered in the District Tuberculosis Register should be registered there and the number transferred to the Category IV Register.
- **Site of disease.** Pulmonary, extra pulmonary or both, Patients with both pulmonary and extra pulmonary TB should be classified as a case of pulmonary TB.
- **Registration group**
- **Weight**
- **BMI, Second-line drugs received for more than one month prior to registration**
- **DST.** Date sample taken, date of DST result and the results. Enter the DST that resulted in the patient being registered as a Category IV patient. Follow-up DSTs are not recorded in the register.
- **GeneXpert results**
- **Category IV regimen.** Record the initial Category IV regimen using the drug abbreviations.
- **Date of start of Category IV treatment**
- **Smear and culture monitoring result.** Record all smear and culture results
- **Final outcome HIV status.** Testing results, CPT and ART treatment information

9.4.4 Laboratory Register for culture and DST

Laboratories will have separate registers for sputum smear microscopy and culture (*5*), while reference laboratories carrying out DST should have additional space in the culture register for DST results. The Laboratory Register for culture and DST should contain samples from all MDR-TB suspects, indicating the registration group, and be filled in from the request form.

The Laboratory Register should be compared regularly with the Category IV Register to ensure that all confirmed MDR-TB cases are entered in the Category IV Register.

TB Sputum-smear Examination Request Form. This form should be used by health care workers who for follow up smear exams

Laboratory Register for Sputum-smear Examination: Where the facility registers the patients smeared every day

TB Culture/sensitivity Request Form – for request of follow up cultures as detailed in the guidelines

Drugs and other supplies:

Daily Activity Drug Register (DADR) – to monitor the use of the MDR-TB drugs on a daily basis

Facility CDRR (Consumption Drug Report & Request) Form- to summarize the consumption of drugs in the MDRTB treatment centre

Others: Bin Card and S11.

9.4.5 Quarterly report on MDR-TB detection and Category IV 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. This report should be accompanied by a copy of the patient register to update the national MDR TB patient line register.

The report should be made by the unit managing MDR-TB. The quarterly report includes:

- All drug resistant TB cases should be accounted for using the quarterly reporting tool. This tool segregates them by the resistance pattern, sex, age and HIV status as in TIBU.
- The number of confirmed MDR TB patients in that quarter
- Number of MDR TB patients started on treatment in that quarter split by registration group
- The number of confirmed XDR-TB cases

9.4.6 Six-month interim progress assessment of confirmed MDR-TB cases

Since treatment takes on average two years before final results are known, the TB control programme needs more updated information on treatment progress. Bacteriological results are based on the smear and culture data during months 5 and 6 of treatment. Consider the 6-month progress assessment unknown for a particular patient if a culture or smear result is unknown for either month 5 or 6. All cases from the Category IV 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.

9.4.7 Annual report of treatment result of confirmed MDR-TB patients starting Category IV treatment

This report shows the final result of treatment by year of treatment start. All the patients are classified by previous use of anti tuberculosis drugs (none, only first-line drugs, also second-line drugs). If relevant, results for patients with XDR-TB could be added. All data can be extracted from treatment cards and Category IV Register. The report is made at 24 months after the last

patient in the cohort started treatment. Most of the patients will have finished treatment by 24 months, allowing preliminary assessment of cure rates. Since a few patients may be on treatment for longer than 24 months, the form will be completed again at 36 months, which will then be considered the final result.

9.4.8 Drug Resistant Patients Not on Treatment – All patients diagnosed with drug resistant TB should be put on treatment immediately. While awaiting the baseline results, a home visit should be carried out and the patient's family educated on the disease, duration of treatment, infection control, adherence, psychosocial support among others. All patient contacts should also be screened for drug resistance and all names recorded in the patient treatment log book (last page) and in the suspect/contact register for follow up.

9.4.9 Assuring the quality of the recording and reporting system

In order for the information system for DR-TB to function well:

- Adequate training on DOTS information system and the specifics of the Category IV forms.
- Regular supervisory visits
- Regular meetings between MDR TB teams and other staff at different levels to share information

Weekly comparisons of the Category IV Register with the DST register in all the laboratories performing DST to ensure that all patients in whom MDR-TB is diagnosed are started on Category IV treatment. The inclusion of MDR-TB patients from the Laboratory Register should take into consideration the quality of the DST performed in the laboratory. Patients diagnosed with MDR-TB in laboratories without proper quality assurance (i.e. in many private laboratories, the quality of DST is completely unknown) should not be included in the Laboratory Register for Culture and DST until their DST has been confirmed in a qualified laboratory.

9.4.10 Referral of DR TB patients

Category IV Patients who may need specialized treatment or hospitalization will be referred to county or regional hospitals that are appropriately equipped to manage MDR-TB patients. The patient should be referred after filling the referral form

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Annex 1: Adult & Adolescent Dosages for Secondline Anti TB medicines

Drugs	Weight Class			
	Average daily dosing	33-50kg	51-70kg	>70kg
Isoniazid (H) (100,300 MG)	10-20 mg/kg daily	200 - 300 mg daily	300mg daily or	300mg
Rifampicin ® (150, 300m mg)	10-20 mg/kg daily	450-600 mg	600 mg	600 mg
Ethambutol (E) (100, 400 mg)	25 mg/kg daily	800-1200 mg	1200-1600 mg	1600-2000 mg
Pyrazinamide (Z) (500 mg)	30-40 mg/kg daily	1000-1750 mg	1750-2000 mg	2000-2500 mg
Streptomycin (S) (1 G vial)	15-20mg/kg daily	500-750 mg	1000 mg	1000 mg
Kanamycin Km (1G vial)	15-20mg/kg daily	500-750 mg	1000 mg	1000 mg
Amikacin (AM) (1G vial)	15-20mg/kg daily	500-750 mg	1000 mg	1000 mg
Capreomycin (CM) (1G vial)	15-20mg/kg daily	500-750 mg	1000 mg	1000 mg
Ofloxacin (Ofx) (200,300,400mg)	The usual adult dosefor MDR-TB is 800 mg	800 mg	800 mg	800-1000 mg
Levofloxacin (LFX) (250,500 mg)	The usual adult dose for MDR-TB is 750 mg	750 mg	750 mg	750-1000 mg
Moxifloxacin (Mfx)	The usual adult dose for MDR-TB is 400 mg	400 mg	400 mg	400 mg
Gatifloxacin (Gfx) (400 mg)	The usual adult dose for MDR-TB is 400 mg	400 mg	400 mg	400 mg
Ethionamide (Eto) (250 MG)	15-20 mg/kg daily	500 mg	750 mg	750-1000 mg
Prothionamide (Pto) (250 MG)	15-20 mg/kg daily	500 mg	750 mg	750-1000 mg
Cycloserine (Cs) (250 MG)	15-20 mg/kg daily	500 mg	750 mg	750-1000 mg
Terizidone (Trd) (300 MG)	15-20 mg/kg daily	500 mg	750 mg	750-1000 mg
PAS 4gm sachets	150mg/kg daily	8gm	8gm	8-12gm

The drugs are administered once a day for six days per week. Each dose is given as directly observed therapy throught the course of treatment.

Annex 2: Pediatric Dosages for Secondline Anti TB medicines

Medication	Dose	Maximum daily dose
Isoniazid(H)	10mg/kg daily	300mg
Rifampicin (R)	15mg/kg daily	600mg
Ethambutol (E)	25mg/kg daily	1200mg
Pyrazinamide (Z)	30 -40 mg/kg daily	1500mg
Streptomycin (S)	20 - 40mg/kg daily	1000mg
Kanamycin (K)	15 -30mg/kg daily	1000mg
Capreomycin (Km)	15 -30mg/kg daily	1000mg
Ofloxacin (Ofx)	15 - 20mg/kg daily	800mg
Levofloxacin (Lfx)	15 - 25mg/kg daily	1000mg
Moxifloxacin (Mfx)	7.5 -106mg/kg daily	400mg
Ethionamide (Eto)	15 – 20 mg/kg daily	1000mg
Cycloserine (Cs)	10 – 20mg/kg daily	1000mg
Terizidone(Trd)	10 – 20mg/kg daily	1000mg
Para – aminosalisylic acid (PAS)	150mg/kg daily	8g(PASER)

Annex 3: Side-effects follow-up

Document the treatment being used – drug(s) and dosages

Name:				Current treatment regimen – drugs and dosages:		
Week of treatment						
Date						
Sweats						
Cough						
Abdominal pain						
Constipation						
Nausea						
Vomiting						
Anorexia						
Diarrhoea						
Headache						
Periph neuro						
Hypothyroidism						
Low magnesium						
Low potassium						
Skin rash						
Itching						
Joint pain						
Dizziness						
Vision loss						
Hearing loss						
Psychosis						
Convulsions						
Others						