FEDERAL DEMOCRATIC REPUBLIC OF ETHIOPIA

MINISTRY OF HEALTH

GUIDELINES ON PROGRAMMATIC MANAGEMENT OF DRUG RESISTANT TUBERCULOSIS IN ETHIOPIA

Second Edition

December 2013

Addis Ababa

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State Minister (Program), Ministry of Health

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ACRONYMS

ADR	Adverse drug reaction
AFB	Acid-fast bacilli
AIDS	Acquired Immuno Deficiency Syndrome
ART	Anti-retroviral therapy
BCG	Bacille-Calmette-Guérin
CBC	Complete blood count
COC	Combined oral contraceptives
CPT	Cotrimoxazole Preventive Therapy
CXR	Chest X-ray
DOT	Directly observed treatment
DOTS	Direct observed Therapy short-course
DR-TB	Drug-resistant tuberculosis
DST	Drug susceptibility testing
FBS	Fasting blood sugar
FIND	Foundation for Innovative New Diagnostics
FLD	First line anti-TB drugs
GDF	Global drug facility
GFATM	The Global Fund to fight AIDS, Tuberculosis and Malaria
HCG	Human Chorionic Gonadotropin
HCW	Health care worker
HEW	Health Extension worker
HIV	Human immunodeficiency virus
IUCD	Intra-uterine contraceptive device
LED	Light-emitting diode
LFT	Liver function test
LPA	Line probe assay
MDR-TB	Multidrug-resistant tuberculosis
NGO	Nongovernmental organization
NSAIDs	Non-steroidal anti-inflammatory drugs
NTP	National tuberculosis control programme
OI	Opportunistic infections
PMDT	Programmatic management of drug resistant Tuberculosis
PPM	Public–private mix
RFT	Renal function test
RHB	Regional health bureau
RR-TB	Rifampicin-resistant tuberculosis
SLD	Second line anti-TB drugs
TFC	Treatment follow up center
TIC	Treatment initiating center
TSH	Thyroid stimulating hormone
TB	Tuberculosis
TBL	Tuberculosis leprosy
WHO	World health organization
XDR-TB	Extensively drug-resistant TB
Xpert MTB/RIF	Xpert Mycobacterium Tuberculosis/ Rifampicin test
ZN Stain	Ziehl Neelsen otherwise called AFB stain

FOREWORD

Ethiopia is a high TB, TB/HIV and MDR TB Burden country. The FMOH is implementing a comprehensive TBL and TB/HIV control program and has achieved a lot in the past decade and is on track to achieve the MDG targets regarding TB and HIV.

The increasing emergence of drug-resistant strains of TB is due to treatment defaulters and other challenges ranging from delays in initiating treatment, inadequate bed capacity, poor infection control in health facilities, and new infections.

The following policy guidelines are intended for use by health care professionals involved in the complex and difficult task of MDR- and XDR-TB patients in Ethiopia. The guidelines focus on the clinical management, referral mechanisms and models of care. However, psychosocial support to ensure comprehensive management of the patients, strategies for infection prevention and control, and health services for health care workers (HCWs) are covered.

Management of DR-TB is an evolving strategy, and needs to be adapted through evidence-based information. These guidelines contain recommendations based on the most recent and available scientific evidence and expert opinions. Comments and suggestions from those working in the field are essential to ensure a dynamic process, aimed at optimal control of DR-TB in Ethiopia.

1. INTRODUCTION TO THE GUIDELINE

The national TB control program has released the first PMDT guideline in 2009 and has been implementing the DR-TB program since then. The first edition of the guideline is revised in order to incorporate scientific updates and best practices on PMDT both from in country and abroad.

Since the publication of the first edition of the PMDT guideline in 2009 several new developments occurred in the diagnosis and management of DR TB globally. Some of the key changes include evidence based policy update on PMDT, expanded role of rapid diagnostics in DST for LPA and Xpert MTB/RIF Tests, updates on definitions and reporting framework for tuberculosis, new drugs like bedaquiline, new guidance on contact investigation, new guidance on ethics of TB control, role of rapid tests in SLD DST.

The second edition of the guideline has tried to incorporate all the new developments internationally and tries to build upon the successes of PMDT implementation nationally.

Summary of the key changes made in the second edition of the guideline

Section two presents the basic principles of DR TB causation. It also summarizes the DR TB control frame work of Ethiopia.

Section three presents the program design, coordination and management aspects of DR-TB in Ethiopia. It describes the shift made in the treatment model from hospitalized to outpatient Ambulatory model of care as it benefits decentralization of the service and reduce burden on the patients. Elaboration is made on the role of treatment centers in the provision of care, treatment and support to the patient during the course of treatment. Communication and referral mechanism has to be strong between treatment centers through CAM and Mentoring.

In the case finding strategy and laboratory aspects of DR-TB section, this edition emphasized on the need for systematic identification of presumptive DR-TB cases and use of WHO approved rapid DST techniques like LPA and Xpert MTB/RIF. Separate DR-TB diagnostic algorithms are introduced to be used at HF and reference laboratory level. Further elaboration is provided on how to use the sample transportation system to access culture and DST services and annexed Standard operating procedure for proper sample collection and transport.

Section on the DR-TB case definition and registration is updated based on the new WHO definitions and reporting framework, 2013. New changes on Rifampicin resistant TB (RR-TB) cases to be enumerated and reported separately, case definition based on WHO newly approved confirmatory results like Xpert MTB/RIF and revised definition for cure and treatment failure are incorporated. In addition, ethically

acceptable and nonjudgmental terms are inserted as and “presumptive TB” instead of “TB suspect” and “lost to follow up” for “Defaulter”.

Section seven to nine deals with the treatment aspects of DR-TB. It presents the treatment principles in designing effective regimen to treat DR-TB Tuberculosis and describes Cm-Lfx-Pto-Cs-Z as the preferred Standardized regimen in Ethiopia.in Ethiopia. Kanamycin is alternate drug for Capreomycin in the regimen. Prothionamide is a prodrug for Ethionamide is preferred in the regimen for its better tolerance though either of them can be used interchangeably based on the availability. The treatment duration is also redefined as minimum of 8 months or four month after culture conversion, and total duration of 20 months or 18 months after culture conversion.

In the management of pre-XDR and XDR cases, the use of newly WHO approved drugs can be used if there are no adequate drugs to construct likely effective regimen.

The wide range and frequent occurrence of Adverse drugs reactions to Second line TB drugs complicates the case management of DR-TB patients and at large the success of the program. This section gives due emphasis to assist health professionals to develop the necessary knowledge and skill to systematically screen patient for ADRS and identify early and treat promptly.

Patient preparation and monitoring section presents how to prepare, monitor and support patient receiving DR-TB treatment and place Direct observed therapy throughout treatment. Besides, justifies why psychosocial support is part and parcel of treatment packages and advice on the package and modalities of support to the eligible population.

2. BASIC CONCEPTS AND NATIONAL CONTROL FRAMEWORK

2.1 Basics of Drug Resistance in Tuberculosis

Resistance to anti-tuberculosis drugs is a natural phenomenon occurring in all wild-type populations of M. tuberculosis by spontaneous chromosomal mutations. Within wild-type M. tuberculosis populations, small populations of mutants are found to be resistant to anti-tuberculosis drugs.

For instance, in a given wild-type population 3.5×10^{-6} are resistant to INH and 1.2×10^{-8} are resistant to Rifampicin. As resistance to the various drugs is not linked genetically, for a bacillus to be resistance to more than one TB drug is even rarer phenomena: $3.5 \times 10^{-6} \times 1.2 \times 10^{-8} = 4.2 \times 10^{-14}$ are resistant to the combination of INH and RIF. Hence, the chance for wild-type resistant mutants to cause clinically significant TB with either mono- or poly- resistant forms in an untreated M. tuberculosis population is extremely rare as it would require very large number of mutant bacilli.

Rather, the selection of naturally occurring drug-resistant mutants by inadequate TB treatment is mainly responsible for the population of M. tuberculosis bacteria to become increasingly drug-resistant. As the drug-susceptible organisms are killed during sub-optimal treatment, the drug-resistant mutants gradually become an increasing proportion of the disease burden, and results in emergence of drug resistant form of TB.

The chance for having single chromosomal mutation to cause resistance to two or more anti-TB drugs is an extremely rare event. Hence, Poly- or multi-drug-resistant TB is caused by sequential mutations in different genes. Susceptible TB bacilli develop resistance first to one drug (-acquired resistance) and subsequently to another drug by amplification of resistance. This evolution involves multiple cycles of "fall and rise" phenomena where susceptible strains will be killed leaving the resistant strains to multiply and predominate the bacillary population.

Despite the fact that HIV epidemic 'speeds up' the emergence of drug resistance in communities by shortening the natural history of TB, resulting in a higher proportion of individuals to develop TB disease, there is no evidence of an association of drug resistance with HIV infection per se.

2.2 Definitions of drug resistance in tuberculosis

Drug resistance among New TB patients*:* refers to resistance in patients who have no history of treatment for tuberculosis for a period longer than one month.

Drug resistance among previously treated TB patients*:* refers to resistance in patients who have been treated for TB for a period lasting more than one month.

2.3 Causes of drug-resistance in Tuberculosis management

Causes associated with the emergence of drug resistance in an individual could be either microbial, clinical and programmatic. However, common causes are essentially man-made errors following an **inadequate or poorly administered treatment regimen** that allows a drug-resistant strain to become the dominant strain in a patient infected with TB. Table 1.1summarizes the common causes of inadequate treatment although DR-TB can then spread from one person to another.

These potential causes of inadequate treatment can be broadly categorized in to:-

- Health care factors: provider, program related factors
- Drug related factors
- Patient related factor

Table: Causes of inadequate Anti- tuberculosis treatment

Health-care provider/ program related factors	Drug related factors	Patient- related factors
• Inappropriate guidelines • Non-compliance with guidelines • Absence of guidelines • Poor training • Poor supervision • No monitoring of treatment provision • Poorly organized or funded TB control program • Inadequate regimens • Lack of DST • Poor access to health care	• Poor quality medicines • Unavailability of certain drugs due to stock-outs of delivery disruptions • Poor storage conditions • Wrong doses or combinations (manufacture related) • Poor regulation of medicines	• Poor adherence/default • Lack of information • Lack of money • If Treatment not given for free • Lack of transportation money or support • Drug adverse effects/interaction, • Mal-absorption • HIV • Diabetes mellitus • Malnutrition • Psychiatric condition • Substance/alcohol dependence • Social barriers

2.4 Prevention of development of DR TB

Environments conducive for TB transmission in general, including crowding, poor ventilation, and poor infection control practices in health facilities and other places where transmission occur, also contribute to transmission of MDR-TB.

Similar to drug-susceptible TB, DR-TB only progresses to active disease in a minority of those infected, and DR-TB infection can remain latent for long periods of time. A poorly functioning immune system increases the risk of progression, and therefore all factors that can impair the immune system (e.g. HIV, under-nutrition, diabetes, silicosis, smoking, alcohol abuse, a wide range of systemic diseases and treatments with immunosuppressant) are risk factors for DR-TB disease in a person initially infected with a DR-TB strain.

Evidences show that poor standardized TB treatment and transmission of resistant strains as major causes for development of Drug resistant TB in the community.

There are four standard ways to prevent DR-TB:

i. Early detection and high quality treatment of drug-susceptible TB.
ii. Early detection and high quality treatment of DR-TB. For people with DR-TB, early diagnosis, proper treatment and patient support are key elements to decrease transmission and amplification of resistance.
iii. Health system strengthening and regulation: integration of services, strengthen lab capacity, strengthen TB Infection Control and Drug regulation (Quality and availability of both 1st and 2nd line medicines need to be assured, such that regulation of registration, import and manufacturing of TB drugs is addressed).
iv. Addressing underlying risk factors and social determinants: Poverty, Vulnerable groups (Refugees, Prison), HIV, Diabetes, Malnutrition, Substance abuse (alcohol, Cigarette)

Cognizant of this, national TB control program (NTP) has decentralized TB control activities in the community through the health extension program, with primary aim of improving case finding, adherence support and treatment success.

The national TB program through integrated management of both drug susceptible and resistant forms of Tuberculosis will focus on early identification of TB cases, administration effective treatment, and strengthening of infection prevention practices to prevent and control the threat of all forms of TB, including DR TB.

2.5 Epidemiology of Drug Resistant Tuberculosis

Globally in 2012, there were an estimated 450 000 (range: 300 000–600 000) new cases of MDR-TB. Data from drug resistance surveys and continuous surveillance among notified TB cases suggest that 3.6% (95% CI: 2.1–5.1%) of newly diagnosed TB cases and 20% (95%CI: 13.3–27.2%) of those previously treated cases are estimated to have MDR-TB. A total of 94 000 TB patients eligible for MDR-TB treatment were detected in 2012. At least one case of extensively drug-resistant TB (XDR-TB) had been reported by 92 countries by the end of 2012. Nonetheless, on average, 9.6% of MDR-TB cases are estimated to have XDR-TB.

Globally, only 48% of MDR-TB patients in the 2010 cohort of detected cases were successfully treated, reflecting high mortality rates and loss to follow-up. A treatment

success rate of 75% or more for patients with MDR-TB was achieved in 34 of 107 countries.

Global Plan to Stop TB 2011–2015 sets targets to screen 20% of all new bacteriologically-positive TB cases and all previously treated cases with DST for at least rifampicin and isoniazid, and Planned to perform SLDs DST for all patients with MDR-TB. However, in 2012, only 5% of new and 9% of previously treated cases was tested for MDR-TB. In Ethiopia, FLD DST was performed for 469(<1%) new and 180(4%) retreatment TB cases, respectively, in 2012 to confirm 284 MDRTB; 30 among new and 102 among previously treated cases.

The 2003-2005 drug resistance TB survey result showed, 1.6% of new cases and 11.8 % of retreatment cases in Ethiopia to be resistant to at least isoniazid and rifampicin. The global TB Report 2013, has estimated 2,010(1,200-3,000) MDRTB cases to occur among all notified TB cases in 2012, comprising of 1600 (830–2 700) among new and 480 (230–870) among retreated TB cases.

2.6 National DR-TB Control Framework

For the provision of comprehensive and quality diagnostic and treatment services for MDR-TB, implementation of the STOP TB STRATEGY must be adapted to the context of DR-TB control framework. It addresses TB/HIV and MDR-TB, health system strengthening, engagement community and all care providers and operational researches in addition to DOTS.

Each component of the extended DR-TB strategy, shown below, contributes for the success of the program. Each of these components involves more complex and costly operations than those for controlling drug sensitive TB. However addressing multidrug-resistant TB will strengthen the existing TB control program.

National DR-TB Implementation frame work:

1. **Sustained political commitment**
   - Addressing the factors leading to the emergence of MDR-TB
   - Long-term investment of staff and resources
   - Coordination of efforts between communities, local governments and international agencies
   - A well-functioning DOTS program
2. **Appropriate case-finding strategy** including quality-assured culture and drug susceptibility testing (DST)
   - Rational triage of patients into DST and the DR-TB control programme
   - Relationship with supranational TB reference laboratory
3. **Appropriate treatment strategies** that use second-line drugs under proper case management conditions
   - Rational treatment design
   - DOT
   - Monitoring and management of adverse effects
   - Properly trained human resources
   - Active pharmacovigilance in the introduction of new drugs or novel regimens
4. **Uninterrupted supply of quality-assured second-line anti-tuberculosis drugs**
5. **Recording and reporting system** designed for drug resistance-TB control programs

3. MDR-TB Programmatic Design, Coordination and Management

3.1 MDR-TB Program Design

National Tuberculosis program in Ethiopia has shifted the hospitalized model of care for DR-TB case Management, mentioned in the first edition of PMDT guideline, to Clinic –based Ambulatory model of care as it is more feasible for decentralized implementation of the program in the local context and would be convenient for patient follow up.

Clinic-based Ambulatory Model of care: is designed to deliver the treatment course on outpatient basis so long as the patient is fit to be followed as ambulatory. The place of temporary inpatient care is reserved mainly for patients who develop severe adverse events during the course of treatment. However, patients either with serious medical or social reason may be admitted with the decision of the panel team.

3.2 MDR-TB treatment centers

In treatment of DR-TB patients in Ethiopia, health facilities could serve as either treatment initiating centers (TIC) or treatment follow up centers (TFC) or both. These two levels of treatment centers have complementary roles in order for the program to function efficiently and deliver comprehensive DR-TB care, treatment and support.

Treatment initiating centers (TIC): are health facilities selected by the TB program to provide patient care and treatment services right from time of DR-TB diagnosis and throughout the course of treatment with SLDs. The clinical panel of team in these centers is authorized to initiate treatment, perform all scheduled clinical evaluation and lab monitoring tests, manage difficult cases and those with serious complications and/or ADR and decide on the need of regimen modification when indicated.

Responsibilities of Treatment Initiation center (TIC)

- Designate space for inpatient and outpatient MDRTB treatment service
- Involve in case finding process of DR-TB
- handle all Patient preparation and initiation of treatment with SLDs
- Admit difficult cases and those with serious complications

Treatment follow up centers (TFC): are health facilities with TB DOTS clinic where clinically stable patients continue to receive DOT for SLDs and perform routine screening of adverse events and management with the aim to decentralize the delivery of treatment services closer to the patient residence.

Responsibilities of Treatment follow up center (TFC)

- manage all patients referred/transferred from treatment initiation center
- Involve in case finding process of DR-TB
- Routine screening of adverse events, supervise DOT and administer injection

3.3 Phases of treatment in treatment delivery

The national TB program designed the DR TB treatment to be delivered in three phases whereby the respective treatment centers have specific tasks and responsibilities at each phase in order to implement the standard patient care packages defined by the national guidelines.

Phases of MDR-TB treatment delivery:

Phase I: Intensive phase: stabilization
Phase II: Intensive phase: out patient
Phase III: Continuation Phase

Phase I: Intensive phase: stabilization

In this phase, all efforts are directed to ensure that patients are both clinically stable and adherent to SLDs; hence, the role of clinical team at TICs is more intensive to provide the necessary clinical, adherence and social support arrangements to enables the patient to be fit enough to be followed at TFC level.

In this phase, TIC is responsible for patient preparation, regimen selection and treatment initiation & monitoring. However, daily Supervision of DOT and administration of injection could be made either at TIC or TFC level considering the patient clinical and social condition, arrangement with TFC or need for adherence.

- Patient can start treatment at TFC level if the panel team decides to link the patient to TFC right from the start for daily DOT and administration of injection. TIC must handle patient preparation and treatment initiation and

arrange weekly evaluation of the patient till stabilization and move to next phase. or

- Patient can stay at TIC level till the panel team decides to transfer to next phase and link the patient to TFC to continue with phase II.

Criteria for transferring patients to next phase include:

- Clinical condition and satisfactory treatment adherence of the patient,
- Having satisfactory follow-up plan with the patient, and
- Arrangement with TFC and the TB program officer.

Indication for in-patient care of MDRTB patients:

Temporary in-patient management of DRTB patients are indicated for:

- Patients who are not able to ambulate for medical or social reason
- Poorly controlled or complicated co-morbidities (diabetes, Liver failure, renal insufficiency, psychiatric illness, cardiac problems and substance dependency)
- Patients from congregate settings (prisoners, refuges and homeless shelters)
- Patient who developed serious ADR or other concomitant illness
- XDR suspect/case or contact of presumed or known XDRTB case
- Adherence problems or with failing MDR regimens*
- All confirmed or presumptive XDR-TB cases*

N.B: Pregnant women and children do not need to be hospitalized if clinically stable.

*Such patients should only be admitted in TB isolation rooms with limited contact with other patients with strict IP precautions to avoid increased risk of transmission of resistant strains within the health facility level.

Phase II - Intensive phase out-patient

In phase II, the clinical management of the patient is similar to stabilization phase, but now the patient has stable clinical condition, satisfactory adherence to treatment and can be followed at TFC level, while TICs continue to perform the scheduled monthly clinical and lab assessment of treatment.

TFC are responsible for daily DOT supervision and routine screening of adverse events. Patient must be referred back to TIC if they develop severe adverse events or serious medical condition requiring admission or expert evaluation.

Phase III – Continuation Phase

The continuation phase of treatment is provided under directed supervision of either HCWs at TFC, HEWs at Health post or by family DOT provider, under close supportive supervision by the treatment follow up center. Supervision of treatment at home level must consider:

- Linkage with the responsible HEWs at HP to support treatment
- Patients clinical condition
- Availability and Capacity family DOT provider
- Demonstrated successful adherence to oral and injectable TB medicines

National Tuberculosis program in Ethiopia has shifted the hospitalized model of care for MDR-TB case Management, mentioned in the first edition of PMDT guideline, to Clinic –based Ambulatory model of care as it is more feasible for decentralized implementation of the program in the local context and would be convenient for patient follow up.

3.4 Management Teams/Committees at Different Levels

For Successful implementation of MDRTB program and service up from the national program down to the health facilities where patient are receiving MDRTB care and treatment; there need to be technical coordinating teams at national, regional and site-level assuming appropriate role and responsibilities as follows:

MDR-TB TWGs at national and regional levels:

Under the national and regional TB technical working groups, there has to be MDRTB subgroups to oversee, monitor and assist the successful PMDT implementation at respective level. The team should be composed of all relevant stakeholders at the respective level.

Health Facility MDR-TB panel team

Every Treatment initiating center needs to establish **a medical/clinical panel team** to assist smooth implementation of the program and provide appropriate patient care at service delivery points. The team is expected to meet every month to review patients' profiles and decide on major action and document their final decision on the appropriate box on patients' treatment card.

Team composition: Clinicians from MDR-TB center, nurses, pharmacist, laboratory technologist, chief Clinical officer, social workers, local health office (-regional, zonal &/or Woreda) TBL officers, and technical advisors from partners.

Responsibilities of the team include:

- Evaluation of clinical and social profile of each patient who is about start treatment
- Decision on mode of treatment initiation for individual patient
- MDR TB treatment based on clinical criteria for selected patients.
- To construct individual treatment regimen when needed
- Arrangement of social support for eligible patients
- To decide on end of intensive phase and continue with continuation phase
- To define patient's interim and final treatment outcome
- To decide patient's transfer to respective TFC
- To assist TFCs, together with the program, to practice standard of care.

3.5 Communication and Support Mechanism between Treatment Centers

In MDRTB program implementation, treatment centers, DST laboratories and programmatic stake holders need to be organized and have clear mechanisms for regular communication in order to deliver standardized level of care for the patients.

3.5.1 Organization of DR-TB treatment centers

The implementation of comprehensive MDRTB care and treatment services requires the combined efforts of health facilities at different levels within the existing heath care system. The integrated service at the hospital, health centers, culture & DST labs and lower community level care needs to be defined so that no component of the comprehensive care neither missed out nor duplicated.

Health facility serving as Ambulatory TIC: All Hospitals and high volume Health centers must initiate treatment with SDLs and provide follow up services for stable and uncomplicated cases.

Health facility serving as referral level TIC: Hospitals with dedicated MDRTB wards with isolations rooms should act as referral medical centers in addition to the services designated to be provided by Ambulatory TIC.

Health facility serving as TFC: All DOT clinics must serve as TFC center whereby screening of all TB cases for possible Drug resistance, MDRTB follow up treatment and care services is to be provided.

3.5.2 Communication and support mechanism

In order to provide the comprehensive and Quality DR TB care and treatment services, centers with different and complementary roles needs to have strong referral communication and support mechanisms. As a result, NTP has arranged 8-10 TFCs under one TIC as a catchment unit so that there will be Catchment area meetings and clinical mentoring support among centers within the same unit. Besides, centers with small number of patients may be supported by supportive supervision and review meetings organized by the TB control program.

Catchment Area Meeting in PMDT: refers to meetings conducted between Treatment centers within same catchment to improve quality of care in the comprehensive DR-TB case management. The meeting shall be held bimonthly till the program matures, and then linked to the quarterly review meetings. The purpose of the meetings includes:

- To strengthen the referral and communication system between TIC, TFC, DST lab, Health offices & various actors in the program
- To improve the case management and clinical decisions skills of HCWs at TFCs
- To foster the spirits of team work to improve quality of care and patient satisfaction
- To deal on areas of improvements identified during the mentoring support visits

Catchment area team members includes HCWs and administrators from Treatment centers, TB officers from local zonal and Woreda offices and representatives of partners supporting TB program.

Clinical Mentoring support in PMDT: refers to regular site-level technical support by DR- TB clinical team from TIC to HCWs at TFC levels in order to improve the clinical case management skill of staffs and hence quality of patient care at TFC levels.

It is recommended to be conducted every month for the first Six month, then every two months for the next six months, and then linked to programmatic support through supportive supervision.

The purpose of conducting mentoring support includes:

- To transfer skill on case management of DR-TB at TFC level
- To ensure practice of DOT and monitoring of side effects
- To support staffs to conduct contact screening and manage
- To assist TFCs to maintain good infection control standards
- To ensure all Recording and reporting forms are kept updated
- To arrange transferring of patients and their SLDs to TFC upon discharge

Clinical Mentoring team comprises of Health workers from TIC who are directly involved in case management of DR TB patients, and/or TB/HIV experts from Regional/ zonal/ wereda/ partners who is experienced on PMDT.

Note that, in areas where logistic arrangement to conduct catchment area meetings and clinical mentoring by hospital staffs from TIC are limited, TB program officer from the respective RHB/Zonal or woreda health offices and partners should provide the necessary technical and programmatic support for HCWs at TFCs through supportive supervision to maintain the quality of patient care.

3.6 Human resource requirement and capacity development

For comprehensive implementation of DR-TB service package at treatment centers and respective TB program management units, the following capacity development are recommended for program managers, health care workers, supportive staffs and hospital administrators.

Professional category	Training package
MD and Health officer or BSC nurse	Five-days Modular PMDT training package for GHWs, or Advanced clinical TB training for clinicians

Lab professionals	Basic AFB and Three-days lab Bio-safety precautions
Pharmacy technicians	Three-days IPLS for TB drugs
TB officers at various levels	Five-days TBL and DRTB training for program managers
General hospital supportive staffs, in particular at referral levels	One day Sensitization on Airborne infection control measures

3.7 Service initiation requirements and preparation

- Orientation to the hospital administration and respective Health office
- Site identification and preparation for DR TB service delivery
- Identify requirement based on the package for the designated service
- Designate rooms with minimum TB IC measures
- Ensure the necessary furnishers and equipment for the designated rooms
- Arrangement for Lab networking and sample transportation for culture and DST
- Ensure availability of recommended lab monitoring tests at the facility
- Provide TB IC material, RR tools, and provider support tools
- Ensure the presence of ancillary drugs in the center
- Trained health professionals and program managers in the respective centers
- Establishment MDR-TB panel team at TIC
- Sensitization forum for service initiation at treatment centers
- Decide on mechanism for mentoring support and catchment area meeting

4. CASE FINDING STRATEGIES

4.1 Introduction

This chapter emphasizes on the national case finding strategy for high risk groups for development of DR TB in Ethiopian context. The national Diagnostic algorithms for DR-TB using DST techniques at health facility and reference laboratory levels are also described with recommended procedure for sample collection, referral and result delivery system.

4.2 Case-finding Strategies for DR-TB

The main aim of DR-TB case finding strategy in the TB program is to diagnose cases early, initiate them on effective treatment and interrupt the chain of disease transmission in the community.

Countries are increasingly moving toward a "universal DST" strategy, testing all patients with active TB disease for drug resistance at the start of therapy. However there is limited resources to perform culture and drug susceptibility testing (DST) for all TB patients and the prevalence of M(X) DR-TB in new patients is very low , and so performing culture and DST for every patient is not cost-effective.

DST should therefore be used selectively for patients at risk for MDR-TB based on a careful history. Patients with medium to high risk for DR TB will be triaged for more efficient use of DST. In Ethiopia DST will prioritize all TB patients who were previously treated with FLDs for one or more months, and those presumed or confirmed TB cases who are either close contact with confirmed/presumed M(X) DR TB cases or working/living in settings where exposure to DR-TB is likely to be high. These settings may include health facilities, prisons, refugees and other congregated settings which favor transmission of TB in the community.

Table 4.1 shows presumptive MDR-TB cases categorized by the level of risk for development of DR-TB as high risk (may reach 60-80%) or moderate risk (usually 20-30%).

Note that, the risk stratification not only helps for prioritization for DST screening but also for subsequent clinical management.

Table 4.1 Presumptive MDR TB cases in Ethiopia.

Risk for DR-TB	Risk group	Action
High	- Failure of the re-treatment TB regimen - Symptomatic close contacts of confirmed/presumed DR-TB cases - Sputum smear positive at 3rd month of TB re-treatment - Failure of New TB regimen - Relapse after second or subsequent course of TB treatment	➢ Perform Rapid DST ➢ If not clinically stable, consider SLD treatment by the MDR-TB panel team decision
Medium	- Relapse , - Return after loss to follow up of TB treatment - Any previously treated patients presenting with presumptive or confirmed TB - Sputum smear positive at 3rd month of treatment of New TB case - presumptive or confirmed TB in patients from congregated settings (prison, homeless shelters, refugee camps) - presumptive or confirmed TB in Health care workers	➢ Perform Rapid DST ➢ Treat with First-Line anti-TB regimen till DST result is available

4.3 Case finding strategies for XDR-TB

All strains of confirmed MDR-TB cases should routinely undergo second-line DST in order to determine susceptibility for the newly constructed TB regimen. However, considering the local epidemiology and resource limitation, the place of second line DST in Ethiopia is prioritized for the following patients/ conditions:

- Symptomatic contacts of known XDR-TB patients
- Lack of culture conversion by end of the fourth months of the standardized regimen
- Bacteriological reversion in the continuation phase after conversion to negative among MDR-TB cases on SLDs
- Evidence of MDR-TB treatment failures
- MDR TB patients who returned after being lost to follow up
- Confirmed MDR TB cases among health care workers and supportive staffs working in MDR TB settings,
- Confirmed MDR TB cases from congregate settings (prisons, homeless shelters and refugee camps) where cases of XDR TB had been reported.

As the national capacity for second line anti-TB drugs (SLDs) DST improves, routine SLDs DST should be performed for all confirmed MDR TB cases.

4.4 Identification and Referral of presumptive DR-TB patients

All health care facilities involved in the diagnosis and treatment of tuberculosis shall actively participate in the identification, prioritization, and confirmation of Drug resistant TB among presumptive cases using nationally recommended diagnostic algorithms.

On-site screening and diagnosis can be performed using Gene X-pert test. However, patients' sample may need to be collected and transported to the nearest testing site for DST based on the laboratory networking arrangements from the TB control program. Collection and transportation of samples to testing sites must follow national Standard procedure for biological transport (Refer to national procedure for sample collection guideline, 2013).

4.5 Specimen collection, packing and transportation techniques and procedures

Considering the problem of accessibility for culture and DST services for all TB DOTS and MDRTB clinics, the national TB program is implementing sample referral and transportation system to minimize risk of infection transmission and reduce indirect cost to patients during transportation. Hence, samples of the presumed MDRTB cases is collected, packed and transported by Courier system to DST labs for processing. (SOP for sample collection and referral Annex 1).

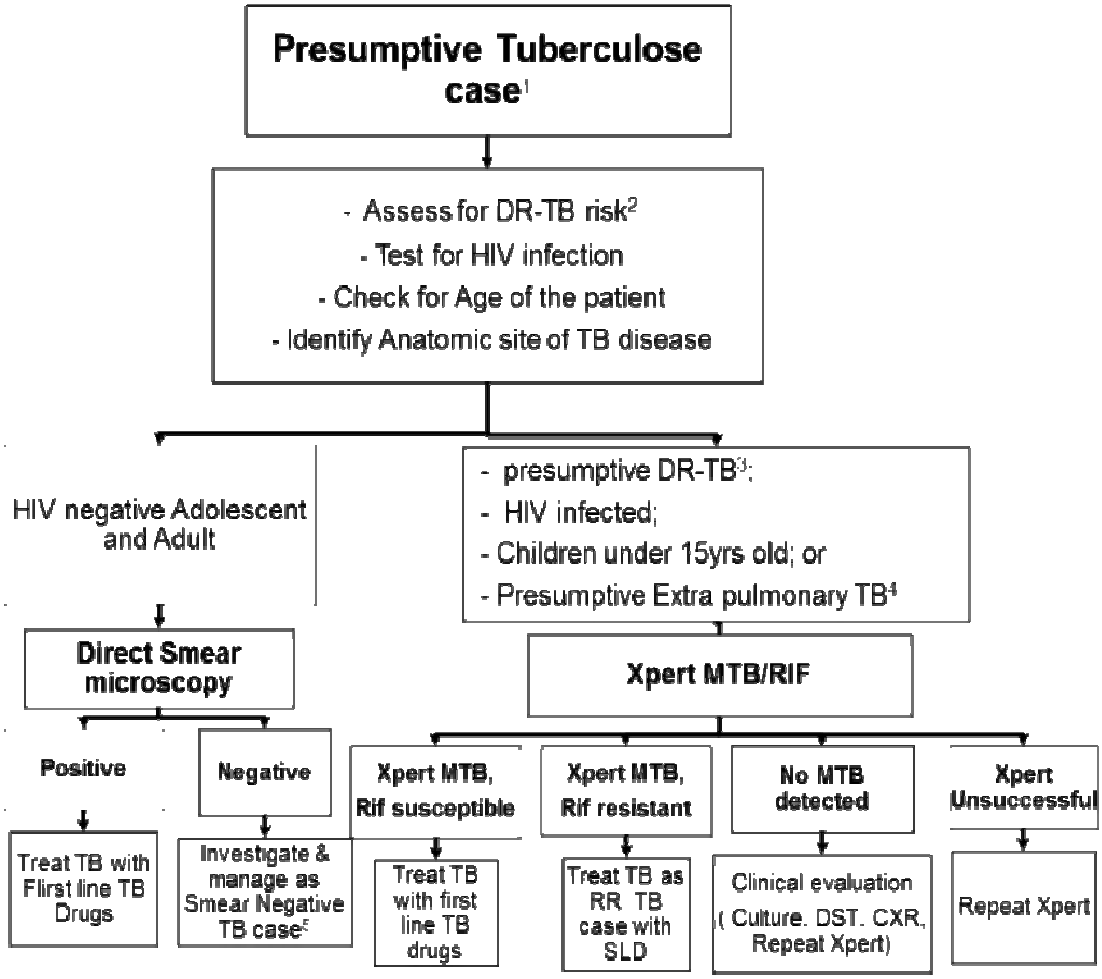
HCWs at Health facility level, Woreda and Zonal TB officers need to:

- Understand the lab network system and identify designated DST testing sites
- Communicate with the sample transport system and the schedule
- Instruct the clients how to produce and collect quality sample
- Collect samples, pack and store using triple packing system
- Store biological samples at recommended temperature using safety precaution
- Organize with the program and facilitate courier system
- Collect the result according to the TAT and manage the patient accordingly
- Link confirmed DR-TB patients to treatment centers

4.6 MDR-TB diagnostic Algorithm in Ethiopia.

Considering the applicability, access & appropriateness of DR-TB diagnostic methods and lead time to diagnosis, the national program has developed DST Algorithms to diagnose DRTB at Health facility and Reference lab levels in Ethiopia. Hence, Xpert test is preferred DST method at health facility level, while Line probe Assay(LPA) is preferred diagnostic test for reference laboratory.

ALGORITHM 1: TB AND DR TB DIAGNOSIS AT HEALTH FACILITY LEVEL



[1]***Presumptive TB***: *cough longer than 2 weeks, or any cough plus any one of hemoptysis, shortness of breath; chest pain, weight loss, fever or night sweats.*

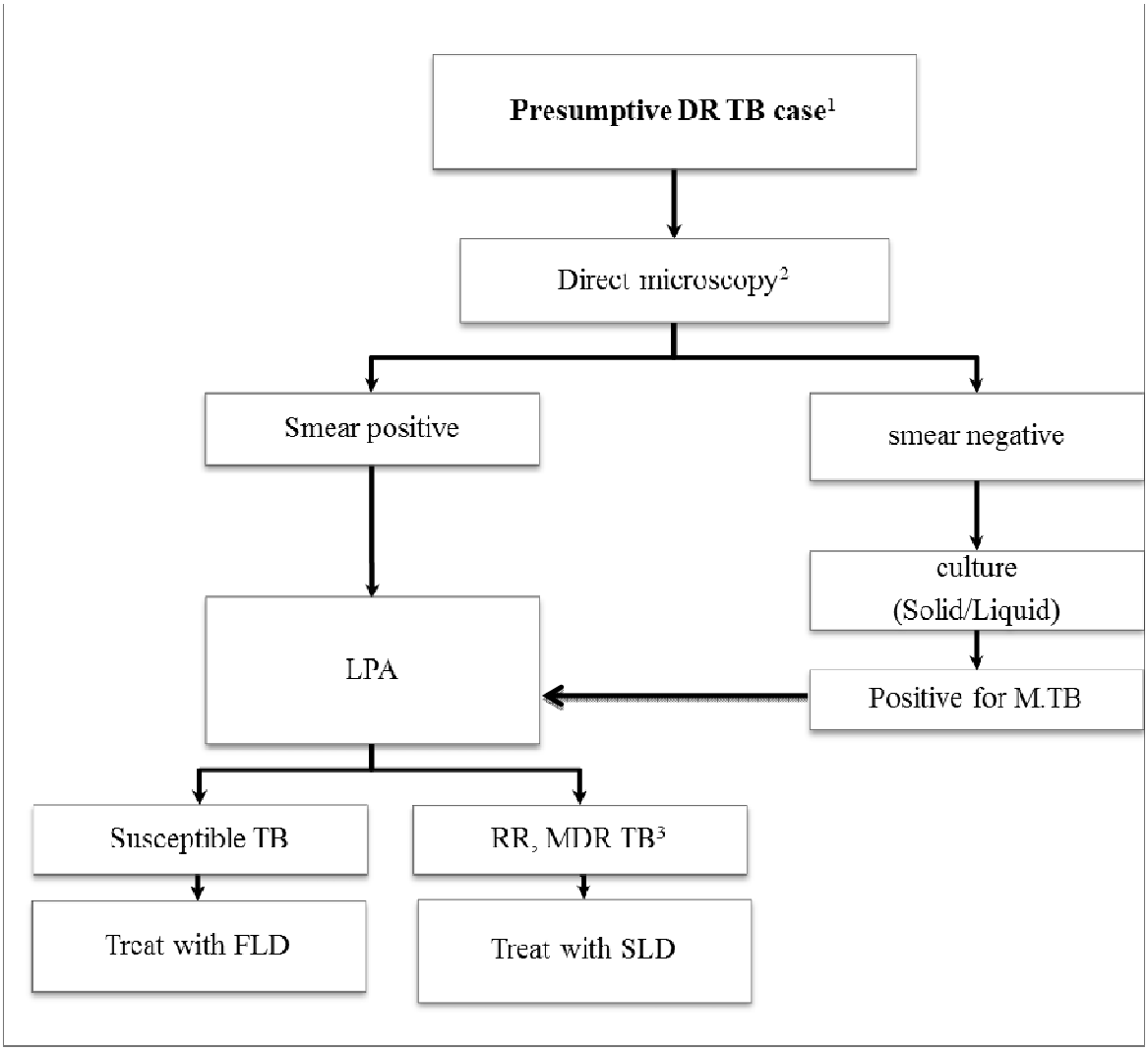
[2]***Assess risk:*** *History of previous TB treatment; TB cases among contacts of known/presumed DR TB cases; Third month follow up smear remains positive; TB cases among HCW or residents in congregated settings (prison, refugee, homeless shelters)*

[3] ***Presumptive DR TB is*** *defined based on National PMDT Guidelines.*

[4]***EPTB diagnosis:*** *CSF, LN aspirate, Pus, Pleural biopsy or fluid samples are recommended for diagnosis of TB by XPERT MTB/RIF test.*

[5]***Investigate for Smear Negative TB*** *as per National TBL Guideline (Repeat sputum, antibiotic trial, CXR)*

ALGORITHM 2: DIAGNOSIS OF DR-TB AT REFERENCE LABORATORY



[1] Presumptive DR TB cases defined based on the national guideline.
[2] If Xpert MTB/RIF test is available: DST can be done using Algorithm for Xpert.
[3] All cases with RR or MDR-TB should also have DST for SLDs whenever available.

As shown above, the diagnosis of RR, MDR-TB cases can be made either at Health facility level using Xpert or at reference laboratory mainly using LPA though conventional DST could also be used. Hence, Samples from presumptive DR-TB case should be processed with DST techniques (Xpert, LPA, or conventional DST) to confirm or rule out the diagnosis of DRTB.

At reference laboratory, direct smear microscopy must be done from samples to decide whether to directly perform LPA, in case of positive smear results, or Do the LPA indirectly if MTB grows on culture after negative smear result.

If the LPA result shows resistant to R and H, or R only, patient must be treated with SLDs, while LPA results of INH resistant but susceptible to Rifampicin and results with susceptible results for R and H, should be treatment with FLD using registration system for Drug susceptible TB. Invalid results from LPA should be reprocessed at the laboratory level as smear negative sample.

At Health facility level, where Xpert is used, Samples from the presumptive DR TB case, Presumptive TB in HIV infected individuals, presumptive TB in children and presumptive EPTB cases are subjected to Xpert test directly.
Those cases with rifampicin resistance should be treated with SLDs using DRTB registration and reporting system, while those cases with Rifampicin susceptible results are managed with FLD using Drug susceptible TB registration and reporting system.

Second line Drug Susceptibility Testing should be done for all confirmed RR/MDR-TB patients. However, due to resource constraints, eligibility for SLDs DST may be prioritized based on the risk and capacity to perform the test.

4.7 Communication of Results from Culture and DST Laboratory

All attempts must be made to communicate the culture and DST results to the provider or the Woreda TB officer as soon as available so that treatment decision for the patient to receive effective TB treatment can be made promptly. The laboratory, together with the Tb program, has to arrange reliable and fast mechanism to return results to the provider. SMS printer machines, SMS messages, emails, or postal system can be applied to minimize the turnaround time of results and expedite the treatment decision.

4.8 DR-TB Patient referral and linkage to MDR TB treatment centers

All confirmed DR-TB cases have to be linked to the designated treatment initiating center (TIC) without delay once the DST results is received from the diagnostic center.

HCWs must provide the following key information for the patient and his/her caregiver:

- Interpretation of the laboratory results and next action to be taken
- Need for clinical evaluation of household and close contacts of the confirmed case
- Infection control measures at home and community to be followed for
- Basic information on the nature of the disease
- Treatment modality and duration of treatment
- Treatment sites and mechanism of follow up of treatment
- Expected follow up visits including necessary laboratory monitoring examinations.

5. LABORATORY ASPECTS OF DR-TB IN ETHIOPIA

The roles of the laboratory are critical in the diagnosis and follow up of Drug-resistant TB (DR-TB). Definitive diagnosis of Drug-resistant TB requires that Mycobacterium tuberculosis be isolated and drug susceptibility results be completed and results conveyed to the clinician. Prompt turnaround time of laboratory results is of paramount importance for rapid diagnosis and appropriate treatment of drug-resistant TB; hence, uses of rapid molecular tests are preferred to expedite the diagnosis of MDRTB in Ethiopia.

5.1 Laboratory infrastructure for culture and DST services

The complex nature of performing tests using Culture and DST techniques restricts programs from routine use for diagnosis of MTB and drug resistance in the field at peripheral laboratories. In the past decade, however, the increasing demand for information on drug resistant pattern of the bacilli from TB patients has increased concerns on the infrastructure quality and safety precaution required to improve access to the service.

Performing the Xpert MTB/RIF assay, however, is relatively simple and involves minimal specimen manipulation. Therefore, the laboratory infrastructure required for Xpert implementation are establishing uninterrupted electric power supply (or UPS with minimum capacity of 2 hours and/or a Generator with fuel supply), closed room with temperature no higher than 30^{o}C and Air Conditioning system in hot areas and adequate storage room for cartridges at temperatures no higher than 28^{o}C.

5.2 Infection Control and Bio-safety in TB Culture and DST Laboratory

Transmission of TB – including drug-resistant forms– is a recognized risk for laboratory workers. Regularly maintained and properly functioning Class II B biological safety cabinet and installment of a negative pressure room are an indispensable piece of laboratory equipment for the performance of culture and DST of specimens from presumptive or confirmed MDR-TB patients. The biological safety cabinet Class II B serves for personnel as well as product protection. Personal protective equipment (PPE) designed to protect from inhalation of airborne bacilli should always be used while processing specimen. Instructions on safe handling of

specimens should be scrupulously followed. Ultraviolet light is useful for surface de-contamination and may be applied to radiate the work area when it is not in use.

Training in laboratory procedures and strict adherence to safety measures should be accompanied by a simple surveillance program whereby the health status of laboratory staff is monitored regularly. Laboratory workers who choose to disclose their HIV-positive status should be offered safer work responsibilities and should be excused from working with MDR-TB specimens. Pregnant women should be reassigned until after childbirth.

Technological advances has made DST techniques to be performed with lower level of biosafety requirement using Xpert MTB/RIF technique, which can be performed at BSC I level similar to direct microscopic examination for AFB.

5.3 Quality Control and Assurance

A comprehensive quality control/quality assurance program is developed in each TB laboratory to ensure the accuracy, reliability and reproducibility of the results obtained and to ensure bio-safety. Quality control/quality assurance procedures should be performed regularly as an integral part of laboratory operations.

The procedures for internal quality control must be performed during each test round to verify that the test is working correctly. The external quality control comprises procedures that are carried out by an external organization to test that the results are correct. Quality assurance is control for the entire process of testing, covering all stages from collection of sputum until the result is reported back to the treatment facility.

A manual of standard operating procedures (SOPs) should be available for each of the laboratory operations. Standard operating procedures must be based on precisely how the procedure is carried out in the particular laboratory and incorporate any minor modifications that may have been made when compared with a standard protocol. The manual should also describe a protocol for regular maintenance checks and repairs of equipment.

The network of supranational TB reference laboratories provides quality assurance service to ensure the quality of laboratory services and regular validation of DST

results. Usually, an external quality assurance program with a supranational TB reference laboratory consists of:

- An initial assessment visit by the laboratory
- Proficiency testing with a panel of coded isolates, and
- Periodic rechecking of isolates obtained within the program.

The national reference laboratory, in turns, provides QA services to culture and DST laboratories found in the regions and reference centers through:

- Site preparation,
- Pre-launching validation of DST service
- Regular site level supervision, and
- Periodic re-checking of isolates obtained within the lab.

5.3.1 Annual Calibration of GeneXpert Machine

Calibration of GeneXpert machine is needed because frequency of use and time might alter performance. It verifies that the system performs within a set of specifications and ensures reading at correct wavelength and temperature ramping are sufficient. The annual calibration must be performed every 2000 tests or every 12 months, whichever occurs first.

5.4 Mycobacterial laboratory services for drug resistant-TB

Definitive diagnosis of DR-TB requires that Mycobacterium tubercu1osis bacteria be detected and resistance to anti-TB drugs determined. This can be done by iso1ating the bacteria by cu1ture, identifying it as M. tubercu1osis, and conducting drug-susceptibi1ity testing (DST) on so1id or 1iquid media or by using WHO-endorsed mo1ecu1ar tests to detect mutations associated with resistance.

5.4.1 Smear Microscopy (ZN/FM): Direct smear microscopy is the cornerstone test for the diagnosis of drug-susceptible pulmonary TB. It is particularly important as the technique is simple, inexpensive and detects those cases of pulmonary tuberculosis (irrespective of the DR status) that are infectious. Microscopy for acid-fast bacilli (AFB) cannot distinguish viable from non-viable

organisms nor differentiate between drug-susceptible and drug-resistant *M. tuberculosis* bacteria or between different species of Mycobacterium.

Therefore, the main uses of direct sputum microscopy for drug-resistant TB are limited to monitoring of treatment response, along with culture and to assess infectiousness of patients.

5.4.2 Culture: Mycobacterium culture test provides a definitive diagnosis of TB. However, growth detection and identification of M. tuberculosis complex may take several weeks. The slow growth of mycobacterial strains (a common characteristic noted in many MDR-TB strains) further lengthens the time to identification and susceptibility testing. Mycobacteria also require a special culture media:

Solid culture media: is culture media (Löwenstien-Jensen) which has several advantages including ease of preparation, low cost, and low contamination rate. Agar-based culture media (Middlebrook 7H10, 7H11) has similar advantages but more expensive. Solid media culture result may take several weeks, 21-42 days, for growth. Solid culture media is the gold standard for diagnosis of MTB.

Colonies of *M. tuberculosis* growing on media

Liquid culture: is a specially enriched broth-based culture method (BACTEC 460, MGIT 960) which reduces the time for MTB growth to 5-10 days. Liquid culture technique is currently limited to few laboratories in country due to high cost of installation and maintenance but it has the advantage of fast turnaround

time especially for DR TB treatment follow up even though contamination rates may be very high.

5.4.3 Drug susceptibility testing (DST): Drug Susceptibility testing (DST) is required to make a definitive diagnosis of M(X)DR-TB. DST can be done either by:

Phenotypic: MTB culture and DST performed by mixing specific concentrations of TB drugs with the culture medium and comparing the rates of growth of the TB culture, also called convention DST. It is considered the gold standard technique to test susceptibility to various drugs used to treat Tuberculosis. However, the technique can only be performed on MTB that has grown on culture media. The result of Phenotypic DST, in addition, is most reliable for INH and Rifampicin; but not for other first line drugs (- STM, E & Z) and many second line TB drugs.

Molecular techniques for DST: Molecular methods for DST are based on detection of specific mutations associated with drug resistance. Most genotypic methods involve two steps: first, a nucleic amplification method such as polymerase chain reaction (PCR) is used to amplify sections of the *M. tuberculosis* genome known to be altered in resistant strains. In the second step, amplification products are assessed for mutations correlated with resistance**.**

i) Line Probe Assay (LPA): is a rapid and accurate test to identify cases with DR-TB and can be done either directly from smear positive sputum sample or from culture isolates if sputum smear is negative.

If a patient with TB is smear positive, the sputum contains enough bacilli to perform line probe assay directly on the sputum and MDR-TB can be proved on the two days' time. If the sputum is smear negative, growth of bacilli should be demonstrated on culture first (preferably on liquid medium) and then, LPA can be performed on the isolates to check for sensitivity for H and R.

ii) Xpert MTB/RIF test: is the rapid test used for detection of MTB and Rifampicin resistance directly from the sputum without need for prior smear

examination. It is fully automated for sample processing, DNA extraction and amplification, making it possible for molecular testing to be performed at service delivery points with less level of expertise. Its bio-safety requirement is similar to smear microscopy. However, it does not inform susceptibility to INH.

5.4.4 Second line Drug Susceptibility Testing

DST for second line drugs is done through conventional phenotypic DST for the injectable drugs (kanamycin/amikacin and capreomycin) and fluoroquinolones at reference laboratories.

LPA is starting to incorporate resistance mutations for second-line anti-TB drugs. The assay shows moderate sensitivity for the detection of fluoroquinolone and second-line injectable resistance, with high specificity. It has the potential to be used as a rule-in test for XDR-TB. But LPA negative for second-line drug resistance does not rule out resistance. Hence, second line LPA cannot be used as a replacement test for conventional phenotypic drug susceptibility testing (DST) and cannot be used to define XDR TB for surveillance. It cannot be used to guide the choice of individual second line drugs to be included in M/XDR TB regimens.

In general the results of any Second line DST should be carefully interpreted by experienced clinician taking into account treatment history besides the susceptibility patterns reported by the laboratory.

Selected XDR TB suspects will be tested for Second line DST initially until full capacity is developed in country. However, all confirmed MDR TB strains should tested for second line drug resistance.

5.5 DST service in Ethiopia

Different WHO-approved DST techniques are recommended to be used for screening of drug resistant strains from samples of Presumptive DR-TB cases. The preferred techniques must provide information on the susceptibility patterns of, preferably all FLDs, at least to Rifampicin. However, the choice of the DST technique in field depends on the simplicity and applicability of the procedure, infection control precaution level and result turn-around time.

In Ethiopian context, Gene Xpert MTB/RIF is the preferred method considering the suitability for use at health facility level, the rapid turnover time of results, and minimal need for expertise & infection control precautions. However, Line probe Assays and conventional DST techniques will continue to be used at reference laboratory (see table 5.1).

Table 5.1 Options for first line DST in Ethiopian context

DST techniques	Turn-around time		DST results	Recommendation
	MTB detection	DST		
GeneXpert MTB/RIF Assay	2hrs	2hrs	R only	Preferred for use at Health facility level with minimal Bio-safety requirements and less experienced professionals
Line probe Assay (LPA)	-	48hrs (direct, smear +ve), 21-42 days (indirect, smear -ve)	R and H	Preferred for use at reference laboratories, and when information on INH susceptibility is required *.
Liquid culture Technique (MGIT system)	8days (smear +ve) 16days (smear –ve)	4 weeks	R, H, E, and S	Preferred for use at reference laboratories, and when information on full DST pattern is required ᵀ.
Solid culture medium (LJ standard medium)	16days (smear +ve) 29 days (smear –ve)	6 weeks	R,H,E, and S	Preferred for use at reference laboratories as gold standard, and when information on full DST pattern is required ᵀ.

*Second line DST can be done by LPA but cannot accurately rule out resistance.
ᵀ Solid or liquid culture techniques can be used to do second line DST.
Adapted from PIH. 2013. The PIH Guide to the Medical Management of Multidrug-resistant Tuberculosis 2nd Edition.pp13.

5.6 Organization and Role & Responsibilities TB Laboratory system

The laboratory network has a pyramidal structure with three inter-linked levels. At the bottom of the pyramid are the peripheral laboratories located in health facilities providing TB diagnostic services for presumptive/confirmed TB and DR-TB cases. At the middle are the regional reference laboratories located mainly at regional administrative level assuming the role of reference laboratories but under the

technical and administrative guidance of the national level reference laboratory found at apex of the pyramid at the national level.

Table 5.2 Different functions and responsibilities TB laboratories at the three different levels of laboratory services system:

National TB reference laboratory	Regional TB reference laboratories	Health facility TB laboratories
• Organize, coordinate and manage the overall national TB lab system including culture and DST services • Update and standardize national laboratory guidelines, training manuals and SOPs • Forecast, quantify and procure TB culture lab reagents and consumables to the designated regional laboratory • Perform national anti-tuberculosis drug resistance surveillance • Organize and deliver the necessary training for laboratory professionals • Provide Quality Assurance services for microscopy, culture and DST performed national level • Organize and manage the sputum sample transport system at national level • Perform TB culture and DST tests for FLD and SLDs	• Perform TB sputum culture and DST tests for FLD and SLDs • Provides training for laboratory personnel from Health facilities • Arrange, organize and manage the sputum sample transport system from the networked Health facilities • Monitor the Quality of sputum sample collection and packing system in each respective catchment Health facilities • Participate in national QA tests from the national reference laboratory • Support to and supervision of peripheral-level staff with respect to microscopy • Quality improvement and proficiency testing of microscopy at peripheral laboratories • All the functions of Health facility TB laboratory	• Perform Gene Xpert MTB/RIF test • Perform smear microscopy using direct microscopy or florescent microscope • Prepare reagent for florescent microscope • Perform internal quality assurance service and participate in EQA • Collect, pack and transport biological samples as per SOP • Keep activity records and regularly report • Cleaning and maintenance of equipment

6. DR-TB PATIENT CLASSIFICATION AND DEFINITION OF TERMS

Standardized definitions, classification, registration and reporting systems have been developed by the World Health Organization to facilitate uniform communication of concepts related to drug resistant TB.

Ethiopia has adopted these case definitions and reporting framework. It is an extension of the Drug susceptible TB information system and is integrated into the national HMIS system.

The categorization, definitions and registration procedures will facilitate:

- standardized patient registration and case notification
- assignment to appropriate treatment regimens
- case evaluation according to disease site, bacteriology and history of treatment
- Cohort analysis of registered DR-TB patients and their treatment outcomes.

6.1 Definitions of Drug-Resistant TB

6.1.1 Classification based on drug resistance:

a) **Mono-drug resistance**: resistance to one first-line anti-TB drug only.
b) **Poly-drug resistance**: resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).
c) **Multi-drug resistance**: resistance to at least both isoniazid and rifampicin.
d) **Extensive-drug resistance**: resistance to any fluoroquinolones and to at least one of three second-line injectable drugs (capreomycin, kanamycin and Amikacin), in addition to multidrug resistance.
e) **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 mono-drug resistance, multi-drug resistance, poly-drug resistance or extensive drug resistance.

Any patient who falls into one of the above listed types of drug-resistance is considered a DR-TB patient. But emphasis is on RR-TB and MDR TB when it is referred in this document.

6.1.2 Classification of DR TB based on Laboratory Confirmation:

- **Laboratory confirmed DR-TB:** refers to those cases with documented laboratory DST (phenotypic or molecular) results for DR-TB or Rifampicin Resistant TB. This could include any of the forms described in section 6.1.1 above.
- **Clinically diagnosed DR-TB:** refers to those cases with no documented DST results but the clinical panel team decided to treat the patient empirically with a course of treatment including SLD based on clinical criteria alone. It includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extra-pulmonary cases without laboratory. When culture and DST results are available these cases will be reclassified as bacteriologically confirmed.

6.1.3 Site of DR-TB disease

a) **Pulmonary DR TB:** DR-Tuberculosis involving the lung parenchyma.

b) **Extrapulmonary TB:** DR-Tuberculosis involving organs other than the lungs.

6.2 Registration group based on history of anti-TB treatment

All RR/MDRTB patients must be registered according to the history of anti-TB treatment. Patients should be classified in two ways:

Classification according to history of previous drug use: Used mainly to assign the appropriate treatment regimen. Registration groups are:

- **New:** A patient who has received no or less than one month of anti-tuberculosis treatment.
- **Previously treated with First line drugs:** a patient who has received first line anti-tuberculosis treatment for four weeks or more.
- **Previously treated with Second line drugs:** a patient who has received second-line anti-tuberculosis treatment for four weeks or more.

Classification according to the history of their previous treatment:

Classification is determined by history of treatment at the time of collection of the sample that was used to confirm MDR-TB. Previous history refers to outcome of the latest TB treatment of the patient.

Registration groups are:

- **New:** A patient who has received no or less than one month of anti-tuberculosis treatment.
- **Relapse:** A patient who was previously treated for TB and whose most recent treatment outcome was "cured" or "treatment completed", and who is subsequently diagnosed with bacteriologically positive TB by sputum smear microscopy, Xpert MTB/RIF, or culture.
- **Treatment after being lost to follow-up*:*** A patient after taking treatment for more than one month who returns to treatment, bacteriologically positive by sputum smear microscopy, Xpert MTB/RIF, or culture, following interruption of treatment for two or more consecutive months.
- **Treatment after failure of New TB regimen:** A patient who has received new regimen for TB and in whom treatment has failed. Failure is defined as sputum smear positive at five months or later during treatment.
- **Treatment after failure of Retreatment regimen:** A patient who has received retreatment regimen for TB and in whom treatment has failed. Failure is defined as sputum smear positive at five months or later during treatment.
- **Transfer in**: A patient who has been transferred from another TIC to continue MDR-TB treatment.
- **Other:** refers to any DR-TB patient who does not fit into any of the above categories.

6.3 Definitions of sputum and culture conversion and reversion

In order for a patient to be considered bacteriologically positive at the start of second-line treatment, the following criteria must be met:

1. At least one pre-treatment specimen was positive for smear, Xpert MTB/RIF or culture

2. The collection date of the sample on which the laboratory examination was performed was less than 30 days before, or 7 days after, initiation of second-line treatment

At least one sputum sample for smear and culture should always be taken at initiation of MDRTB treatment (the result of this will be labeled as month zero in the treatment card and MDR TB register).

Examinations are required at the start of treatment firstly to confirm the diagnosis of TB and determine the infectiousness. Sputum smear positive forms are the most infectious. Both sputum smear and sputum culture testing should be used to monitor patients throughout therapy.

The monitoring of sputum culture is important for decisions on changes in treatment.

Sputum conversion: is defined as two sets of consecutive negative smears and cultures, from samples collected at least 30 days apart. The date of collection for the first sample is considered 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.

6.4. Definitions of DR-TB Treatment Outcomes

All DR-TB patients who are registered to receive treatment with SLDs should be assigned one of the following treatment outcomes upon completion or interruption of treatment by the national program recommendation or with the decision of panel team:

Treatment outcome	Definition
Cured	Treatment completed according to national recommendation without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment completed	Treatment completed according to national recommendation without evidence of failure 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 after intensive phase, or - evidence of additional acquired resistance to fluoroquinolones or second line injectable drugs, or - Adverse drug reactions
Lost To Follow Up (LFTU)	A patient whose treatment was interrupted for two consecutive months or more.
Died	A patient who dies for any reason during the course of treatment.
Not evaluated	A patient for whom no treatment outcome is assigned either due to being transferred out to other facility or still on treatment.

7. MANAGEMENT OF CONTACTS OF DR-TB PATIENTS

Household members or other close contact with a person who has infectious TB are themselves found to have previously undiagnosed, active TB. Besides, various studies indicate that if close contacts of index cases with DR-TB develop active TB, 60-80% of them may have drug-resistant form of the disease.

Based on data collected from systematic review, WHO in 2012 reported a pooled average of **3.5–5.5%** of household members or other close contact with a person who has infectious TB to have previously undiagnosed active TB. This is 5 to 10 times higher compared to the general population.

7.1 Definitions of terms

Index case (index patient): is generally the case identified initially, although she or he may not be the source case. It could be a person of any age in a specific household or other comparable setting in which others may have been exposed. An index case is the case around which a contact investigation is centered.

Exposure may be intense or casual, easily identified or obscure. Close exposure, such as sharing a living or working space, is generally easily identified and quantified, whereas casual exposure, such as on public transport or in social situations, may be unidentifiable.

Household contact: a person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before commencement of the current treatment episode.

Close contact: A person who is not in the household but shared an enclosed space, such as a social gathering place, workplace or facility, for extended periods during the day with the index case during the 3 months before commencement of the current treatment episode. Out-of-household exposure is as likely to result in transmission as household exposure in many situations.

Contact investigation is defined as a systematic process intended to identify previously undiagnosed cases of TB among the contacts of an index case. The

investigation generally focuses on a defined group of potentially exposed people in which other (secondary) cases may be found.

7.2 Reasons for Household contacts screening

The prevalence of active MDR-TB in household contacts of MDR-TB patients is very high:

- Household contacts are likely to be infected because they are in close contact with infectious patients for prolonged periods of time.
- Household contacts are likely to develop active TB because they have recently been infected, and active TB is more likely soon after infection.
- Household contacts of MDR-TB patients have usually been exposed for months or years, longer than household contacts of drug-susceptible TB patients.
- The prevalence of active MDR-TB in household contacts of MDR-TB patients is likely to be higher than that of household contacts of drug-susceptible index cases, and that of XDR-TB higher still.

Advantages of contact investigation

- Early treatment of MDR-TB is cheaper and more effective compared to MDR-TB that is detected late.
- Contacts of MDR-TB patients can be treated immediately with an MDR-TB regimen and prevented from starting an ineffective regimen.
- Contact investigation of MDR-TB prevents the transmission of this strain to others inside or outside of the home.
- Contact investigation is an excellent opportunity to educate family members about the risk of TB, MDR-TB, and other co-morbidities such as HIV.

7.3 Identification and Management of Contacts of DR-TB Cases

7.3.1. Who should do the contact investigation?

Contact investigation should be integrated into routine programmatic management of MDR-TB.

Contact investigation starts with the education of the MDR-TB patient. **Patients** should be educated about the infectiousness of their disease and the high risk of transmission to contacts who share the same living space.

- **The clinical team** (TIC and TFC team) that is responsible for the MDR-TB patient should initiate contact investigation by listing all family members at patient enrollment. The Clinical team will also be responsible for any diagnostic workup needed by the patient's close contacts.
- **The TIC, TFC and the HEW** should interview close contacts as soon as possible after MDR-TB treatment starts, since contacts are most likely to develop active TB soon after becoming infected.
- The **clinical team** is best suited to make sure that close contacts of the MDR-TB patient do not receive empiric treatment for drug-susceptible TB.
- The **HEWs** that provides DOT of the MDR-TB regimen is best situated to do a home visit and the contact investigation, and make sure that household contacts with symptoms are investigated promptly and correctly.

7.3.2 Clinical evaluation and Investigation of contacts of M/X DR- TB

1. Routine screening of all household contacts should include:
    - Asking about cough, fever, weight loss, and other symptoms of TB.
    - Detailed medical history for additional risk factors
    - Physical examination
    - Ask about HIV status of household contacts or do HIV counseling and testing
2. A household contact with any symptoms suggestive of active TB should receive all of the following:
    a. Evaluation by a physician, including history and physical examination.
    b. Chest X-ray to look for signs of active TB (e.g., infiltrates, cavities) or inactive TB (e.g., scarring, granulomas).
        i. The chest X-ray should be kept on file by the clinical team to compare with subsequent X-rays if the contact continues to have symptoms or develops new symptoms in the future.

ii. A chest X-ray should be done even if extrapulmonary TB is suspected, since the contact may have unsuspected pulmonary TB at the same time.

c. Bacteriological investigations of sputum or other samples:

i. Xpert MTB/RIF is the recommended initial diagnostic test because it provides diagnosis of TB and MDR-TB rapidly.

ii. Culture and DST may be sent if Xpert MTB/RIF is negative and suspicion of active TB or MDR-TB remains high.

7.3.3 Management of Symptomatic Contacts

a) Household contacts of MDR-TB patients with active PTB should almost always be treated with an MDR-TB regimen

1. Household contacts of MDR-TB patients who develop active PTB almost always have MDR-TB themselves, even if the pattern of resistance is not always exactly the same. Young children are even more likely than other close contacts to be infected in the home with an MDR-TB strain.
2. If rapid molecular DST is not available, household contacts with active PTB should be empirically treated with the same regimen as the index patient if culture-based DST is expected to take several months. If the DST eventually shows that the contact was infected outside the home by a pan-susceptible strain, the contact can be switched to a regimen of first-line drugs.

b) Household contacts of MDR-TB patients with extra-pulmonary TB

1. Extrapulmonary TB is often culture-negative and DST will not be available. These contacts should be started on an MDR-TB regimen based on the DST of the index patient.
2. Every effort should be made to culture aspirates of pleural, peritoneal, or cerebrospinal fluid, depending on the site, but there is no need to wait for laboratory confirmation of MDR-TB.

c) Household contacts of MDR-TB patients with culture-negative TB

- If cultures are negative or contaminated, close contacts should be continued on the empiric regimen based on the DST of the index patient for the full duration of treatment.

7.3.4 Management of Asymptomatic contact cases

As the risk for developing active TB after exposure with infectious case is increased, all contacts with no active TB at time of evaluation should continue to receive careful clinical follow-up quarterly for a period of at least two years.

If clinical TB is suspected, full clinical evaluation, as mentioned above is recommended.

All contacts and index cases should be educated/ informed about:

- Reason for increased risk of being contact
- Clinical manifestations that could indicate TB
- The risk period after exposure of the index case
- The need for prompt evaluation, if any of these indicators develops
- The higher risk of developing TB in children and PLHIV
- Infection prevention measures at household level and other risky settings
- The need to have regular quarterly clinical follow-up screening

- *If contact is **HIV positive**, he/she should be evaluated promptly, keeping in mind an increased likelihood for extra-pulmonary TB, manifested by local and systemic, rather than pulmonary, symptoms. PLHIV may be less likely to have cough as the predominant symptom and should be fully evaluated if they have systemic symptoms such as fever, night sweats and weight loss.*
- *If the contact is **under 5 years of age**, especial focus should be given to promptly diagnosis as they are highly vulnerable to develop TB and may have more severe forms of the disease.*

***Remark:** Document contact tracing activities on the space provided on DR-TB treatment card*

7.4 Chemoprophylaxis of contacts of MDR-TB index cases

Currently there is no enough evidence to recommend the use of chemoprophylaxis for close contacts of M/XDR TB who developed latent infection.

Therefore the national guideline does not recommend the use of chemoprophylaxis for contacts of DR TB cases.

Close contacts of DR-TB patients, instead, should receive careful clinical follow-up **quarterly for a period of at least two years.**
If clinical TB is suspected at any time, full clinical evaluation, as mentioned above is recommended.

8. TREATMENT OF DRUG RESISTANT TUBERCULOSIS

Treatment of patients with MDR-TB involves second-line drugs. They are much more expensive, less effective and have more side effects than first-line TB drugs. The design of treatment regimens for patients with MDR-TB poses several challenges, complicated by a limited choice of second line drugs, with greater toxicity and less efficacy.

As with drug-susceptible TB, the use of multiple drugs is imperative to prevent the development of additional resistance and there is a need for prolonged chemotherapy to prevent disease relapse.

8.1 Groups of Anti-TB Drugs

Drugs with anti-TB effect are classified into five groups as summarized in the table below.

Table: Drug grouping and basic principles for the selection of MDR-TB Drugs

GROUPING	DRUGS	Principles in DR TB regimen design
Group 1 – **First line oral TB agents**	- Isoniazid (H); - Rifampicin (R); - Ethambutol (E); - Pyrazinamide (Z)	• Pyrazinamide is routinely added to first-line MDR regimens if susceptibility (DST) is documented or if DST is unknown. • Pyrazinamide is generally used for the entire length of treatment, including the continuation phase. • Ethambutol is not recommended in MDR regimens in Ethiopia.
Group 2 – **Injectable TB agents**	- Streptomycin (S); - Kanamycin (Km); - Amikacin (Am); - Capreomycin (Cm);	• All patients should receive an injectable if susceptibility is documented or the drug is considered to be likely effective. • Capreomycin is the preferred injectable.
Group 3 – **Fluoroquinolones**	- Levofloxacin (Lfx); - Moxifloxacin (Mfx);	• Fluoroquinolones are often the most effective anti-TB drugs in an MDR regimen. • The available fluoroquinolones in descending order of potency are Moxifloxacin, Levofloxacin and Ofloxacin. • High dose Levofloxacin is used to treat MDR-TB in Ethiopia. • Moxifloxacin is reserved for special cases (e.g.,

		high resistance, extensive disease, renal failure). • Later-generation fluoroquinolones (Moxifloxacin) may have some efficacy against Ofloxacin-resistant strains.
Group 4 – **Oral bacteriostatic second-line TB drugs**	- Ethionamide (Eto); - Prothionamide (Pto); - Cycloserine (Cs); - Para-Aminosalicylic Acid (PAS);	• Ethionamide and prothionamide are considered the most potent Group 4 drugs. • Prothionamide is preferred to Ethionamide due to reports of better GI tolerance. • Eto/Pto may have cross-resistance with isoniazid. • Cycloserine or PAS should be included in MDR-TB regimens. Both share no cross-resistance to other anti-TB drugs. • Since the combination of Eto/Pto and PAS often causes a high incidence of gastrointestinal disturbances and hypothyroidism, these drugs are usually used together only when three Group 4 drugs are needed.
Group 5 – **New anti-TB drugs and anti-TB drugs with unclear efficacy** (not recommended for routine use in MDR-TB patients)	- Bedaquiline(Bdq) - Linezolid (Lzd) - Clofazimine (Cfz); - AmoxicilliniClavulanate (AmxiClv); - ImipenemiCilastatin (ImpiCln) - Meropenem (Mpm), - High dose INH (16-20 mg/Kg)	• Group 5 drugs are recommended in cases where adequate regimens are impossible to design with the medicines from Groups 1 to 4. In such cases add at least two drugs from this group. • Bedaquiline and linezolid are the only Group 5 drugs with proven efficacy against TB with a randomized placebo-controlled human trial. Neither of these drugs should be added alone to a failing regimen. • Bedaquiline is recommended in the treatment of Pre-XDR TB (fluoroquinolone-resistant or Injectable resistant MDR TB) and XDR TB. • Bedaquiline is listed here in Group 5, although WHO has not yet placed it in any group. • High dose INH may be useful for patients with strains resistant to low concentrations of isoniazid but susceptible to higher concentrations.

8.2 Cross resistance among first line and second line drugs

There is well-known cross-resistance between some of the drugs used in treating tuberculosis. Resistance mutations to one anti-tuberculosis drug may confer resistance to some or all of the members of the drug family and, less commonly, to members of different antibiotic families.

Table: Cross-resistance between anti-TB drugs

Drugs	Cross-resistance
Rifamycins	• Rifampicin and rifabutin have high levels of cross-resistance.
Isoniazid	• Ethionamide/prothionamide can have cross-resistance to isoniazid if the inhA mutation is present.
Aminoglycosides and polypeptides	• Amikacin and kanamycin have very high cross-resistance. • Kanamycin/amikacin and capreomycin have moderate cross-resistance (rrs mutations). • Streptomycin has low cross-resistance with kanamycin/amikacin.
Fluoroquinolones	• Fluoroquinolones have variable cross-resistance. • There is cross-resistance between early generation fluoroquinolones (ofloxacin, ciprofloxacin) and later-generation fluoroquinolones (moxifloxacin, gatifloxacin). • Levofloxacin is the biologically active enantiomer of ofloxacin; mutations that reduce susceptibility to ofloxacin will therefore reduce susceptibility to levofloxacin. • In vitro, strains resistant to early generation fluoroquinolones (e.g., ofloxacin) may retain some degree of susceptibility to later-generation fluoroquinolones (e.g., moxifloxacin), though the clinical significance of this finding is unknown.
Thioamides	• Ethionamide and prothionamide have 100 percent cross-resistance.
Thioacetazone	• Cross-resistance to isoniazid, Eto/prothionamide, and PAS has been reported but is generally considered low.

8.3 Designing MDR-TB treatment regimen

The following are the basic principles involved in any **MDR regimen design and administration:**

- Early MDR-TB detection, before there is extensive lung damage and the prompt initiation of an effective treatment are important factors in obtaining successful outcomes.
- The intensive phase of MDR-TB treatment should consist of **at least four second-line anti-TB** drugs **likely to be effective**. In the case of unclear evidence about the effectiveness of a certain drug, this drug can still be part of the regimen; however, it should not be depended upon for success.
- A single new medicine should never be added to a failing regimen.
- MDR regimens should include **at least** pyrazinamide, a fluoroquinolone, an injectable anti-TB drug, ethionamide (or prothionamide) and either cycloserine or PAS (para-aminosalycylic acid). This recommendation assumes the recommended drugs meet the criteria of 'likely to be effective".
- Ethambutol is not recommended to be included in Second line regimens in Ethiopia.
- Group 5 drugs may be used but are not included among the drugs making up the standard regimen.
- There are conditions when more than five drugs may be started. These conditions would be applicable when the susceptibility pattern or the effectiveness for a drug(s) is unknown or questionable.
- Drugs for which there is a strong contraindication of use (i.e. known drug-drug interactions, overlapping toxicities, history of severe allergy and/or pregnancy) should not be used.
- Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization.
- In the treatment of patients with MDR-TB, an intensive phase of at least 8 months and a total treatment duration of at least 20 months is recommended in patients without any previous MDR-TB treatment.

- Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-tuberculosis drugs, irrespective of CD4 cell-count, as early as possible (within the first 8 weeks) following initiation of anti-tuberculosis treatment.

An anti-TB drug is considered "likely to be effective" when
(Use clinical judgment besides lab data):

1. **History of drug use**: The drug has not been used in a regimen that failed for the individual patient.
2. **DST performed** on the patient's strain indicates that the strain is susceptible. (But remember that only DST for H, R, Cm, Am, Km, and fluoroquinolones is considered reliable. DST for all other drugs is not useful).
3. No known resistance to drugs with high **cross-resistance**. Do not use medicines for which there is high likelihood of cross- resistance.
4. No known close **contacts** with resistance to the drug.
5. In the absence of DST results or for drugs in which individual DST is not reliable, **drug resistance surveys** demonstrating resistance is rare to the drug in patients with similar TB history.

Dosing of medicines for treatment of DR-TB

- **Dosing frequency:** Pyrazinamide and Levofloxacin should be given once a day, as the high peaks attained in once-a-day dosing are more efficacious. Once-a-day dosing is preferred for other second-line medicines depending on patient tolerance. If patient does not tolerate single daily doses of Eto/prothionamide, cycloserine and PAS, these can be given in split doses.
- Each dose is given under **directly observed therapy** (DOT) throughout the treatment. A treatment card is marked for each observed dose. DOT can be performed either at the facility-based or home-based level (often referred to as community-based). Adherence and social support are important components of treatment delivery.

- Treatment of **adverse effects** of drugs should be immediate and adequate in order to minimize the risk of treatment interruptions and prevent increased morbidity and mortality due to serious adverse effects.
- The **dose of an anti-TB medication** is calculated by multiplying the average of the recommended dose (mg/kg) by the actual body weight. Patients weighing > 70 kg are prescribed the **maximum dose** of medication.
- Oral drugs should be given 7 days a week. Injectable drugs can be given 6 days a week. If adverse effects are problematic in a patient, the injectable agent may be given three times a week after conversion.

8.4 DR TB Treatment Strategies

Based on the available resource to perform individual DST for every DR-TB patient and the suitability of strategic approaches to construct treatment strategies, the following approaches are recommended to be used in Ethiopia:

a) Standardised Treatment Regimen

This regimen uses population level Drug-Resistance Survey (DRS) data from representative patient population to base regimen design in the absence of individual DST. All patients in a defined group or category receive the same regimen. Only confirmation of the diagnosis of DR-TB is enough to initiate with standardized regimen except for some condition. This treatment approach is widely used in Ethiopia.

Advantages of choosing Standardized regimen

- Simpler implementation
- Simpler drug supply management
- Easy to train HCWs
- Reduces chance of error in regimen construction
- Minimizes the need for sophisticated culture and DST laboratories

b) **Empiric Treatment regimen**

The standard regimen is used for empiric initiation of MDR-TB treatment for High risk group patients in whom the DST result pends and the patient's Condition does not allow waiting for DST confirmatory result. An empirical regimen may need to be

individualized if Drug resistant pattern on DST result dictates so. Empiric regimen is mainly reserved for children in whom DST confirmation is unlikely.

c) Standardized Treatment Regimen followed by Individualized Treatment:

This approach requires that all patients initiated on standardized Regimen will be individualized based on the result of full DST while on treatment. Hence, samples should be sent for full DST upon treatment initiation for all patients whose DR-TB diagnosis is confirmed.

This approach is preferred regimen strategy recommended for Ethiopia whenever full DST and expert to construct individual regimen are available.

Individualizing a standardized regimen should account for:

- Individual first line and/or second line DST results. Remember that DST is only reliable to isoniazid, rifampicin, second-line injectable and Fluoroquinolones.
- History of previous exposure to the FLD and SLD (Detailed history and review of previous treatment records). Previous exposure for more than one month in a failing regimen suggests the drug is not effective even if DST results reports susceptibility.
- A sound knowledge of cross resistance among Anti-TB drugs is required
- Unnecessary changes that will cause lack of options for possible future use of drugs
- Expert opinion from DR-TB expert and panel team

Standardized regimen in Ethiopia

All newly diagnosed MDR-TB patients receive a standardized regimen.

Intensive phase: 8 Z-Cm_6-Lfx –Pto (Eto) - Cs

Continuation phase: 12Z-Lfx – Pto (Eto) -Cs

However, the following groups of DR-TB patients cannot receive the standardized regimen requiring either regimen modification or dose adjustment.

Patient groups not eligible for standardized treatment regimen:

- History of previous exposure to second-line anti-TB drugs
- Patient who is household contact of a patient with RR-/MDR or XDR TB
- Children
- Pregnant
- Co-morbid diseases (Chronic renal dysfunction, HIV, Liver disease)

8.5 Phases and duration of treatment MDR TB

MDR TB treatment consists of two phases.

a) **Intensive phase**: - refers to the initial period of treatment when maximal bacillary load reduction is aimed. This period is noted by the presence of an injectable drug. The recommended duration of administration of the injectable agent (or the intensive phase), is guided by smear and culture conversion.

b) **Continuation phase**: - refers to the period where the injectable drug is discontinued and patient continues to take oral drugs. The duration of treatment is guided by culture conversion.

Duration of the injectable phase of MDR-TB treatment

- The injectable should be continued for at least eight months and at least four months after the patient becomes culture-negative—whichever is longer.
- Clinicians may use an individualized approach that reviews the cultures, smears, X-rays, and clinical status to decide how long to continue the injectable.
- The injectable can be dosed intermittently in patients with toxicity. Many patients tolerate injectables better when given three times a week (e.g., Monday, Wednesday, and Friday) compared to daily. Intermittent injections should contain the same dose as daily injections.

Total duration of MDR-TB treatment

- Treatment should continue for a minimum of 20 months and at least 18 months after the patient becomes culture-negative—whichever is longer.
- Chronic patients with extensive pulmonary disease may require MDR-TB treatment for 24 months or longer.

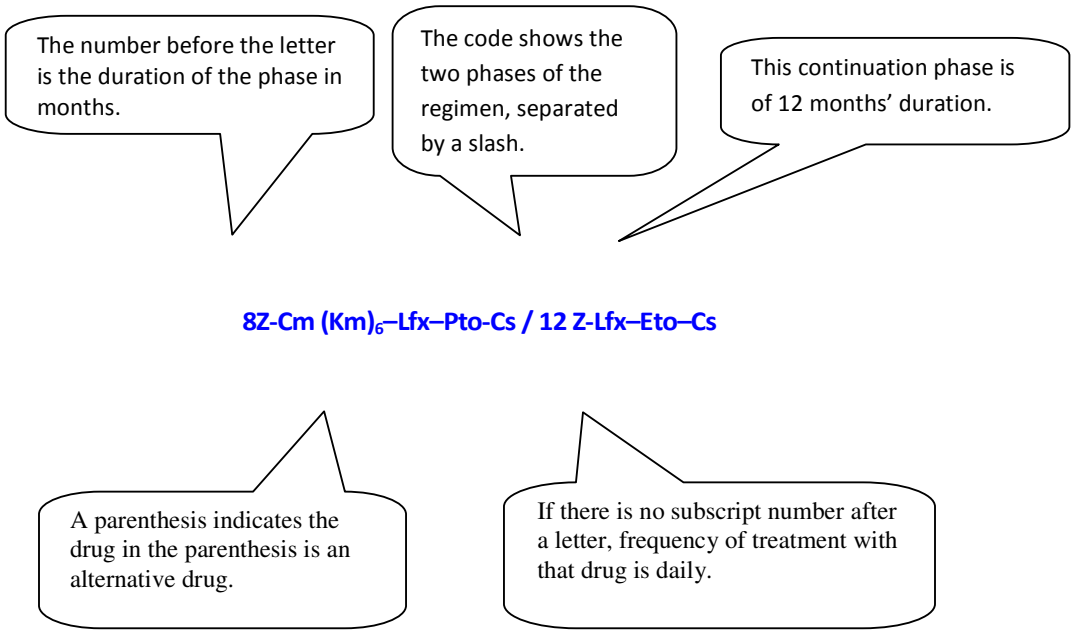
8.6 Standard Code for TB treatment regimens

Coding in MDR-TB treatment regimens follows the same basic principle of basic TB treatment regimens. There is a standard code for writing out TB treatment regimens. Each anti-tuberculosis drug has an abbreviation (see below). A M(X)DR-TB regimen consists of two phases: the first phase is the period in which the injectable agent is used and the second is after it has been stopped. The number shown before each phase stands for phase duration in months and is the minimum amount of time that stage should last. The number in subscript (e.g., 3) after a letter is the number of drug doses per week. If there is no number in subscript, treatment is daily. An alternative drug appears in parentheses.

Reading TB drug code for DR TB treatment regimens

MDR-TB treatment regimens are described using a standard code where each anti-TB drug has an abbreviation: Pyrazinamide(Z), Capreomycin(CM), Kanamycin (Km), Levofloxacin (Lfx), Prothionamide (Pto), Cycloserine(Cs), Moxifloxacin (Mfx), Clf (Clofazimin), Bedaquilin (Bdq).

For instance, the standardized regimen for MDR-TB in Ethiopia is written as:



- The number shown before each phase indicates the duration as a minimum of 8 months of injectable and 12 months after the injectable was stopped.
- Km is put in parentheses as it is used as an alternative drug to Cm. The subscript 6 indicates that the injectable is given 6 times per week.

8.7 Extrapulmonary DR-TB

DR-TB can involve sites other than lung in the same way as drug susceptible TB:

8.7.1 MDR-TB lymphadenitis

Lymph node aspiration or excisional biopsy followed by conventional culture and DST or preferably rapid molecular DST (Xpert MTB/RIF test) can be used to confirm LN DR TB.

The length of therapy should be the same length as treatment for pulmonary MDR-TB.

8.7.2 MDR-TB Spondylitis (Vertebral DR TB)

Bone biopsy or sampling of paravertebral fluid collections should be attempted in order to obtain material for DST (preferably Xpert MTB/RIF test).
Persistent fluid collections on CT despite treatment with first-line anti-TB drugs may be sufficient evidence for empiric DR-TB treatment in some patients.
Operative intervention, either through open debridement or percutaneous drainage of fluid collections, is often required in combination with drug therapy.
Total length of MDR-TB treatment should be at least 24 months.

8.7.3 MDR-TB Meningitis

Xpert MTB/RIF test of CSF samples is recommended for confirming diagnosis as it is moderately sensitive to detect TB in CSF and it can simultaneously detect RR-TB allowing same day initiation of treatment.
Treatment of a patient with presumed or confirmed MDR-TB meningitis is complicated because many second-line drugs do not have good penetration into the CSF.
The fluoroquinolones have variable CSF penetration, with moxifloxacin thought to have better penetration based on animal studies.
Linezolid is believed to penetrate the CNS, and it has been used in meningitis treatment.
Table 5.4: Penetration of anti-TB drugs in cerebrospinal fluid

Penetration Level	Anti-TB drugs
Good penetration	Isoniazid, rifampicin, **pyrazinamide**, **ethionamide**, prothionamide, **cycloserine**, linezolid, imipenem, meropenem.
Penetration only through inflamed meninges	Aminoglycosides (streptomycin, kanamycin, amikacin), fluoroquinolones (moxifloxacin, **levofloxacin**, ofloxacin).
Poor or no penetration	Ethambutol, PAS.
No or little data	Capreomycin, clofazimine, clarithromycin.

In Ethiopia it is recommended to use the standardized regimen and treatment duration should be a minimum of 20 months.

Corticosteroids are generally used at the beginning of treatment of drug-susceptible and MDR-TB meningitis. In MDR-TB meningitis, however, corticosteroids may decrease the penetration of some second-line drugs.

8.8 Adjuvant Therapies in DR TB

A number of other modalities are used to lessen adverse effects and morbidity associated with DR-TB, as well as, to improve treatment outcomes.

8.8.1 Corticosteroids

Corticosteroids may be beneficial as an adjunctive therapy in MDR-TB patients with severe respiratory insufficiency, or central nervous system or pericardial involvement.

Prednisone is commonly used, starting at approximately 1 mg/kg and gradually decreasing the dose by 10 mg per week.

Corticosteroids may also alleviate symptoms in MDR-TB patients with an exacerbation of chronic obstructive pulmonary disease. Prednisone may be tapered over one to two weeks, starting at approximately 1 mg/kg and decreasing the dose by 5 to 10 mg per day.

When a more immediate response is needed, injectable corticosteroids are often used.

Corticosteroids have many side effects. They may have also additive toxicity with the other drugs patients are taking. So their use should be very selective and duration of treatment should not be more than 4-6 weeks.

Avoid corticosteroids in pregnancy and PLHIV.

8.8.2 DR TB AND NUTRITION

Introduction:

- Nutritional support is particularly important for MDR-TB patients.
    - MDR-TB patients often are extremely wasted and have poor nutritional status.
    - Second-line drugs can also decrease appetite, making adequate nutrition a greater challenge.

- Without nutritional support, patients, especially those already suffering from baseline malnutrition, can become enmeshed in a vicious cycle of malnutrition and disease.

Nutrition Assessment Counseling and Support (NACS)

- It comprises of assessment of nutritional status, providing counseling on importance and impact of proper nutrition on DR TB and providing nutritional support for patients found to have malnutrition.
- Assess nutritional status of all DR TB Patients at every contact:
  - Measure weight in kilograms to the nearest 100 grams and height in meters to the nearest centimeter at every visit and then calculate the BMI.
  - If height or weight cannot be measured (e.g. Bed ridden or edematous or pregnant patient) measure the Mid Upper Arm Circumference (MUAC).
  - Then compare the BMI or MUAC with the national nutrition guideline standards and classify the patient's nutritional status.

Table: Nutritional Care Plans for DR TB patients

Care plan	Degree of malnutrition	Intervention	Duration
A	Severe Acute malnutrition (SAM)	Ready to Use Therapeutic Foods (RUTF) or PlumpyNut*	3 months (Shift to MAM for 3 months when improved)
B	Moderate Acute malnutrition (MAM)	Ready to Use Supplementary Foods (RUSF) or PlumpySup[#]	3-6 months
C	Mild or no acute malnutrition	Nutritional counselling on essential elements of nutrition	Throughout DR TB treatment

**PlumpyNut is an energy dense fortified therapeutic food designed for the treatment of SAM. Recommended dose: 4 sachets per day for adults*

[#]PlumySup is an energy dense fortified supplementary food designed for treatment of MAM. Recommended dose: 2 sachets per day for adults

Essential elements for Nutritional counseling of all patients with Active TB or DR TB:

- Have your nutritional status checked (especially weight) every time you visit your clinic for treatment monitoring.
- Eat more and a variety of food stuffs
- Maintain a high level of hygiene and sanitation
- Drink plenty of clean and safe (boiled or treated) water
- Maintain a healthy lifestyle and practice infection control at home
- Get tested for HIV
- Seek early treatment for ADRs
- Take your medicines properly and on time in the presence of your DOT supporter
- Follow instructions on when to take your TB medicine in relation to food and other drugs

8.8.3 Surgery for DR-TB

- Surgery as an adjunct to chemotherapy for patients with localized disease can significantly improve outcomes where skilled thoracic surgeons and excellent pre- and postoperative care are available.
- Specialized surgical facilities should have stringent infection control measures in place. Infectious aerosols are generated in large quantities during surgery, mechanical ventilation, and pulmonary hygiene manipulations in the post-operative period.
- Patients being considered for surgery should be fully informed about the risks of surgery and anesthesia; a complete preoperative evaluation should be done.

Indications for surgery as adjunct to drug therapy for DR TB:

- Failure to demonstrate clinical or bacteriologic response to chemotherapy after three to six months of treatment.
- Recurrence of positive cultures during MDR-TB treatment.
- Relapse following completion of MDR-TB treatment.
- High likelihood of failure or relapse, due to a high degree of resistance or extensive parenchymal involvement, regardless of smear and culture status. Extensive bilateral disease is a contraindication to surgery.

Surgery may also be indicated for treatment of **complications of TB or DR TB** like:

- Life-threatening complications of parenchymal disease, including hemoptysis, bronchiectasis, pneumothorax, broncho-pleural fistula, or empyema.
- Treatment of constrictive pericarditis, vertebral abscesses compressing the spinal cord or superficial and accessible abscesses in cases of osteo-articular TB.

Timing of surgery

Resective surgery should ideally occur early in therapy, normally within the first few months of treatment following smear or culture conversion. If conversion is not possible, then at least three months of anti-TB treatment is recommended prior to surgery.

Length of treatment after surgery:

- In patients who are smear- or culture-positive at the time of surgery, treatment is continued for minimum of 18 months after documented culture negativity, and generally includes an extended period of injectable.
- In patients who are smear- and culture-negative at the time of surgery, treatment should be continued for a minimum of 18 months after culture conversion and no less than six months after surgery.
- If pathology reveals viable bacilli on culture, it may be reasonable to continue therapy for 18 to 24 months after the surgery rather than 18 months after the previous conversion of sputum.

8.9 Treatment of XDRTB

XDR TB is defined as MDR TB that is also resistant to one of the three second line injectables and any of the fluoroquinolones.

It has proven much more difficult to treat than MDR-TB and extremely difficult in HIV-infected patients. But XDR-TB can be cured with administration of an adequate regimen and proper monitoring and patient support.

Because of the high pill burden and poor clinical condition of the patients the frequency of ADR will be higher and drug-drug interactions are complex. Hence

XDR TB patients should preferably be managed by centers with experience and good infection control setups with isolation rooms.

The treatment design and regimen selection principle is basically the same as for MDRTB.

The following principles must be applied when designing a plan for management of patients with XDR-TB:

- At least four drugs likely to be effective (based on susceptible DST or the patient has not been exposed to) should be included.
- Use any Group 1 agents that may be effective;
    - Pyrazinamide is routinely added in XDR TB treatment regimens.
- Use an injectable agent to which the strain is susceptible and consider an extended duration of use (12 months or possibly the whole treatment). If resistant to all injectable agents it is recommended to use one the patient has never used before; If toxicity is a limiting factor for use of the injectable agent consider using three times weekly dosing.
- Use a higher generation fluoroquinolone such as Moxifloxacin;
- Use all Group 4 agents that have not been used extensively in a previous regimen or any that are likely to be effective; drugs to be considered are PAS, Prothionamide and Cycloserine.
- Use two or more drugs from Group 5, including bedaquiline and linezolid. Clofazimine can also be considered.
- Consider high-dose INH treatment if low-level resistance or absence of the katG gene is documented
- The total number of drugs will depend on the degree of uncertainty and the regimen will often contain five or more drugs
- Consider compassionate use of new TB drugs based on national protocol
- Consider adjuvant surgery if there is localized disease
- Ensure strong infection control measures
- Manage HIV co-infection and other comorbidities
- Provide comprehensive monitoring and full adherence support.
- Provide comprehensive palliative and end of life care

There is currently no international consensus on the optimum duration of XDR-TB treatment; a longer duration of treatment is expected and decision should be based on smear and culture conversion and clinical response to decide on the termination of XDR-TB treatment.

XDR-TB regimen for Ethiopia

Treatment of XDR TB should always be individualized as much as possible based on previous exposure to FLD and SLD drugs and DST results. It shall be led by an expert at a nationally identified MDR-TB referral center. All treatment initiating centers need to report to the national TB program when they strongly suspect or confirm XDR-TB case.

For Ethiopia the following drugs are suggested to be included when designing XDR TB treatment regimens based on availability and cost:

- **Z-Km-Mfx-PAS-Cfz-Amx/Clav-High dose INH**
- **Z-Km-Mfx-PAS-Cfz-LZD-Amx/Clav**

When bedaquiline is available it can be included in designing an XDR TB treatment regimen.

Duration of XDR TB treatment

As mentioned before there is no international consensus on the duration of treatment for XDR TB. Duration should be decided based on clinical and bacteriologic data. But in general the following recommendations can be used as a guide to make decision for patients who are responding clinically as well as bacteriologically.

- **Intensive phase** for 6 months after culture conversion and a minimum of 12 months
- **Continuation phase** to be continued for 18 months after culture conversion and a minimum of 24 months.

This recommendation is based on the WHO guidelines and experience from other Countries national TB programs.

8.10 Management of Fluoroquinolone or Second line Injectable resistance (Pre-XDR TB).

8.10.1 Fluoroquinolone resistance

In case of fluoroquinolone resistance neither Levofloxacin nor Moxifloxacin will be counted as one of the drugs with 'certain effectiveness'. Thus PAS is added when resistance to quinolones is confirmed.

This is the regimen which can be used in Ethiopia:

Z-Cm-Mfx-Pto(Eto)-Cs-PAS.

N.B: Bedaquiline can be used as an additional drug in case of resistance to fluoroquinolone.

8.10.2 Second line Injectable Resistance

In cases of resistance to kanamycin the polypeptide injectable capreomycin can be used, and in case of resistance to capreomycin the aminoglycoside injectable Kanamycin can be used. Hence, in cases of resistance to injectable, do the following:

- If DST shows Kanamycin resistance, use Capreomycin, or
- If DST shows Capreomycin resistance, use Kanamycin,

And the regimen can be strengthened by adding PAS.
Regimen to be used in Ethiopia: Z-Cm (Km)-Lfx-(Pto)Eto-Cs-PAS.

8.11 Management of Mono- and Poly-Drug Resistant TB cases

Patients with either mono or poly-resistant TB will be identified during the course of case-finding for M(X) DR-TB. Very few randomized clinical trials have been performed so far to determine the best treatment regimen for mono- or poly-resistant TB. Use of combinations of second line with first line anti-TB drugs is not recommended as it may result in XDR TB.
In Ethiopia, access to full first line DST may not obtained routinely to inform the full drug resistant pattern but data from the first DRS survey and routine case

finding reports showed that the prevalence of INH mono-resistance is very low. However, combinations of INH resistance with S and/or Z and/or E are more frequent in the previously treated cases.

INH Resistant TB: the commonest scenario will be information about INH resistance from LPA performed by reference laboratories. Hence, there will be incomplete data to suggest specific regimens for INH resistance as it may be combined with either or all of S, E & Z.

Registration and Management: Patients with INH resistance shall follow case definitions and classification system as for drug susceptible TB cases and are registered on the Unit TB Register (Drug susceptible TB register) with an additional remark.

Such patients shall receive **RHZE for 9 months** without any change in regimen during continuation phase.

Patient Monitoring and outcome: These patients are advised to be monitored similarly as Drug susceptible TB. Do Sputum AFB smears at the second, fifth and ninth month of treatment. Do Rapid DST using Xpert MTB/RIF test or LPA test if the patient remains sputum smear positive at the third month or revert back to smear positivity after documented negative AFB test result, as the patient might have developed resistance to Rifampicin. If the DST shows resistance to rifampicin, STOP first line anti-TB treatment and switch over to SLD treatment using MDR-TB treatment registration system.

Note that patients with rifampicin resistance (with or without additional S, E, or Z) should be defined as Rifampicin resistant-TB (RR-TB) case, registered and reported using DR-TB system and be treated using SLDs

9. EVALUATION AND MONITORING OF PATIENTS ON TREATMENT

Patients to be initiated on second line anti-TB drugs should have a thorough pretreatment evaluation and, after initiation of treatment should have regular scheduled clinical evaluations. Patients should be evaluated on emergency basis when they develop adverse effects to treatment or any other concomitant illness.

9.1 Pre-Treatment Evaluation and Screening

Before the patients are started on MDR-TB treatment the following must be done at the time of diagnosis:

1. Ensure that all details regarding the treatment are communicated to the patient and sign informed consent;
2. Counsel and educate the patient and family member.
3. Address any patient concerns.
4. Verify patient's physical and work address.
5. Do baseline clinical assessment including lab investigations
6. Adherence preparation.
7. Enquire about close contacts at home or work.
8. Arrange for screening of and testing of all contacts.

- **Pre-treatment assessment** should be systematically conducted on all patients in order to identify those patients at greater risk of adverse effects, poor outcomes, and to establish a baseline for monitoring.
- It also helps understand the patient's psychosocial and economic situation, and identify potential barriers to treatment.
- The pretreatment evaluation should include a thorough medical history, physical examination, and laboratory investigations.
    - **History**: Demographic data and social history, TB Treatment history, past medical history, contact history to TB or MDR TB or XDR TB patient, review of systems to look for current symptoms.

- **Physical examination**: Vital signs, anthropometric data, Examination of skin, head, neck, oropharynx, cardiovascular system, pulmonary system, abdominal organs, extremities, and nervous system.

- The following **co-morbidities** may affect the initial treatment regimen or other important management decisions: HIV infection, Diabetes mellitus, Hypertension, Acute or chronic renal insufficiency, Acute or chronic liver disease, Thyroid disease, Mental illness, Drug or alcohol dependence, Pregnancy, epilepsy or seizure disorder.

- All patients starting MDR-TB treatment should have the following tests:
  - Sputum smear, culture, and DST.
  - Baseline potassium, creatinine, and liver function tests.
  - Baseline audiometry (if it is available).
  - HIV rapid testing.
  - Pregnancy test for women of child-bearing age.
  - Thyroid-stimulating hormone (TSH) if there are symptoms of hypothyroidism or goiter.
- Patients co-infected with HIV should have additional tests:
  - CBC (especially if planning to start AZT in the future).
  - CD4 cell count (CD4 percent in children).
- Patients receiving bedaquiline should have a baseline ECG to rule out QT prolongation.
- Additional laboratory tests may be indicated based on the medical history, physical examination, and results of initial screening tests.

- The monitoring of treatment and the management of adverse effects may have to be more intensive in patients with pre-existing conditions or conditions identified at the initial evaluation.

9.2 Treatment Monitoring and Follow Up

Each MDR-TB patient should be monitored closely for signs of both treatment efficacy and adverse effects of the medications. The success of the programme

treatment depends on the intensity and quality of monitoring and supervision activities.

Patients should be seen by a doctor or experienced Health officer after discharge from the DR-TB Centre, at monthly intervals until the end of treatment. The responsible clinician should assess clinical, microbiologic, and radiologic response to treatment, measure weight, assess possible adverse reactions, and encourage the patient to continue treatment. Treatment cards should be updated after the follow-up visit.

It should be remembered that patients initiating treatment as outpatients should have weekly clinical and adherence assessment until they stabilize at least for the first two to four weeks of treatment (Stabilization phase).

Treatment follow up centers should also screen patients for symptoms of adverse drug reactions while attending the daily direct observation of treatment and work on adherence counseling.

Patients generally improve within the first few months of treatment and their clinical progress should be assessed during the scheduled visits.

The monitoring should follow standard clinical assessment:

a) Clinical history:

- Resolution or worsening of symptoms of TB (cough sputum production, hemoptysis, chest pain, respiratory distress, fever and weight loss). Generally improve within one to two months of treatment.
- Asses for adherence (missed PO doses, missed injections, reasons)
- Symptoms for drug adverse events
- Systematic assessment for co-morbid illness
- Reproductive age women: Assess for Pregnancy, assess FP need.

b) Physical examination.

- Vital signs

- Anthropometry: Height Weight, BMI, Mid Upper Arm Circumference
- Focused systemic examination (HEENT, CVS, Respiratory, Abdomen, Skin, Musculoskeletal, Neurologic)

c) Laboratory monitoring

Laboratory monitoring and other investigations are important for documenting response and identifying complications earlier. Laboratory tests should be done based on schedules and when necessary based on clinical indication as depicted in the table below.

Table: Schedule for Clinical monitoring in DR TB Treatment

Parameter	Baseline	Intensive phase	Continuation phase
Clinical assessment	√	Monthly	Monthly
Audiometry	√	4^{th} month	If clinically indicated
Simple hearing test	√	Monthly	If clinically indicated
Sputum smear	√	Monthly	Monthly
Sputum culture	√	Monthly	Every 2 months (1-3 months)
Liver function tests	√	If clinically indicated	If clinically indicated
Serum Creatinine	√	Monthly	If clinically indicated
Serum potassium	√	Monthly	If clinically indicated
Thyroid stimulating hormone (TSH)	√	3^{rd} and 6^{th} month	Every 6 months
HIV testing	√	If clinically indicated	If clinically indicated
Pregnancy test	√ (15-49 age women)	If clinically indicated	If clinically indicated
CBC	HIV or Anemia	If clinically indicated	If clinically indicated
Chest X-ray	√	End of Intensive phase	End of treatment

General Notes on Monitoring

- Objective laboratory evidence of improvement often lags behind clinical improvement.
- For children, height and weight should be measured regularly to ensure that they are growing normally. A normal growth rate should resume after a few months of successful treatment.
- The chest radiograph(CXR) may be unchanged or show only slight improvement (lesion regression may require 3 to 9 months), especially in patients with chronic pulmonary lesions, thus regular chest radiographs may not add a value unless a surgical intervention is being considered, or the patient's clinical situation has worsened.
- The most important objective evidence of improvement is conversion of the sputum smear and culture to negative. While sputum smear is still useful clinically because of its much shorter turnaround time, sputum culture is much more sensitive and is necessary to monitor the progress of treatment. Sputum examinations are also dependent on the quality of the sputum produced, so care should be taken to obtain adequate specimens.
- Most patients who are adherent to an effective regimen will convert cultures to negative by three months of treatment.
- Patients with fewer effective drugs in their treatment regimens (e.g., XDR-TB patients) will convert more slowly.
- The recurrence of TB symptoms after sputum conversion, for example, may be the first sign of treatment failure.
- Persistently positive cultures beyond the month six of treatment are a sign of likely treatment failure. Non-Tuberculous Mycobacteria (NTM) could also be possible reasons.
- For patients who remain smear- and culture-positive during treatment or who are suspects for treatment failure, second line DST should be requested.
- Recurrence of positive cultures after culture conversion is a sign of likely treatment failure, especially if it occurs after month six of treatment.

- Paucibacillary culture results should not be automatically regarded as negative when treating DR-TB. Acquired drug resistance and treatment failure often begin with the growth of one or two colonies on a sputum culture.
- Culture conversion should not be considered to be equivalent to cure. A certain proportion of patients may initially convert and later revert to positive sputum culture.
- Treatment outcomes should be assigned based laboratory and clinical criteria during the course of DR TB treatment.

9.3. Post-treatment Monitoring

Post treatment monitoring is important to:

- Assess for relapse
- Monitor adverse events like neuropathy, ototoxicity, hypothyroidism and psychosis
- Assess and manage sequelae of DR TB like bronchiectasis, pneumothorax, lung fibrosis, cor pulmonale
- Contacts screening

Once the patient has completed the course of treatment, the assessment must be performed every six months during the following two years. The assessment should include the following examination:

  - Clinical history and focused physical examination
  - Body weight and anthropometry
  - Sputum smear examination and culture
  - Chest X-ray
  - DST (if culture result is positive)

If the patient has stopped treatment before completing the recommended full treatment, the patient should still be assessed every 6 months for at least 2 years. The assessment should include the above recommended steps.
If during any post-treatment examination the patient shows evidence of active TB, a full course of treatment with an individually constructed regimen based on history and DST must be restarted.

10. ADHERENCE SUPPORT and DIRECTLY OBSERVED TREATMENT

Treatment for DR TB is long and often complicated. Success of treatment relies heavily on adherence, which in turn relies on:

- A good understanding by the patient of the fundamentals of DR TB and its treatment;
- Commitment from the patient to participate in treatment;
- Support of the patient by the family; and
- Good communication between the provider, the patient, and the family.

Hospitalization is not necessary for the majority of the patients with MDR TB and may actually decrease rates of adherence.

10.1 Adherence Support

10.1.1 Assessment for Barriers to Adherence and Counseling

Adherence to the long course of DR TB treatment is a complex, dynamic phenomenon with a wide range of factors impacting on treatment-taking behavior.

At every clinic visits, health care providers needs to assess the following potential barriers for adherence to treatment in a respectful and non-judgmental manner.

Patient related factors	Socioeconomic factors	Health system-related factors	Treatment-related factors
• Low level of Knowledge about DR TB and its treatment • Psychiatric illness • Substance abuse • Age (children, teenagers and the elderly). • Low literacy status • Stigma and discrimination • Family, community and house hold influence	• Unemployment /Low income • Homelessness • Lack of social support; • Long distance from home to clinic; • Cost of transport to the health center; • Cost of treatment or investigations;	• Access and convenience of to services (distance, waiting time, privacy, confidentiality); • Poor Condition of the clinic, • Attitude of health care provider to patient and the disease. • Low level of knowledge of the HCW about DR TB and treatment • Health personnel beliefs (e.g., fear of being infected).	• High pill burden • Prolonged duration of treatment, • Co-morbidities like HIV • Failure of previous treatments; • Adverse effects: real

Patients should be observed closely for signs that they might default from treatment, such as missed visits or refusal to take doses.
Based on assessment findings identified barriers need to be addressed timely by the MDR TB panel team.

10.1.2 Factors that favors adherence

- Availability of drugs at no cost to patient, including those for adverse effects.
- Optimized relationship between staff and patients.
- Good quality of care.
- Easy access to health services for treatment.
- Convenience of health service scheduled hours.
- Short waiting time for patient care at appointments
- Quiet environment and privacy fostering trust and an encouraging atmosphere.

10.1.3 Interventions to Improve Adherence

Patient centered adherence support strategy should be designed with the commencement of therapy and should be a continued process.

a) Educate patient, family and treatment supporter on DR TB:

Educational interventions should commence at the start of therapy and continue throughout the course of treatment with the goal of obtaining commitment to the treatment plan. Education can be provided by the attending doctors, nurses, community health workers, and other health care workers. Materials need to be appropriate to the literacy levels of the population and should be culturally sensitive.

- Causes of DR TB, Modes of transmission and some basics about household infection control
- Discuss where treatment will start.
- Treatment regimens, frequency & route of administration and where to get the drugs

- Teach the patient about monitoring requirements for smear and culture and laboratory tests for side effects.
- Importance of treatment adherence and risks of treatment interruption
- Use of adherence support card
- The most common side effects of from second line drugs
- When or how often the patient must go to the health service
- Family member screening
- Communication with TFC and TIC
- Healthy lifestyles (Stop smoking, drinking and /or chewing Khat; good nutrition; exercise etc).

b) Provision of treatment by DOT

c) Early detection and appropriate management of ADRs

d) Use of patient socioeconomic and emotional support packages

Community interventions:

i. Support groups: Promote mutual support among current and former patients
ii. Promote productive employment for people affected by DR-TB (see economic strengthening section below)
iii. Strengthen the abilities, experiences and resources of basic social organizations to address the TB problem in their community.

10.1.4 Indicators to assess adherence to treatment

The following indicators may be of help in assessing treatment adherence:

- Conversion of smear and sputum culture from positive to negative:
- Reduction of symptoms.
- Clinical improvement.
- Weight gain/loss.
- Daily attendance at the health service, confirmed by review of treatment cards.
- Rate/number of no-shows for treatment appointments.

- Reduction of desertion rates, which can be measured each time the DR-TB cohort, is assessed (usually 30 months after the last patient of the year begins treatment).
- Study of user satisfaction through surveys on knowledge, attitudes and practices relating to TB treatment.
- Health care provider's satisfaction level accessed via survey.

10.2 Directly Observed Treatment

DOT is one of the key components of MDR-TB management and its full implementation will help prevent the development of further resistance and XDR-TB. Each and every dose must be strictly observed regardless of the treatment delivery setting (in-patient or outpatient).
DOT should not place a burden on patients and their families; therefore DOT must be conducted in the place where it is most convenient for the patient.

The DOT provider can be a HCW, a HEW or a **trained** community member (DR TB Supporter). The DOT Provider should not be a family member as family relationships is often complicated for the MDR-TB patient; a family member could be subject to subtle manipulation by the patient, however, a family member may be a DOT provider if no other person can be identified as a last resort).

The DR TB Supporter is responsible for supervising the oral intake at home or at any place appropriate for the patient.

The DR TB Supporter should notify the DR TB Community Nurse within 24 hours of a missed dose.

In fully community-based DOT:

- All doses are observed by a DR TB Supporter in the patient's home.
- During the injectable phase, a nurse or another qualified individual should inject the patient at a suitable location.

In combined facility/community-based DOT:

- Facility health workers supervise the morning dose. The facility should be the one closest to the patient's home. During the injectable phase, a facility nurse should inject the patient each morning.
- A DR TB Supporter supervises doses during the evenings, weekends, and holidays.

In Ethiopia both DOT strategies will be used, depending on the patient's situation.

- Some patients cannot visit a facility, such as those suffering from severe illness or side effects, patients with complex work schedules, patients suffering from mental illness, or patients who are children or in old age. There may not be a nearby health facility for patients in rural areas. For these patients, fully community-based DOT should be used.

DOT should be organized in accordance to the needs of the patient.

- The DR TB Supporter generally supervises doses in the patient's home, but in exceptional cases the patient may visit the home of the DR TB Supporter, for example, for reasons of confidentiality.

- DOT may occasionally be administered in other places, such as the patient's workplace. Where available, a workplace health facility may be used. In such cases, employers play a big role in supporting adherence and should be engaged as part of the team.

10.3 DOT Procedures

- The prescribed medications are taken under direct observation and the whole daily dose is taken in one sitting, unless the physician indicates that medicine can be split up to lessen side-effects. (Pyrazinamide, injectable agents and FQs are always given in a single dose. Ethionamide, cycloserine, and PAS may be given twice a day to reduce side-effects if patient can't tolerate single daily doses.)
- Treatment is administered in the same designated place, according to the schedule, keeping the same sequence.
- The DOT Provider should lay out the pills and check the dosage.
- Before handing over the medicines, the DOT Provider should ask the name of the patient, check the note on the vial or the plastic bag containing the

patient's pills, and only after that give them to the patient. The injection should be given at the same time as oral drugs.

- The injection is to be given by a HCW (Nurse, HO or other trained person). The injection must be followed by oral intake of SLDs.
- The patient, standing or sitting in front of the responsible person, should swallow the drugs immediately.
- After swallowing the tablets, the patient drinks some water. The patient should show their mouth, palms and cup to the DOT Provider. If the patient does not do this, the DOT Provider should ask the patient to do so.
- The next patient can be served only once the Provider is sure that the previous one has taken all their medicines.
- If the patient is absent and/or does not take the drugs, the DOT Provider should inform the TIC by the end of the working day;
- If side-effects occur, the DOT Provider should inform the TIC immediately.
- After making sure that patient has taken all medication, the DOT Provider should make a mark in the **MDR-TB Treatment Card.**

10.4 Psychosocial and Economic Support

Patients with MDR-TB have probably previous repeated failed treatments with poor health status leading to unemployment or low productivity.This results in economic hardship for the patient and the family. Such socioeconomic problems can make patients nonadherent to treatment. The long duration of treatment, combined with severe side-effects of the drugs, may also contribute to depression, anxiety and further difficulty with treatment adherence.

Emotional support to MDR TB patients will imporve their adherence and hence treatment outcome. It can be provided by health care workers, health extension workers, volunteers and family members.The MDR TB Panel team (comprising of physician, health officer, nurse, pharmacy and lab personnel) and family adherence supporter should work together for continous patient support, adherence monitoring and counselling.

Patients who successfully completed MDR TB treatment should be encouraged to establsih expert Support groups and can be involved in adherence support, emotional support and contact tracing activities.

Socio-economic problems should be addressed to enable patients and their families to adhere to the M(X)DR-TB treatment.

10.4.1 Patient Support Packages

Patient motivation commonly wanes once the patient begins to feel better and may affect the patient's commitment to the treatment plan. The use of **patient support packages** is a strategy reported to be effective in assisting patients in maintaining adherence to treatment.

Support packages include "small rewards" given to patients to encourage them through the lengthy treatment and monitoring period and also to things that assist a patient to **overcome a barrier**, such as the provision of transport fee to attend a clinic appointment when a patient is without a means of transportation.

Possible patient support packages include:

- Health care free of charge (lab, CXR, ancillary drugs and SLDs).

- Food parcels for DR-TB patients
- Legal support
- Reimbursement of travel expenses
- Temporary shelter in a housing facility or in a rented home for DR-TB patients;

They will be included as part of the treatment regimen for all patients.
A package should contain variety of food items to supplement the patient's nutritional requirements that will facilitate early recovery from the disease. Cereals (like maize, rice, wheat flour, Oats), Pulses (like peas, beans, lentils), Cooking Oil, Sugar and milk are the commonly included items in food packages.
The TB Control Programm will provide food packages on monthly basis depending on availability of resources to all patients on treatment.

At the onset of DR TB treatment, a comprehensive socioeconomic and home assessment (assessment tool annexed) should be done. And those identified as needy should be enrolled into an economic strengthening package.

10.4.2 Economic Strengthening

The above package will not cover the living expenses of significant proportion of the M/XDR TB patients, so additional support packages are required to sustain the patient and the family once the patient starts to feel better. Involving M/XDR TB patients in economic strengthening activities for those who are found to be eligible as per the experience from the National HIV program should be implemented.
The key Economic Strengthening activities include:

- Vulnerability assessment,
- Market analysis,
- Feasibility studies,
- Basic business skills training,
- Establish saving groups,
- Avail Matching funds.

These activities shall be implemented in close collaboration with the HIV program.

10.5 Support groups

A support group allows patients with DR TB to meet and socialize with other patients and provide emotional support to each other.

- A HCW or someone trained in facilitating support groups should facilitate the support group.
- Clear eligibility criteria should be created for participation in each support group.
  - Participation should be generally reserved for patients who are sputum negative and are no longer infectious.
  - Cured patients may also be invited to support groups, as they provide hope to patients who are still in treatment.
- Support groups may need help in inviting participants, finding a safe meeting place and other organizational issues.
- At the end of each support group meeting, the facilitator and co-facilitator should stay behind to discuss and analyze the proceedings.

11. MANAGEMENT OF DR TB TREATMENT INTERRUPTIONS AND LOST TO FOLLOW OF UP

All efforts should be made to ensure that M/XDR TB patients do not interrupt treatment or lost to follow up. Action should be taken to promptly retrieve patient who fail to come for DOT for 2 days.

- **Treatment interrupters** are those patients who miss doses or who have discontinued treatment for less than 02 months.
- **Lost to follow up patients** (previously defaulters) are those patients who interrupt treatment for 2 or more consecutive months and return back for treatment**.**

Perform a review of the clinical record and a full clinical evaluation:

- When did the patient stop taking treatment?
- How long did the patient take treatment before stopping?
- What sort of adverse effects was the patient experiencing the last time he/she was taking treatment?
- Was the patient smear- or culture-positive at the time that he or she stopped treatment?

Why did the patient stop taking treatment?

- Meet with the community team and discuss ways to improve adherence before restarting treatment.
- Restarting treatment without addressing the issues that led the patient to stop will lead to the same result.

11.1 Management of treatment interruptions

Patients in IP/CP who miss doses:

All the missed doses during intensive phase must be completed prior to switching the patient to CP. Similarly all missed doses during CP must be administered prior to ending treatment.

A. Patients who interrupt treatment for less than 2 months during IP:

When the patient returns to resume treatment the IP will be continued, however the duration of treatment will be extended to complete IP. The follow up cultures will be done as per the revised schedule.

B. Patients who interrupt treatment for less than 2 months during CP:

When the patient returns to resume treatment, the CP will be continued, however the duration of treatment will be extended to complete the CP. The follow up cultures will be done as per the revised schedule.

11.2 Management of patients who return after Lost to follow up (LTFU)

Patients who after taking DR TB treatment for at least 1 month and have interrupted treatment for 2 months or more are labeled as Lost to Follow Up.

Such patients will be given an outcome of "return after lost to follow up" and then will be ***re-registered*** for further treatment which is based on the duration of lost to follow up period as per the flow charts given below.

General principles

1. Have the patient sign a new consent.
2. Perform a full history and physical exam.
3. Obtain a smear and culture and possibly GeneXpert. If positive, culture should be sent for 2nd line DST.
4. Obtain a radiograph and repeat the initial laboratory data.
5. The treatment regimen and duration to be used for patients restarting therapy depends on the month at which the patient abandoned therapy and the clinical state at which the patient returns to therapy.

A) Reinitiating treatment for DR TB patient who is Lost to Follow Up (LTFU) for 2 to 6 months

Length of treatment received prior to interrupting therapy	**Result of last culture prior to interrupting treatment -OR- Result of smear and culture upon return to treatment**	**Actions**
<3 months	Positive or negative	• Restart original regimen; patient will need full course of treatment. • Send sputum for culture and DST and adjust regimen according to the results.
3 months to end of Intensive Phase	Negative	• Continue the regimen the patient was taking before the interruption including the injectable until two cultures return. • All patients in this category should get a minimum of 24 months of therapy total
	Positive	• Restart original regimen; patient will need full course of treatment. • Send sputum for culture and DST and adjust regimen according to the results. • If treatment failure was suspected before interruption, consider designing a new regimen instead of restarting original regimen.
Continuation Phase	N/A	• If patient has no evidence of clinical deterioration during the interruption, the continuation phase can be restarted. • Send sputum for culture and DST; o If negative- continue CP o If positive- do SLD DST and review with report and design new DR TB regimen • All patients in this category should get a minimum of 24 months of therapy total.

B) Management of M/XDR patients who lost to follow up and return for treatment after 06 months

- If patient is clinically stable and bacteriologically negative, it may be advisable to first to determine if the patient has active TB before restarting treatment. Follow up patient periodically for minimum of 2 years.
- If Culture is positive, do DST
    - MDR or RR TB: Put on MDR TB Treatment regimen
    - XDR TB: Put patient on XDR TB treatment regimen

12. MANAGEMENT OF MDR-TB TREATMENT FAILURE

12.1 Assessment of patients at risk for failure

Patients who do not show signs of improvement after four months of treatment are at risk for treatment failure. In all patients who show clinical, radiological or bacteriological evidence of progressive active disease, or re-appearance of smear and/or culture positivity beyond 4 months of treatment should be considered as being at high risk for treatment failure.
The following steps are recommended in such patients:

1. Confirmation of adherence to treatment.
    a. Check the Treatment Card and discuss with the patient, TB treatment supporter and the DOT Provider.
    b. Assess socioeconomic status of the patient that might interfere with adherence to the treatment.
    c. Assess if side-effects occur during treatment, preventing the patient from properly continuing with the drug intake.
    d. Confirm that DOT was actually used. Otherwise the question of whether the patient had actually taken all prescribed medicine will arise.
2. The treatment regimen should be reviewed in relation to medical history, contacts and all DST reports. If the regimen is deemed inadequate, a new regimen should be designed.
3. Illnesses that may decrease absorption of medicines (e.g. chronic diarrhea) or may result in immune suppression (e.g. HIV infection, Diabetes Mellitus) should be excluded.
4. Illnesses that mimic failure (chronic infection with non-TB mycobacteria) should be excluded.
5. The bacteriological data should be reviewed. Often, the smear and culture data are the strongest evidence that a patient is not responding to therapy.
    a. One single positive culture in the presence of an otherwise good clinical response can be caused by a laboratory contaminant or error. In this case, subsequent cultures that are negative or in which the number of

colonies is decreasing may help prove that the apparently positive result did not reflect treatment failure.

b. Positive smears with negative cultures may be caused by the presence of dead bacilli and therefore may not indicate treatment failure.
c. Repeated culture- and smear-negative results in a patient with clinical and radiological deterioration may indicate that the patient has a disease other than DR-TB like Bronchiectasis, COPD or lung abscess.

12.2 Management of DR TB treatment failure

A) Change of regimen

MDR-TB treatment often consists of a treatment cycle; if no response is seen, reassessment of the regimen and treatment plan and formulation of a new plan of action are necessary.

If the current regimen seems to be inadequate, a new regimen containing at least four likely to be effective drugs should be designed. The present treatment should be declared a failure and the patient should be re-registered as "treatment after failure". Remember adding one or two drugs to a failing regimen should be avoided.

B) Surgical resection

Surgical resection as adjunct in the management of DR TB Treatment failure is indicated for patients with limited disease, unilateral lung involvement and who have sufficient respiratory reserve. A well equipped center with an experienced cardiothoracic surgeon and good TB IC measures in place is required.

The patient should be put on chemotherapy for a minimum of 3 months prior to surgery and treatment should continue for a minimum of 24 months past culture conversion.

C) Suspending treatment

It takes 3-4 months to evaluate whether a change in treatment plan has been effective. If the patient continues to deteriorate despite the measures described in the previous section, treatment failure should be considered. There is no single set of parameters to indicate cure is possible (or impossible) or absolute time frame to determine whether a treatment regimen is failing.

The clinical decision to suspend therapy is made after the clinical search for all other options has been exhausted and cure of the patient is considered to be highly unlikely.

Signs that indicate that the patient is unlikely to improve include:

- Persistent positive smears or cultures past month 8-10 of treatment;
- Progressive extensive and bilateral lung disease on chest X-ray with no option for surgery;
- High-grade resistance (often XDR-TB) with no option to add two additional agents;
- Overall deteriorating clinical condition that usually includes weight loss and respiratory insufficiency.

It is not necessary for all of these signs to be present to identify failure of the treatment regimen. However, a cure is highly unlikely when they are all present.

Continuation of ineffective therapy would lead to undue cost, unnecessary morbidity from side-effects of drugs and amplification of drug resistance (against second-line drugs).

The MDR TB Panel team should have a sympathetic discussion with the patient and the family. For treatment suspension it is necessary to make the patient and family understand and accept the withdrawal of treatment. The final decision to terminate the treatment must be taken by MDR TB Panel team.

There are two important considerations when suspending therapy:

- **The public health concern to the highly resistant TB**: Patient and family education on TB infection control at home and in the community are of paramount importance.
- **The patient's quality of life**: palliative care measures addressing physical, psychological, spiritual and social aspects of patient's problems are essential.

For management of MDR-TB patients whose treatment is terminated refer to palliative care section of this guideline.

13. TREATMENT OF DRUG-RESISTANT TUBERCULOSIS IN SPECIAL SITUATIONS

13.1 Pregnancy

Considerations

1. Pregnancy should be avoided while undergoing treatment for MDR-TB because some of the second-line anti-TB drugs may cause birth defects.
2. Determination of the degree of TB disease severity in the pregnant woman is critical:
   - Severity of symptoms of active TB.
   - Degree of weight loss and ability to do normal daily activities.
   - Extent of disease on chest X-ray.
   - Bacteriological evaluation (e.g., sputum smear and culture).
   - Gestational age

3. The decision to postpone the start of treatment should be agreed upon by the patient and doctor after discussion of the risks of untreated TB versus the benefits delaying exposure of the fetus to teratogens.
   - Untreated MDR-TB in pregnant women carries similar risks of morbidity and mortality compared to nonpregnant women.
   - The fetus can develop congenital TB or, more commonly, can be infected in the postnatal period and progress rapidly to disease.
   - The safety of many second-line anti-TB drugs is uncertain.

Management

- The risk of drug birth defects in MDR-TB treatment is highest in the first trimester of pregnancy. The gestational age of the fetus should be determined, either through calculation based on the last menstrual period or by dating using ultrasound.
- The benefit of treating MDR-TB in pregnancy in most circumstances outweighs the risks.
  - Most patients should start treatment as soon as the diagnosis is made.
  - Treatment can be deferred until the second trimester only if the patient is clinically stable with minimal disease.

- The initial MDR-TB regimen in pregnancy should be composed of three or four oral second-line anti-TB drugs. These drugs should have demonstrated efficacy against the infecting strain.
- Avoid aminoglycosides during the first trimester due to the risk of toxicity to the developing fetal ear. Capreomycin may carry a lower risk of ototoxicity and is the drug of choice if an injectable cannot be avoided.
- Avoid ethionamide due to the increased risk of nausea and vomiting, as well as its potential teratogenicity.
- Levofloxacin, cycloserine, and PAS have limited data on safety and long-term use in pregnancy but are considered the drugs of choice for MDR-TB treatment in pregnancy.
- The regimen may be reinforced with an injectable and other drugs immediately postpartum.
- Total treatment duration is the same as in nonpregnant patients.

Summary for the management of drug-resistant tuberculosis and pregnancy:

- Close follow-up of the pregnancy with regular care (at a minimum)
- Patient involvement in therapeutic decisions
- Individualized management
- Ideally, avoid treatment during first trimester, but consider treatment regardless of trimester if life-threatening conditions are present
- During first 20 weeks, avoid injectables if possible or use capreomycin preferentially
- Initiate DR-TB therapy during second or third trimester to achieve smear conversion prior to delivery
- Consider risks and benefits to mother and foetus
- Use pyridoxine (50–100 mg) in all patients on ethionamide and/or cycloserine
- Recommended regimen: **Z-(Cm)-Lfx-Cs-PAS**

13.2 Breastfeeding

- A woman who is breastfeeding and has active drug-resistant TB should receive a full course of anti-tuberculosis treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to her Baby.

- In lactating mothers on treatment, most anti-tuberculosis drugs are found in the breast milk in minute concentrations compared to the therapeutic doses used in treating infants. However, any effects on infants of such exposure during the full course of MDR-TB treatment have not been established.

- Where feasible, alternative infant feeding options may be provided. It should be noted, however, that ***breast milk*** *is often the best and the only feasible feeding option for most infants in Ethiopia*. Any arrangement to care for the baby must take into account the dangers of unsafe replacement feeding practices. For this reasons breast feeding is a better option in Ethiopia.

- In addition, bonding of the infant with the mother or other suitable guardian should be promoted to provide adequate psycho-emotional stimulation.

- If the mother is sputum smear-positive, the care of the infant may be left to family members until she becomes sputum smear-negative, if this is feasible. When the mother and infant are together, this common time should be spent in well-ventilated areas or outdoors. The mother should be offered a surgical mask until she becomes sputum smear-negative.

13.3 Family planning

All women of childbearing age should be using a reliable contraceptive method

- All women of childbearing age should have a pregnancy test during the initial evaluation before starting MDR-TB treatment.
- Birth control is strongly recommended for all women receiving MDR-TB treatment.

- Oral contraceptives are not recommended. MDR-TB patients often have nausea and vomiting due to side effects. There are also drug interactions with rifampicin. Non-adherence over the long course of treatment is a problem with oral contraceptives.
- If use of Oral contraceptives is the only option, patients should be advised to take their contraceptives apart from times when they may experience vomiting caused by the anti-tuberculosis treatment.
- Better options for birth control include medroxyprogesterone (DepoProvera) administered by intramuscular injection every 12 weeks or placement of an intrauterine device (IUCD) or implants (e.g. Implanon).
- All patients are encouraged to use condoms to prevent sexually transmitted disease, but condoms should not be relied upon as the sole method of birth control.

13.4 Diabetes Mellitus
Considerations

1. Patients with diabetes are at increased risk for developing MDR-TB.
2. TB can be more difficult to diagnose in patients with diabetes due to a higher occurrence of atypical chest X-ray findings and extrapulmonary TB.
3. Patients with diabetes and MDR-TB are at increased risk for poor outcomes.
   - Patients with diabetes mellitus have impaired immunity compared to healthy individuals.
   - Elevated blood sugar can worsen the clinical course of TB; TB can worsen glycemic control in diabetics.
   - Sequel of diabetes may potentiate the adverse effects of anti-TB drugs, especially renal dysfunction and peripheral neuropathy.

Management

- All patients with MDR-TB should be screened for diabetes as part of the initial clinical evaluation.
- Diabetes must be optimally managed throughout the treatment of MDR-TB. Management of diabetes is the responsibility of the MDR TB panel team treating the patient for MDR-TB.

- Providers and patients should adhere closely to the foundations of diabetes management, including adoption of a diabetic diet, monitoring of symptoms of hypo- and hyperglycemia, and practicing good foot care.
- Patients with diabetes usually have some underlying chronic diabetic nephropathy. This increases the risk of injectable nephrotoxicity.
  - Creatinine and potassium levels should be monitored frequently—weekly for the first month and then at least monthly thereafter while receiving the injectable.
  - An ACE inhibitor should be considered in all patients with diabetes to prevent progression of diabetic nephropathy.
- Patients should have regular monitoring of blood glucose levels and other important markers of diabetes management.
  - Goal blood glucose levels are 70-140 mg/dL before meals and 100-180 mg/dL before bedtime.
  - Goal hemoglobin A1c is < 7.5 percent. If available levels should be checked every three months. Checks can be extended to every six months in stable clinical situations.
  - Patients with diabetes should undergo a yearly retinal exam.
  - Blood pressure should be checked monthly.
- Tight control of blood glucose can be achieved through pharmacologic therapy.
  - Oral hypoglycemic drugs can be used during the treatment of MDR-TB but may require increases in dosage due to drug-drug interactions. Blood glucose levels can be monitored twice weekly for patients on oral drugs.

13.5 Renal Insufficiency Considerations

- Chronic kidney disease is common in MDR-TB patients. Etiologies include renal TB disease, damage due to previous injectable toxicity, diabetes mellitus, and HIV-associated nephropathy.
- Anti-TB drugs that are excreted by the kidney can accumulate to toxic levels in patients with renal dysfunction.

Management of Renal Dysfunction

- Renal function should be estimated by calculating the creatinine clearance in all patients receiving MDR-TB treatment (refer to the formula below).
- Anti-TB therapy should be adjusted in patients with decreased creatinine clearance (refer to the table below)

Additionally the commonly used ARV, TDF may have nephrotoxic effects. In a patient with advanced HIV, the combination of TDF and Cm can lead to an electrolyte wasting syndrome with life-threatening hypokalemia. So when injectable SLDs and TDF are used concomitantly close monitoring should be done. Drugs should be stopped until the patient recovers and potassium should be replaced. In cases of acute renal failure, consider stopping nephrotoxic medication.

Creatinine Clearance can be calculated using the Cockroft-Gault formula:

$$\text{Men: } \frac{(140 - \text{age in Years}) \times \text{Weight in Kg}}{72 \times \text{Serum Creatinine, mg/dl}}$$

$$\text{Women: } \frac{(140 - \text{age in Years}) \times \text{Weight in Kg} \times 0.85}{72 \times \text{Serum Creatinine, mg/dl}}$$

Normal values for creatinine clearance are:

- Men: 97 to 137ml/min
- Women: 88 to 128ml/min

Patients with calculated GFR below 60ml/min and especially with GFR below 30ml/min need adjustment of dosage of drugs.

Table: Adjustment of anti-tuberculosis medication in renal insufficiency

Drug	Change in frequency of administration	Recommended dose and frequency for patients with creatinine clearance <30 ml/min or for patients receiving hemodialysis
Isoniazid	No change	300 mg once daily, or 900 mg three times per week
Rifampicin	No change	600 mg once daily, or 600 mg three times per week
Pyrazinamide	Yes	25–35 mg/kg per dose three times per week (not daily)
Ethambutol	Yes	15–25 mg/kg per dose three times per week (not daily)
Levofloxacin	Yes	750–1000 mg per dose three times per week (not daily)
Moxifloxacin	No change	400 mg once daily
Cycloserine	Yes	250 mg once daily, or 500 mg/dose three times per week
Prothionamide	No change	250–500 mg per dose daily
Ethionamide	No change	250–500 mg per dose daily
P-Aminosalicylic Acid	No change	4 g/dose, *twice daily*
Streptomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)
Capreomycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)
Kanamycin	Yes	12–15 mg/kg per dose two or three times per week (not daily)
Bedaquiline (Bdq)	No change	Mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution)
Linezolid (Lzd)	No change	
Clofazimine (Cfz)	No change	
Amoxicillin/Clavulanate (Amx/Clv)	Yes	1,000/250 mg twice daily for creatinine clearance 10-30 mL/min 1,000/250 mg once daily for creatinine clearance < 10 mL/min

Source: *Guidelines for the programmatic management of drug-resistant tuberculosis (WHO 2008) and PIH Medical management of DR TB 2013*

13.6 Liver Disorders

Considerations

- Patients with liver disease are at increased risk of hepatotoxicity due to anti-TB drugs.
- Of the first-line drugs, isoniazid, rifampicin, and pyrazinamide are associated with hepatotoxicity. Pyrazinamide carries the highest risk.
- Of the second-line drugs, ethionamide, prothionamide, and PAS can also be hepatotoxic, although less so than first-line drugs. Hepatitis occurs rarely with the flouroquinolones.

Management

- The presence of liver disease should be assessed prior to initiation of therapy. History and physical exam should specifically focus on evaluation of symptoms and signs of chronic disease, history of viral hepatitis, history of medication-induced hepatotoxicity, and degree of alcohol consumption.
- Patients with a history of liver disease should have liver function tests checked prior to treatment and monthly while on treatment.
- In general, patients with chronic liver disease should not receive pyrazinamide. All other drugs can be used with close laboratory monitoring of liver function. Stoppage of offending drugs should be considered if significant liver inflammation occurs.
- Uncommonly, a patient with TB may have concurrent acute hepatitis that is unrelated to TB or anti-TB treatment. In this case, clinical judgment should be used in determining whether treatment should proceed or be delayed until resolution of the hepatitis.
- Once a patient on second line drugs develops hepatitis, other etiologies should also be excluded such as viral hepatitis, alcoholic hepatitis, drug induced hepatitis by non-TB drugs.
- In some cases, it is possible to defer antituberculosis 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-hepatotoxic drugs is the safest option,

but whenever possible a fluoroquinolone should be included to ensure the efficacy of the regimen.

- Alcohol consumption should be discouraged while patients are on anti-TB therapy.

13.7 Seizure Disorders

Some patients requiring treatment for drug-resistant TB will have a previous or current medical history of a seizure disorder. The first step in evaluating such patients is to determine whether the seizure disorder is under control and whether the patient is taking anti-seizure medication.

If the seizures are not under control, initiation or adjustment of anti-seizure medication will be needed before the start of drug-resistant TB therapy. In addition, any other underlying conditions or causes of seizures should be corrected.

Cycloserine should be avoided in patients with active seizure disorders that are not well controlled with medication. However, in cases where cycloserine is a crucial component of the treatment regimen, it can be given and the anticonvulsant medication adjusted as needed to control the seizure disorder. The risks and benefits of using cycloserine should be discussed with the patient and the decision on whether to use cycloserine made together with the patient.

In mono- and poly-resistant cases, the use of isoniazid and rifampicin may interfere with many of the anti-seizure medications. Drug interactions should be checked before their use.

Seizures that present for the first time during anti-tuberculosis therapy are likely to be the result of an adverse effect of one of the anti-tuberculosis drugs.

13.8 Psychiatric Disorders

It is advisable for psychiatric patients to be evaluated by a health-care worker with psychiatric training before the start of treatment for drug-resistant TB.

The initial evaluation documents any existing psychiatric condition and establishes a baseline for comparison if new psychiatric symptoms develop while the patient is on treatment. Any psychiatric illness identified at the start of or

during treatment should be fully addressed. There is a high baseline incidence of depression and anxiety in patients with MDR-TB, often connected with the chronicity and socioeconomic stress factors related to the disease.

Treatment with psychiatric medication, individual counselling and/or group therapy may be necessary to manage the patient suffering from a psychiatric condition or an adverse psychiatric effect caused by medication. Group therapy has been very successful in providing a supportive environment for MDR-TB patients and may be helpful for patients with or without psychiatric conditions. (Adequate measures to prevent infection risk should be in place for the group therapy.)

The use of cycloserine is not absolutely contraindicated for the psychiatric patient. Adverse effects from cycloserine may be more prevalent in the psychiatric patient, but the benefits of using this drug may outweigh the potentially higher risk of adverse effects. Close monitoring is recommended if cycloserine is used in patients with psychiatric disorders.

All health-care workers treating drug-resistant TB should work closely with a mental health specialist and have an organized system for psychiatric emergencies.

Psychiatric emergencies include psychosis, suicidal ideation and any situation involving the patient's being a danger to him or herself or others.

Recommended regimen is: Z-Cm(Km)-Lfx-Eto-PAS

13.9 Substance Dependence

Patients with substance dependence disorders should be offered treatment for their addiction whenever possible. Complete abstinence from alcohol or other substances should be strongly encouraged, although active consumption is not a contraindication for anti-tuberculosis treatment. If the treatment is repeatedly interrupted because of the patient's dependence, therapy should be suspended until successful treatment or measures to ensure adherence have been established.

Good DOT gives the patient contact with and support from health-care providers, which often allows complete treatment even in patients with substance dependence. Cycloserine will have a higher incidence of adverse effects (as in the psychiatric patient) in patients dependent on alcohol or other substances, including a higher incidence of seizures. However, if cycloserine is considered important to the regimen, it should be used and the patient closely observed for adverse effects, which are then adequately treated.

13.10 Drug Resistant TB and HIV

Introduction:

HIV co-infection is a significant challenge for the diagnosis, treatment and prevention, of drug-resistant tuberculosis, especially in the case of MDR-TB and XDR-TB. Reports have shown high mortality rates among HIV-infected patients with DR-TB, and alarming mortality rates in patients co-infected with XDR-TB and HIV.

HIV is a powerful risk factor for all forms of TB and DR-TB outbreaks; including XDR-TB outbreaks in HIV-infected patients do appear common. DR-TB is often associated with higher mortality rates in the HIV-infected compared to the non-infected, however the use of ART in addition to treatment of DR-TB has been reported to improve outcomes of DR-TB in the HIV infected.

Early diagnosis of DR-TB and HIV, prompt treatment with adequate regimens, sound patient support, and strong infection control measures are all essential components in the management of DR-TB in HIV persons.

These activities are the backbone of the WHO TB/HIV collaborative strategy In Ethiopia, current data show that up to 20% of MDR-TB patients are HIV positive.

DR-TB/HIV collaborative activities Recommended Standard of Care:

- Perform provider-initiated HIV testing and counseling in all DR TB suspects and confirmed DR-TB patients.
- Use standard algorithms to diagnose pulmonary and extra-pulmonary tuberculosis.

- Use mycobacterial cultures and, where available, newer more rapid methods of diagnosis such GeneXpert.
- Perform DST at the start of TB therapy.
- Determine the extent (or prevalence) of TB drug resistance in patients with HIV.
- Introduce antiretroviral therapy (ART) promptly in DR-TB/HIV patients.
- Consider empirical therapy with second-line antituberculosis drugs.
- Provide co-trimoxazole preventive therapy (CPT) for patients with active TB and HIV.
- Arrange treatment follow-up by a specialized team.
- Implement additional nutritional and socioeconomic support.
- Ensure effective infection control.
- Involve key stakeholders in DR-TB/HIV activities.

DR-TB and HIV Co-management

The treatment of DR-TB in patients with HIV is essentially the same as that in patients without HIV. Observational studies have shown that without ART mortality due to DR-TB with HIV co-infection is very high (91-100%).
Antiretroviral therapy in HIV-infected patients with TB improves survival for both drug-resistant and susceptible disease.
Undue delay in the start of ART could result in significant risk of HIV-related death among patients with advanced disease
Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-TB drugs, irrespective of CD4 cell-count, as early as possible (within the first 8 weeks) following initiation of anti-TB treatment
The recommended standard first-line ART regimen for drug-susceptible TB is two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitors (NNRTI) i.e. AZT or TDF + 3TC or FTC + EFV

However, DR-TB with HIV co-management faces lots of challenges: high pill burden, adverse drug reactions, immune reconstitution inflammatory syndrome and stigma and discrimination to patients.

In general, HIV patients have a higher rate of adverse drug reactions to both TB and non-TB medications, and the risk of adverse drug reaction increases with the degree of immune-suppression. The multiple medicines involved in DR-TB with recognized high toxicity risks, often combined with ART, results in a high incidence of adverse effects.

Some toxicities are common to both anti-TB treatment and ART, which may result in added rates of adverse events. Common adverse reactions that can be caused by both ARVs and second line anti-TB drugs are listed in the table below.

Identifying the source of adverse effects in patients receiving concomitant therapy for DR-TB and HIV is often difficult. Monitoring needs to be more intensive for both response to therapy and adverse effects. When possible, avoid the use of agents with shared side-effect profiles.

Table: Potential overlapping toxicity from anti-retrovirals and anti-tuberculosis medicines

Potential Toxicity	**Antiretroviral drugs**	**Anti-tuberculosis drugs**
Peripheral Neuropathy	**Stavudine**, didanosine	**Cycloserine, INH**, flouoroquinolones, streptomycin, kanamycin, amikacin, capreomycin, ethionamide/prothionamide, linezolid
Psychiatric symptoms	**Efavirenz**	**Cycloserine**, INH, fluoroquinolones, ethionamide/prothionamide
Hepatitis	**Nevirapine**, ritonavir boosted protease inhibitors, efavirenz, etravirine, maraviroc	**Pyrazinamide**, **INH, rifampicin**, PAS, ethionamide/ prothionamide, fluoroquinolones
Gastrointestinal intolerance	**Zidovudine**, protease inhibitors, didanosine	**Ethionamide,/prothionamide**, PAS, pyrazinamide,
Renal Toxicity	**Tenofovir,** indinavir	Streptomycin, **kanamycin, amikacin, capreomycin**, viomycin, rifampicin
Bone marrow toxicity	**Zidovudine**	**Linezolid**, rifampicin/rifabutin
Lactic acidosis	**Stavudine**, didanosine, zidovudine	**Linezolid**
Stevens-Johnson syndrome	Nevirapine, efavirenz, etavirine	Cycloserine, linezolid, streptomycin
Arrhythmias/ QT prolongation	**Atazanavir/ ritonavi**r, saquinavir/ritonavir,	**Fluoroquinolones**, **bedaquiline**

	lopinavir/ritonavir	
Rash/prutitis	**Neirapine**, efavirenz, etravirine, abacavir	**Rifampicin/rifabutin**, pyrazinamide

Immune reconstitution inflammatory syndrome (IRIS) may complicate therapy. IRIS is relatively common in mild to moderate forms in patients with TB or DR-TB started on ART. It generally presents within three months of the initiation of ART and is more common with a low CD4 cell count (<50 cells/mm3). It is important to note that IRIS is a diagnosis of exclusion. Treatment includes NSAIDs in mild disease and corticosteroids in moderate-severe disease. Most patients can be treated without interruption of ART.

Given that the regimens together are particularly difficult to take, the stigma of both diseases can result in serious discrimination, and the risk of mortality is very high, patients with HIV-associated DR-TB may require special socioeconomic, nutritional, and psychosocial support in order to successfully complete treatment.

The management of MDR-TB in HIV should be carried out at referral centers until the patient stabilizes.

Scenario 1 Patient not on ART:

- Start standard regimen for MDR-TB
- Start Co-trimoxazole preventive therapy
- Start ART as soon as possible (within 8 weeks of initiation of MDR-TB treatment)
- Preferred regimen: AZT+3TC+EFV or NVP.
- If CD4 count is very low (<50/µl) start ART within 2 weeks of commencing MDR-TB treatment.

Scenario 2 Patient on ART:

- The development of TB while on ART might be a sign of IRIS (if ART < 6 months) or treatment failure. Further workup (CD4 count, viral load) is needed.
- If a patient develops MDR-TB while on ART:

- Start the standard treatment for MDR-TB
- Rule out ART treatment failure if the patient has been on ART for at least 6 months. In case there is evidence of ART failure, consider switching to second line ART regimen. However, patient should be kept on appropriate first line ART regimen until 6 to 8 weeks of MDR-TB treatment.
- Substitute TDF by AZT until the end of the intensive phase of MDR-TB treatment. This is because of the overlapping nephrotoxixicity of TDF and injectable second line antituberculous drugs (Capreomycin, Kanamycin Amikacin). Once the Intensive Phase is completed, TDF can be restarted.
- Modify the ARV as needed considering possible drug-drug interaction or overlapping side effect or ART treatment failure.
- Look for and treat other Opportunistic diseases.
- Continue/ re-start CPT.

14. DRUG-RESISTANT TB IN CHILDREN

14.1 Introduction

Acquired drug resistant TB in children with active TB seldom develops as they often have low bacillary load with non-cavitary Tuberculosis. DR-TB in children is mainly transmitted from household contacts with drug resistant strains.
Active DR-TB in children usually develops within two years of infection. Thus, follow up of exposed children to known or presumed DR-TB patients should be a high priority to find incident DRTB cases in children.

14.2 DR TB Case Finding in Children

Case-finding strategy for DR-TB in children involves the systematic and timely screening of children at risk of DR-TB.

Children with the following conditions should be presumed to have DR-TB:

i) Features in the index case suggestive of drug resistant TB

- Index case remaining smear-positive after 3 months of treatment
- History of previous TB treatment interruption or recurrence after completion of TB treatment

ii) Features in a child suggestive of having drug resistant TB

- Contact with a known case of MDR-TB
- Failure to improve clinically after 3 months of first line treatment in well adherent child, including persistent smears or cultures, persistence of symptoms, and failure to gain weight
- Child with TB recurrence after completing TB treatment

However, contact investigation is the main strategy to be followed to find children with DR-TB.

14.3 Diagnosis of MDR-TB in children

Children often have smear negative and Extrapulmonary TB. Young children usually fail to expectorate sputum and have paucibacillary TB which makes bacteriologic confirmation and performing DST difficult.

The presence of three or more of the following should strongly suggest a diagnosis of TB in children:

1) Chronic symptoms suggestive of TB
2) Physical signs highly suggestive of TB. The two most suggestive are:
    - fever, >14 days and after other causes such as malaria have been ruled out,
    - weight loss and failure to thrive)
3) Positive TST test result
4) Chest X-ray suggestive of TB.

For bacteriologic confirmation of DR-TB in children, samples from sputum, gastric aspirates, or extrapulmonary sites should be pursued aggressively and subjected to Xpert MTB/RIF test, or culture and DST. See Annex 3 for samples from children.

However, in cases where confirmation is not possible, Clinical diagnosis of DR-TB should be made by the MDR TB panel team at treatment initiating center.

The following group of children should be considered for empiric DR-TB treatment:

- **For household contacts of Presumed or confirmed DR-TB patient:**
    - who is too sick to await DST results
    - who is a Presumed EPTB case
    - culture negative but clinical evidence of TB
    - For whom sample for DST is not available
- **For well adherent children receiving first-line TB treatment:**
    - Not showing clinical improvement after third month of treatment
    - Treatment failure for whom DST result is not available

However, every effort must be taken to perform bacteriologic confirmation, even after initiation of regimen with SLDs.

14.4 Treatment of MDR-TB in Children

Treatment of DR-TB in children generally follows the basic principles of regimen design used in Adults. Empiric treatment is more likely needed in children and should include strong regimen that can be scaled up by DST and possible development of Adverse events. The duration of treatment should be 20 months for those in whom culture results is not available and with decision by panel team or 18 months after culture-conversion for those culture conversion results.

Principle of MDR-TB treatment in children:

- The basic principles of regimen designing, treatment duration and monitoring of DR-TB treatment in children generally similar to adults.
- Case definitions, registrations and treatment outcome definitions are the same.
- Children diagnosed based on clinical evidence of active TB disease and contact, receive empiric MDR-TB regimen based on the DST pattern of the index case.
- Children who fail to improve clinically on TB regimens and decided to start MDR-TB treatment with empiric clinical diagnosis should receive standardized regimen.
- All drugs should be dosed at the higher end of the recommended ranges (see Annex II)
- Most SLDs do not have paediatric formulations & cutting/crashing pills is necessary.
- Dosing of Antituberculosis drugs should be calculated based on current body weight and should be adjusted regularly as weight changes during treatment.
- Administer all doses on once-daily basis under strict supervision
- None of the antituberculosis drugs are absolutely contraindicated for use in children.
    - Fluoroquinolones, Ethionamide, PAS and Cycloserine have been used effectively in children and are well tolerated.
    - Capreomycin and Prothionamide are preferred over kanamycin and Ethionamide.

- Treatment monitoring in children mainly depends on monitoring of clinical responses, growth and development as obtaining samples for culture test is often difficult.
- Measure weight and height on every visit and plot on standard growth curve.
- Do BMI/MUAC to assess nutritional status and manage accordingly.
- Adherence support interventions should involve the child and care giver.
- Children generally tolerate second-line drugs better than adults and develop adverse events less commonly.

14.5 Treatment Failure in children

In children who are culture positive at treatment initiation, clinical and bacteriologic criteria will be used to define failure.
In children who are not culture-positive initially, treatment failure is difficult to assess. Weight loss or failure to gain weight adequately is often the first (or only) sign of failure.
So, children who do not gain weight or show clinical deterioration should be presumed to have developed treatment failure and be evaluated by MDR-TB panel team at TIC.

If treatment failure is confirmed, use the same principle of management of MDR-TB treatment failure in Adult.

15. MANAGEMENT OF ADVERSE DRUG REACTIONS

15.1 Screening for Adverse Effects

Screening of adverse effects is an important part of MDR-TB treatment

- Close monitoring of patients is necessary to ensure that adverse effects of second-line drugs are recognized quickly. The ability to monitor patients for adverse effects daily is one of the major advantages of DOT over self-administration of MDR-TB treatment.
- The majority of adverse effects are easy to recognize, and patients will readily explain that they are experiencing them. It is important, however, to have a systematic method of patient interviewing since some patients may be reluctant to report adverse effects, even severe ones. Other patients may be distracted by one adverse effect and forget to tell the health care provider about others.
- Laboratory screening is necessary for detecting certain adverse effects that are occult (not obviously noted by taking the patient's history or through physical examination).
- Pharmacovigilance data (side effects that occur while patients are on treatment) should be recorded and reported to the FMOH.

15.2 General considerations

- Second-line drugs have more adverse effects than first-line anti-TB drugs. These adverse effects should be managed promptly and aggressively to give the patient the best chance to tolerate the regimen, maintain adherence, and achieve a good treatment outcome.
- The patient should be educated regarding the potential for adverse drug effects before starting treatment:
    - Review the common adverse effects associated with each prescribed medication in the regimen.
    - Patients should be told to anticipate that most medication adverse effects manifest themselves at the beginning of treatment. They should be reassured that the majority will improve over time.
    - Warning signs of important complications requiring immediate medical attention should be stressed.

    - Patient should also be instructed on how to notify a health care provider if they develop any concerns about their health while on MDR-TB treatment.
- DOT supporters should play a major role in helping the patient deal with side effects. Supporters are crucial in early detection and triage of symptoms and provide psychosocial support while side effects are being controlled. Patient support groups are another means of providing psychosocial support to patients.
- Proper management starts from the pre-treatment preparation of the patient.
- **ADR can be prevented** or minimized by:
    - Pretreatment screening of patients for other concomitant illnesses.
    - Avoid drugs with overlapping toxicities
    - Avoid drugs with potential interactions.
    - Regular monitoring of treatment for early detection of signs of adverse effects/toxicities.
    - Pyridoxine (vitamin B6) should be given to all patients receiving cycloserine to help prevent neurological adverse effects. The recommended dose is 50 mg for every 250 mg of cycloserine prescribed.
- Monitoring and management of ADRs may have to be more aggressive in patients with **concomitant conditions** such as: pregnancy, diabetes mellitus, renal insufficiency, acute or chronic liver disease, thyroid disease, mental illness, drug or alcohol abuse and HIV infection.
- During the intensive phase of treatment, patients should be evaluated for ADRs weekly and recorded in the ADR Monitoring part of the patient treatment card. In the continuation phase patients should be evaluated for ADRs at least monthly utilizing the same treatment card.
- ADRs may be classified according to their severity as mild, moderate or severe (see table below).
- **Mild adverse effects** are common. They should be managed symptomatically with ancillary drugs while continuing the treatment regimen. Mild adverse effects may disappear or diminish with time, and patients may be able to continue receiving the drug without interruption.

Table: Classification and Management of ADRs

ADRs	Recommended Management at TIC	Management at TFC
Mild	• The condition should be explained to the patient and reassured. • The necessary supportive measures and ancillary drugs need to be given. • do not require treatment interruption or change in dose/frequency	• Patient counselling and reassurance. • Supportive treatment with ancillary drugs
Moderate	• Requires temporary discontinuation or reduction of the dose of the causative agent(s) for short time • Dose reduction of drugs should be within the acceptable treatment dosage ranges. • The health care provider should closely follow the patient and reintroduce the medication as soon as the adverse event is reversed. • Prolonged drug discontinuation and use of very low doses of a drug can predispose for TB treatment failure.	• Resuscitate and Refer immediately to TIC for proper management
Severe and life-threatening	• Severe toxicities like hepatitis, psychosis, suicidal ideation or a severe hypersensitivity reaction to the drugs requires discontinuation of the offending drug or temporary discontinuation of the whole regimen.	• Discontinue all drugs, Resuscitate and Refer to TIC immediately

- The adverse effects of a number of second-line drugs are highly dose-dependent. With cycloserine and ethionamide, for example, a patient may be completely intolerant at one dose and completely tolerant at a slightly lower dose. However, every effort should be made to avoid under dosing.
- Temporary suspension of medications can also be used if an adverse effect is particularly resistant to dose adjustment. Complete discontinuation of drugs, however, should be avoided if possible.
- Any decision to suspend a drug must be made while weighing the risk of continued side effects against the benefit of improving the chances of curing a deadly disease.

15.3 Specific Management of Adverse Drug Reactions (ADRs)

A. Allergy: Rash

Possible anti-TB drug causes: Any drug

Possible ART causes: NVP, ABC, EFV, d4T, and others

Suggested management strategy	Comments
1. Evaluate for signs of severe rash (involvement of mucous membranes, angioedema, and skin necrosis). 2. For severe rash, stop all therapy pending resolution of reaction. 3. In the case of anaphylaxis, manage with standard emergency protocols. 4. Check liver enzymes, since many rashes can be accompanied by hepatitis. 5. Review the patient's active medications to identify the likely offending drug. Check for other potential causes of allergic skin reaction (like scabies or other environmental agents). 6. Initiate ancillary medications to control symptoms of minor skin reactions, including: o Antihistamines. o Hydrocortisone cream for localized rash. o Prednisone in a low dose of 10 to 20 mg per day for few weeks in refractory cases. 7. Once rash resolves, reintroduce drugs one at a time with the most likely culprit last. Consider not reintroducing in the challenge any drug that is highly likely to be the culprit. 8. Suspend permanently any drug identified to be the cause of a serious reaction.	• History of previous drug allergies should be carefully reviewed. Any known drug allergies should be noted on the treatment card. • Drug eruptions can have a variety of manifestations, ranging from mild maculopapular rashes and hives to severe systemic reactions like toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS). • Flushing reaction to rifampicin or pyrazinamide is usually mild and resolves with time. • Cotrimoxazole, Nevirapine and Abacavir can cause skin rash in HIV-positive patients. • Any drug that is thought to have caused severe reactions like anaphylaxis or Stevens-Johnson syndrome should never be reintroduced to the patient, not even as a challenge.

B. Gastrointestinal: Nausea and vomiting

Possible anti-TB drug causes: Eto/Pto, PAS, H, Z, Amx/Clv, Cfz, Lzd, Imp/Cln, Bdq

Possible ART causes: AZT

Suggested management strategy	Comments
1. Assess for danger signs including dehydration, electrolyte disturbances, and hepatitis. Serum electrolytes and renal function should be	o Nausea and vomiting are common in early weeks of therapy but usually improve over

checked. 2. Patients with dehydration should be treated with oral or intravenous rehydration therapy immediately to correct volume status. Electrolyte disturbances should be corrected. 3. Adjust timing of anti-TB drug dosing (without lowering overall dose or compromising the regimen): divided doses of Eto/Pto and PAS can be given. 4. Give a light snack (biscuits, bread, rice, tea) before the medications. 5. Start antiemetic therapy if nausea and vomiting persist despite adjustments to the dosing schedule. – Metoclopramide 10 mg taken 30 minutes before anti-TB drugs (maximum dose is 15 mg twice daily). – Ondansetron 8 mg taken 30 minutes before anti-TB drugs, repeated every eight hours – Promethazine 25 mg taken 30 minutes before anti-TB drugs or before meals, up to three times daily. 6. Decrease the dose of the offending drug if symptoms are not controlled with anti-emetics. 7. Alternatively, symptoms can often be controlled by stopping the offending drug for a few days (two to four days) and then adding it back by gradually increasing the dose. This often results in better tolerance. 8. Permanent discontinuation can be considered in extreme cases when all other interventions have failed.	time and with supportive therapy. Some degree of symptoms may need to be tolerated in the initial period of treatment. o Symptoms are usually reversible upon discontinuation of the offending drug. o For patients who are particularly anxious about the nausea, or have anticipatory nausea/vomiting, a small dose of an anti-anxiety medicine can be given. o Nausea and vomiting can be signs of hepatitis or a new pregnancy. o Emesis that looks like coffee grounds is a sign of upper gastrointestinal tract bleeding, usually from a stomach ulcer, and should be considered a medical emergency. o Whenever stopping a medicine because of side effects, advise the patient the medicine is being stopped temporarily and will be restarted back gradually.

C. Gastrointestinal: Dyspepsia and abdominal pain

Possible anti-TB drug causes: PAS, Pto/Eto, Cfz, fluoroquinolones, H and Z

Possible ART causes: Most ARVs have been associated with abdominal pain

Suggested management strategy	Comments
1. Initiate symptomatic management with the use of H2 blockers (ranitidine 150 mg twice daily or 300 mg once daily) or proton-pump inhibitors (Omeprazole 20 mg twice daily).	1. Dyspepsia is a common side effect of MDR-TB treatment, especially in patients who have received multiple previous treatments. • Symptoms associated with

2. Dyspepsia is very common and hence prophylactic H2 blockers (Ranitidine) or proton pump inhibitors (Omeprazole) may be initiated with MDR-TB treatment for selected patients. 3. Avoid the use of antacids as they decrease absorption of fluoroquinolones. If antacids must be used, they should be administered two hours before or three hours after MDR-TB drugs so as to not interfere with the absorption of the fluoroquinolones. 4. Decrease the dose of the offending drug if symptoms are not controlled with H2 blockers or proton pump inhibitors. 5. For severe abdominal pain, stop suspected drug for short periods of time (one to seven days). 6. Discontinue suspected drug permanently if this can be done without compromising regimen.	Dyspepsia include bloating, nausea, epigastric burning or discomfort, and a sour taste in the mouth. Symptoms are often exacerbated in the morning or prior to eating. • Severe Dyspepsia or gastric ulceration as manifested by severe postprandial pain or blood in the vomit or stool is relatively rare. 2. Abdominal pain can also be associated with serious adverse effects, such as pancreatitis, lactic acidosis, and hepatitis. 3. Consider other possible causes of Dyspepsia and abdominal pain. • Stop any non-steroidal antiinflammatory drugs (e.g., Aspirin, ibuprofen) that the patient may be taking. • Diagnose and treat *Helicobacter pylori* infections.

D. Gastrointestinal: Diarrhea

Possible anti-TB drug causes: PAS, Eto/Pto, fluoroquinolones, Amx/Clv

Possible ART causes: All protease inhibitors, didanosine

Suggested management strategy	Comments
1. Assess for danger signs including dehydration and electrolyte disturbances (especially hypokalemia) if diarrhea is severe. 2. Loose stools are common in the initial phase of MDR-TB therapy. Encourage patients to tolerate mild degrees of loose stools and flatulence. 3. Encourage fluid intake. 4. Treat uncomplicated diarrhea (no blood in stool and no fever) with Loperamide 4 mg by mouth initially followed by 2 mg after each loose stool to a maximum of 10 mg per 24 hours.	• Fever and diarrhea and/or blood in the stools indicate the diarrhea may be secondary to something other than an adverse effect of the anti-TB drugs. Consider other causes of diarrhea like parasites, protozoa, and bacterial causes: • Loperamide can be used in children over 2 years.

E. Gastrointestinal: Hepatitis

Possible anti-TB drug causes: Z, Pto/Eto, PAS H, R

Possible ART causes: NVP, EFV, PIs

Suggested management strategy	Comments
1. If liver enzymes are more than 5 times the upper limit of normal (ULN) without symptoms or more than 3 times ULN with symptoms, stop all anti-TB drugs and any other hepatotoxic drugs. 2. Evaluate and treat other potential causes of hepatitis. a. Check serology for hepatitis B virus, hepatitis C virus. b. Alcohol use should be investigated and alcoholism addressed if found. 3. Reintroduce anti-TB drugs once liver enzymes return to baseline. Anti-TB drugs should be reintroduced in serial fashion by adding a new medicine every three to four days. The least hepatotoxic drugs should be added first, while monitoring liver function tests after each new exposure. 4. Consider suspending the most likely offending drug (pyrazinamide) permanently if it is not essential to the regimen.	• Mild elevation of liver enzymes, especially at baseline, may be related to TB rather than an adverse effect of treatment. • Hepatitis is characterized by nausea, vomiting, jaundice, scleral icterus, tea-colored urine, pale stool, and diminished appetite in the setting of elevated liver function tests. • Generally, hepatitis due to medications resolves upon discontinuation of suspected drug. • Any history of hepatitis should be carefully analyzed to determine most likely causative drugs; these drugs should be avoided when designing a treatment regimen. • NVP can cause hepatitis.

F. Musculoskeletal: Arthralgias

Possible anti-TB drug causes: Z, fluoroquinolones, Eto/Pto, Bdq

Possible ART causes: ABC

Suggested management strategy	Comments
1. Initiate therapy with non-steroidal anti-inflammatory drugs: Diclofenac 100mg PO/PR daily or ibuprofen 400 to 800 mg three times a day. 2. Lower dose of suspected drug (most commonly pyrazinamide) if this can be done without compromising regimen. 3. Discontinue suspected drug if this can be done without compromising regimen.	• Arthralgias, arthritis, and myalgias are transient symptoms most commonly encountered in the early months of MDR-TB therapy. • Symptoms generally diminish over time without intervention. • If acute swelling, redness, and warmth are present in a joint, consider aspiration for diagnosis (for example, gout, infection, and autoimmune disease). • Uric acid levels may be elevated in patients on pyrazinamide. No need to treat high

	uric acid levels unless patient has gout.

G. Renal: Electrolyte abnormalities

Possible anti-TB drug causes: Cm, Km, Am

Possible ART causes: TDF **(rare)**

Suggested management strategy	Comments
1. Monitor serum potassium, magnesium, and calcium frequently in patients with vomiting/diarrhea and patients receiving injectables. 2. Normal serum Potassium is 3.5-5.0mEq/L. 3. Hypokalemia definitions and degrees ○ **Mild Hypokalemia** is when serum Potassium is 3.1-3.5 mEq/L. ○ **Moderate Hypokalemia** is when serum Potassium is 2.6-3.0 mEq/L ○ **Severe hypokalemia** is when serum Potassium ≤ 2.5 mEq/L, or when symptomatic hypokalemia is present. 4. Hypomagnesemia is defined as serum magnesium < 1.5 mEq/L. 5. Hospitalization is necessary in severe cases of hypokalemia. 6. Replete potassium and magnesium; see tables for guidance. ○ Hypokalemia may be refractory if concurrent hypomagnesemia is not also corrected. ○ If unable to check serum magnesium give one to two doses of IV Magnesium sulphate (shown in table below). 7. Check an electrocardiogram (ECG) in patients with significant serum electrolyte disturbances at referral centers. Drugs that prolong the QT interval should be discontinued in patients with evidence of QT interval prolongation. **8.** Electrolyte abnormalities are reversible upon discontinuation of the injectable. But electrolyte replacement therapy	• Hypokalemia and hypomagnesemia are common in patients receiving MDR-TB treatment. Common causes in MDR-TB patients are: Vomiting, diarrhea and Renal tubular toxicity from the injectable (Cm>Km). Injectable toxicity more common in HIV Co-infected Patients. • Hypokalemia and hypomagnesemia are often asymptomatic. • Moderate cases may present with fatigue, myalgias, cramps, paresthesias, lower extremity weakness, behavior or mood changes, Constipation, nausea, Vomiting, Abdominal cramping, Polyuria, Palpitations, somnolence, psychosis and confusion. • Severe disturbances can lead to tetany, paralysis, and life-threatening cardiac arrhythmias. • In general, 1 mEq/L drop in potassium correlates to a loss of 100-200 mEq of total body potassium. • Oral potassium chloride(KCl) 600mg tablets (contains 8 mEq of potassium): ○ Oral (over days to weeks) is the preferred route for potassium repletion because it is easy to administer, safe, inexpensive, and readily absorbed from the GI tract. ○ Give two hours before or four hours after fluoroquinolones as they can interfere with fluoroquinolone absorption. ○ It can cause nausea, vomiting and dyspepsia. Oral magnesium can cause diarrhea. • Dietary intake of potassium should be encouraged. **Nuts, Avocados, Bananas, oranges, tomatoes,** and **grapefruit juice**

may be continued for several months after completion of the injectable phase of MDR-TB treatment.	are good sources of Potassium. • Spironolactone 25 mg PO daily may decrease potassium and magnesium wasting due to the injectable and may be useful in severe cases that are refractory to replacement therapy.

Table: Potassium replacement therapy

Serum Potassium level	Dosing	Monitoring frequency
≥ 3.6	None	Monthly
3.1-3.5	40-80 mEq PO daily	weekly
2.6-3.0	40-80 mEq PO three times daily	Daily
≤2.5	10 mEq/hr IV and 80 mEq PO every six to eight hours	One hour after infusion, every six hours with IV replacement

Note: The normal preparation of a potassium chloride infusion is 40 mEq in 200 mL of normal saline. Do not exceed an infusion rate of 20 mEq/hr (100 mL/hr).

Table: Magnesium replacement therapy

Magnesium level	Total daily dose	Monitoring frequency
2.0 or more	None	Monthly
1.5-1.9	1,000 mg-1,200 mg	Monthly
1.0-1.4	2,000 mg	One to seven days
< 1.0	3,000 mg-6,000 mg	Daily

Note: Quantities greater than 2,000 mg are usually given IV or IM. The normal preparation is magnesium sulfate 2 g in 100 mL or 4 g in 250 mL of 5 percent dextrose or normal saline. Do not exceed an infusion rate of 150 mg/min (2 g in 100 mL administered over one to two hours, 4 g in 250 mL administered over two to four hours).

H. Renal: Nephrotoxicity (acute renal failure)

Possible anti-TB drug causes: Km, Am, Cm

Possible ART causes: TDF (rare)

Suggested management strategy	Comments
1. Monitor serum creatinine and electrolytes frequently in patients receiving injectables. 2. Patients with pre-existing kidney disease,	• The injectables (Km>Cm) are the most common cause of acute renal failure in MDR-TB patient.

diabetes, or HIV are at high risk of injectable nephrotoxicity and shall be monitored more frequently. 3. Any increase of serum creatinine above normal limits or a doubling of serum creatinine above baseline should be considered acute renal insufficiency. 4. Check serum electrolytes when serum creatinine is found elevated as they may coexist. 5. Discontinue the suspected drug (usually the injectable). If the acute renal failure is severe, then stop all drugs. • Nephrotoxicity due to the injectable is frequently reversible after the injectable is stopped, but permanent damage can result if it is not detected early. • If the acute renal insufficiency is severe or resolving slowly, the dose of other renally excreted drugs should be adjusted. 6. Consider other contributing etiologies (pre-renal, intrinsic renal, and pos-trenal causes). 7. Follow serum creatinine and electrolytes closely until the creatinine has returned to baseline or has stabilized. 8. Consider reintroducing the injectable with a reduced dosing interval (two or three times a week) if the drug is essential to the regimen. • Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen. • Consider strict weight-based dosing of the injectable if the patient's weight is less than 50 kg. • Suspend the injectable permanently if the nephrotoxicity recurs despite a reduced dosing interval.	• Injectable nephrotoxicity is often asymptomatic in the early stages and can only be diagnosed with routine laboratory monitoring. • End-stage renal failure may present with oliguria/anuria or signs of volume overload including peripheral edema and shortness of breath. Mental status changes due to uremia or electrolyte abnormalities are a late symptom. • Other common causes of acute renal failure: o Pre-renal aetiologies include dehydration from vomiting or diarrhoea as a side effect of anti-TB therapy. o Etiologies intrinsic to the kidney like acute interstitial nephritis from antibiotics like beta-lactams and sulfa drugs. • Tenofovir may cause renal injury. • Even without the concurrent use of tenofovir, HIV-infected patients have an increased risk of renal toxicity secondary to aminoglycosides and capreomycin. Frequent creatinine and electrolyte monitoring is recommended. o Avoid tenofovir in patients receiving aminoglycosides or on capreomycin. o If tenofovir is absolutely necessary, serum creatinine and electrolytes should be monitored frequently (weekly at the start of treatment).

I. Neurological: Ototoxicity (hearing loss or vestibulopathy)

Possible anti-TB drug causes: Km, Am, Cm,

Possible ART causes: TDF (rare)

Suggested management strategy	Comments
1. Perform a monthly assessment of hearing loss and balance. Audiometry may be helpful if it is available and the hearing loss is mild. 2. If the patient is experiencing clinically significant ototoxicity, decrease the dosing frequency of the injectable to two to three times a week. Consider switching to capreomycin. 3. Stop the injectable if symptoms worsen despite dose adjustment, and additional drugs are available to reinforce the regimen. • Even when additional drugs are not available, decision should be based on the patient's desire to maintain hearing. • Hearing loss and vestibular dysfunction are generally not reversible upon discontinuation of therapy. • Substitution with newer agents such as bedaquiline when signs of auditory or vestibular toxicity appear may prove to be a useful strategy.	• Ototoxicity refers to damage of the hearing apparatus of the inner ear (the cochlea, vestibule, semicircular canals, and cranial nerve VIII). • Symptoms include tinnitus and hearing loss, as well as vestibular symptoms such as disequilibrium and vision problems. • Ototoxicity is commonly observed in patients receiving large cumulative doses of injectable agents. Capreomycin may be less ototoxic than the aminoglycosides. • Some degree of hearing loss occurs with most patients taking an injectable, but high-frequency loss may not significantly affect the patient's quality of life. • Patients with previous exposure to aminoglycosides, patients with renal insufficiency and patients who are concomitantly taking furosemide are at the highest risk of incurring ototoxicity. • Mild disequilibrium can also be caused by cycloserine, fluoroquinolones, ethionamide/prothionamide, isoniazid, or linezolid. Stopping all anti-TB drugs for several days can help to distinguish the cause of disequilibrium. • Some patients may choose to tolerate significant hearing loss to achieve a higher chance of cure. • The benefit of hearing aids is minimal to moderate in overcoming auditory toxicity but may be helpful in some patients.

J. Neurological: Peripheral neuropathy

Possible anti-TB drug causes: Cs, H, Pto/Eto, Lzd**,**

Suggested management strategy	Comments
1. Assess other potential causes of neuropathy (diabetes mellitus, HIV, alcohol use, hypothyroidism, other drugs, and vitamin deficiencies). Correct any vitamin or nutritional deficiencies.	• Peripheral neuropathy is a common side effect of MDR-TB treatment caused by drug toxicity to the nerves of the peripheral nervous system. • Diagnosis is usually clinical. Nerve conduction studies may be done to confirm if available. • Symptoms first manifest in the lower

2. Increase pyridoxine to the maximum daily dose of 200 mg per day. 3. Consider lowering the dose of likely offending drugs, if possible without compromising the regimen. 4. Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms. 5. Tricyclic antidepressants are useful adjunct treatments. Start amitriptyline 25 mg at bedtime. And increase the dose according to response (maximum 150 mg per day). 6. Gabapentin may also be effective in relieving pain and other symptoms of peripheral neuropathy.	extremities. Sensory disturbances like numbness, tingling, burning, pain, and loss of temperature sensation are common. More severe manifestations include decreased deep tendon reflexes, weakness, and gait instability. • Patients taking isoniazid, cycloserine, or linezolid should receive prophylactic pyridoxine. • Patients with comorbidities (e.g., diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of second-line anti-TB drugs. • Neuropathy may be irreversible, but many patients experience improvement when offending drugs are suspended. • The neuropathy associated with linezolid is common after prolonged use and often permanent. For this reason, suspension of this drug should be considered when neuropathy develops.

K. Neurological: Depression

Possible anti-TB drug causes: Cs, H, fluoroquinolones, Eto/Pto

Possible ART causes: EFV

Suggested management strategy	**Comments**
1. Assess the degree of depression. If patient has suicidal ideation: o cycloserine should be suspended immediately. o The patient should be hospitalized and placed under 24-hour safety surveillance until the risk of suicide has passed. o Psychiatric consultation should be sought for assistance with management. 2. Assess patients for other potential causes of depression including hypothyroidism, substance abuse and underlying psychosocial stressors. 3. Initiate individual psychotherapy (or group counseling if the patient is smear- and	• Depression is a mood state that causes a **persistent feeling of sadness** and **loss of pleasure**. Other symptoms include loss of interest in previously enjoyed activities, lack of energy, psychomotor retardation, appetite and sleep disturbances, feelings of guilt, helplessness or hopelessness, inability to concentrate, and suicidal ideation. • Depression is common in patients with MDR-TB due to underlying psychosocial stressors, chronic disease, stigma, and anti-TB medications. • Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression. • Depression may fluctuate during

culture negative). 4. Initiate antidepressant therapy with amitriptyline or fluoxetine, or a similar drug for moderate to severe depression, or when symptoms are refractory to psychotherapy. 5. Lower the dose of the suspected offending drug if this can be done without compromising the regimen. o The dose of cycloserine is commonly lowered to 500 mg daily in an attempt to reduce depressive symptoms. 6. In rare situations, the suspected offending drug may need to be discontinued due to extreme refractory symptoms.	therapy and may improve as illness is successfully treated. • History of previous depression is not a contraindication to the use of the drugs listed but may increase the likelihood of depression developing during treatment. If significant depression is present at the start of treatment, avoid a regimen with cycloserine if possible. • EFV is associated with depression. Consider substitution if severe depression develops.

L. Neurological: Headache

Possible anti-TB drug causes: Cs, Bdq

Possible ART causes: AZT, EFV

Suggested management strategy	Comments
1. Rule out more serious causes of headache including bacterial meningitis, cryptococcal meningitis, and other infections of the central nervous system. o HIV co-infected patients should receive a head CT scan and cerebrospinal fluid analysis. 2. Start analgesics like ibuprofen or paracetamol. Also encourage good hydration. 3. Consider low-dose tricyclic antidepressants for refractory headaches.	• Headaches are common during the initial months of MDR-TB therapy. They can present as migraine or cluster headaches. • In order to minimize headaches at the start of therapy, cycloserine is often started at lower doses of 250 to 500 mg and gradually increased over one to two weeks to achieve the target dose. • Headaches due to cycloserine, AZT, and EFV are usually self-limited. • Pyridoxine (vitamin B6) should be given to all patients receiving cycloserine to help prevent neurotoxicity. The recommended dose is 50 mg for every 250 mg of cycloserine prescribed.

M. Neurological: Psychosis

Possible anti-TB drug causes: Cs, H, fluoroquinolones, Eto/Pto

Possible ART causes: EFV

Suggested management strategy	Comments
1. Evaluate potential causes of psychosis including anti-TB drugs, psychosocial stressors, depression, hypothyroidism, other medications, and illicit drug and alcohol use. 2. Check serum creatinine and electrolytes in patients with new-onset psychosis to rule out a decrease in renal function leading to high cycloserine level or electrolyte disturbances as a cause for psychosis. 3. Stop cycloserine while psychotic symptoms are brought under control. 4. Initiate antipsychotic therapy for moderate to severe symptoms of psychosis with a. haloperidol 0.5 to 5.0 mg twice daily, or b. risperidone 0.5 to 5.0 mg twice daily, or c. chlorpromazine 75-300mg PO daily in divided doses. 5. Hospitalize the patient in a ward with psychiatric expertise if there is a risk to the patient or others. 6. Increase pyridoxine to maximum daily dose (200 mg per day). 7. Once psychosis has resolved, reinitiate cycloserine at a lower dose if this can be done without compromising the regimen. • The most common approach is to restart cycloserine at 500 mg daily. • If cycloserine is continued at a lower dose, antipsychotic therapy may need to be continued while the patient remains on the medication. 8. In situations with recurrent or refractory symptoms, cycloserine may need to be discontinued if this can be done without compromising the regimen. 9. Once all symptoms resolve and patient is off cycloserine, antipsychotic therapy can be tapered.	• Psychosis refers to a group of symptoms that reflect a disintegration of personality or a loss of contact with reality. Visual or auditory hallucinations, paranoia, catatonia, delusions, and bizarre behavior are hallmarks of the syndrome. • Psychosis is most commonly associated with cycloserine, but other anti-TB drugs have also been implicated. • Previous history of psychiatric disease is not a contraindication to cycloserine, but it may increase the likelihood of psychotic symptoms. • Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy. Attempts to taper antipsychotics should be done with a psychiatrist trained in the adverse effects of second-line anti-TB drugs. • Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending drug. • Pyridoxine (vitamin B6) should be given to all patients receiving cycloserine to help prevent neurotoxicity. The recommended dose is 50 mg for every 250 mg of cycloserine prescribed. • EFV has a high rate of CNS adverse effects (dizziness, impaired concentration, depersonalization, abnormal dreams, insomnia, and confusion) in the first two to three weeks of use but typically resolve on their own. Frank psychosis is rare with EFV alone. Closely monitor for side effects when used with cycloserine.

N. Neurological: Seizures

Possible anti-TB drug causes: Cs, H, fluoroquinolones

Suggested management strategy	Comments
1. Evaluate possible causes of seizure including anti-TB medications, infection, hypoglycaemia, electrolyte abnormalities, hypoxia, alcohol withdrawal, other drugs, uraemia, and hepatic failure. ✓ Check serum electrolytes including potassium, sodium, calcium, magnesium, and chloride. ✓ Check blood glucose level. ✓ Check serum creatinine in patients with new-onset seizures to rule out a decrease in renal function as a cause for high blood levels of cycloserine and resulting seizure. 2. Hold cycloserine, fluoroquinolones, and isoniazid pending resolution of seizures. 3. Initiate anticonvulsant therapy (Carbamazepine, phenytoin, or valproic acid is most commonly used). ✓ Phenytoin: Load 10 to 20 mg/kg (1,000 mg in typical adult) IV, no faster than 50 mg/min. Oral load: 400 mg initially, then 300 mg in 2 hours and 4 hours. Maintenance: 5 mg/kg or 100 mg PO three times a day. ✓ Carbamazepine: 100 to 400 mg PO twice or three times a day. ✓ Valproic acid: Start 15 mg/kg PO daily or in two daily divided doses, maximum 60 mg/kg daily. 4. Increase pyridoxine to maximum daily dose (200 mg per day).	• A seizure is an abnormal, paroxysmal, electrical activity of the brain. It can manifest as tonic clonic movements, convulsions, or altered mental status. Presentation may include a preceding aura, loss of consciousness, bowel-bladder incontinence, and a postictal state of confusion of somnolence. • Anticonvulsants are generally continued until MDR-TB treatment is completed or until the suspected drug is discontinued. • Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy. Cycloserine should be avoided in these patients (if possible without compromising the regimen) or until the seizure is well controlled. • Most anticonvulsants have significant drug-drug interactions with ART and many other drugs. • When seizures have resolved, restart medications one at a time. Cycloserine should not be restarted unless it is absolutely essential to the regimen. If cycloserine is reinitiated, start a dose one weight band lower.

O. Endocrine: Hypothyroidism

Possible anti-TB drug causes: Eto/Pto, PAS

Suggested management strategy	Comments
1. TSH levels should be checked at third month and then every six months after starting MDR-TB treatment with Ethionamide/Prothionamide or PAS.	• Ethionamide (or Prothionamide) and PAS have a direct toxic effect on the thyroid that interferes with thyroid hormone synthesis.

○ In patients with hypothyroidism, most adults will require 75 to 200 mcg of levothyroxine daily. ○ Older patients should begin treatment with 50 mcg daily. ○ Patients with significant cardiovascular disease should be started at 25 mcg daily. ○ The following doses are recommended based on TSH level: i. TSH 10-50 mUnits/l=Thyroxine 50 mcg daily ii. TSH 50-100 mUnits/l =Thyroxine 100mcg daily iii. TSH >100 mUnit/l =Thyroxine 150mcg daily **2.** Monitor TSH every two months and increase dose by 25 to 50 mcg until TSH is in normal range. Adjust dose more slowly in the elderly and patients with cardiac conditions. After normal TSH achieved check TSH level every 6 months. **3.** Hypothyroidism is reversible upon discontinuation of Ethionamide/Prothionamide or PAS. Upon completion of MDR TB therapy ○ Continue to follow TSH ○ Expect normalization of TSH after 3 months; ○ Discontinue thyroxine according to TSH results ○ If TSH testing not available, discontinue thyroxine after 3 months and follow symptoms	• Symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, as well as depression and inability to concentrate. Thyromegaly and delayed deep tendon reflexes may be encountered on exam. • Patients may develop symptoms as soon as a few weeks after exposure to offending medications. • In primary hypothyroidism, the diagnosis is confirmed by a serum level of TSH greater than10.0 mU/L. No other thyroid tests (e.g., free T4, T3) are necessary for diagnosis or treatment monitoring. • Children clear thyroxine faster than adults, so daily replacement doses may be higher. ○ Toddlers (1-3 years): 10-15 mcg/kg/day (maximum dose is 200 mcg). ○ Older Children (4-15 years): 4 mcg/kg/day (maximum dose is 200 mcg). • When it is not possible to measure TSH levels, a lower prophylactic dose of thyroxine (25-50 mcg) may be started for all patients taking Pto/Eto (especially for patients who are taking Pto/Eto with PAS).

P. Cardiovascular: QT prolongation (Cardiac arrhythmia)

Possible anti-TB drug causes: Fluoroquinolones, Cfz, Bdq

Possible ART causes: Protease inhibitors, EFV

Suggested management strategy	Comments
1. Any patient found to have a QTc value greater than 500 ms should be managed carefully. ✓ Repeat ECG and confirm the prolongation.	• The QT interval is measured from the end of the QRS complex to the beginning of the T wave on a standard electrocardiogram. The QT is corrected for heart rate, which is referred to as the QTc and calculated by

✓ Bedaquiline should be stopped for QTc value greater than 500 ms. Consider stopping other drugs that prolong the QT interval. ✓ Check potassium, calcium, and magnesium. Electrolyte levels should be maintained in the normal range. ✓ It is suggested to maintain potassium levels of more than 4 mEq/L and magnesium levels of more than 1.8 mg/dL. ✓ Avoid other drugs that increase the QT interval. 2. Monitor the patient's renal and hepatic function and adjust dose of fluoroquinolones if impairment is present. 3. Consider suspension of the fluoroquinolone if risk of torsades de pointes (Ventricular arrhythmia) outweighs the benefits of the drug.	most ECG machines. A normal QTc is generally < 440 ms. • Values above QTc 440 ms are referred to as prolonged. Patients with prolonged QTc are at risk of developing cardiac arrhythmias like torsades de pointes, which can be life-threatening. Patients with QTc greater than 500 ms are at the greatest risk for developing these arrhythmias. • The fluoroquinolones cause prolongation of the QTc. Moxifloxacin causes the greatest QTc prolongation, while levofloxacin and ofloxacin have a lower risk of QTc prolongation. • QT prolongation can occur with Bedaquiline (SIRTURO). Use with drugs that prolong the QT interval may cause additive QT prolongation. • Currently, ECG monitoring prior to the initiation and during MDR-TB therapy is not required, as the therapeutic benefit of fluoroquinolones is considered to outweigh the risks associated with QT prolongation.

Q. Hematologic: Anemia or pancytopenia

Possible anti-TB drug causes: Linezolid

Possible ART causes: AZT

Suggested management strategy	Comments
1. Perform additional laboratory tests to assess potential cause of anemia. o Check mean corpuscular volume (MCV) to assess whether anemia is normocytic versus microcytic versus macrocytic. o Check reticulocyte count to assess whether the bone marrow is producing red cell precursors. o Check LDH, bilirubin, and haptoglobin to assess for hemolysis. 2. Stop drugs that are likely to cause anemia (Lzd, Co-trimoxazole, AZT). 3. Consider blood transfusion if anemia is severe.	• Anemia is defined as a decrease in red blood cells (defined hematocrit (Hct) < 41 percent or hemoglobin (Hb) < 13 g/dL in men, and Hct < 36 percent or Hb < 12 g/dL in women). • However Hb <10.5g/dl is clinically significant and action is required in such cases. • Symptoms of anemia include fatigue, exertional dyspnea, and angina. Physical exam findings include pallor, tachycardia, and orthostatic hypotension. • Linezolid can cause aplastic anemia and thrombocytopenia.

16. PALLIATIVE CARE IN DRUG RESISTANT TB

16.1 Definitions and Principles of palliative care in DR TB

Palliative Care is defined as an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems-physical, psychosocial and spiritual.

There is significant suffering associated with M/XDR TB illness and its treatment. These burdens add the possibility that the patients will not be able to adhere to treatment and, as a result fail to cure. The need for palliative care and end of life care is being increasingly recognized as an important part of the continuum of care for MDR TB patients.

The benefits Palliative Care for M/XDR TB patients:

- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as second-line anti-TB medications against M/XDR TB, and includes those investigations needed to better understand and manage distressing clinical complications.
- Uses a team approach to address the needs of patients and their families, including bereavement counseling, if indicated;
- Will enhance quality of life, and may also positively influence the course of illness;
- Provides relief from pain and other distressing symptoms;
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death;
- Offers a support system to help the family cope during the patients illness and their own bereavement ;
- Intends neither to hasten or postpone death;
- Affirms life and regards dying a normal process;
- Helps to ensure infection control practices are applied, especially in patients that remain infectious

Hence palliative care is needed in all phases of the management of M/XDR TB patients from diagnosis to end of treatment or death of the patient and should be provided as a continuum of care. It should not be looked at as only care at the time of death.
Palliative care, including symptom management should be applied as early as possible in the course of the illness.

Components of palliative care include:

- Pain and symptom relief (like cough, shortness of breath etc)
- Psychological care: may include assessment and management of common psychiatric problems in M/XDR TB patients like depression, anxiety and psychosis and counselling services (group and individual counselling, peer support groups, family counselling) and culturally-appropriate end-of-life care and bereavement services.
- Spiritual care may include assessing and managing spiritual distress or referral for spiritual care.
- Social support may include economic strengthening activities, social and legal protection, and training and support of caregivers.

In the context of M/XDR TB palliative care should be provided as follows

- Pain and symptom management. *(refer to sections 15 and 16)*
- Adverse drug reactions assessment and management. *(refer to section 15)*
- Management of complications of M/XDR TB like lung fibrosis, cor pulmonale, bronchiectasis, pneumothorax. *(refer to section 16.3)*
- Psychosocial and economic support. *(refer to section 11.4)*
- End of life care. *(See below)*

16.2 Terminal Illness and End of life care

As described above, palliative care should begin when M/XDR TB is diagnosed, and continues regardless of whether or not the patient is expected to be cured or fail treatment.

Unfortunately, in patients with extensive lung disease, highly resistant strain, and a non response to a course of second-line anti-TB drugs, the only realistic option is

palliative care by addressing all the four dimensions of the patient's needs (physical, psychological, social and spiritual).

Terminally ill patients, where circumstances permit, may be discharged for care by family members, with the consent of the family.
Conditions, under which the patient may be discharged, include:

- The patient will remain within the confines of his/her home.
- There are no young children or persons with known HIV infection in the household who will be placed at risk.
- All necessary measures would be taken to prevent spread of infection.
- Access to the patient by other people will be restricted or controlled.

Effective support at the end of life requires a broad multidisciplinary approach that includes the family and makes use of available community resources; it can be successfully implemented even if resources are limited.

End-of-Life Palliative Care services for Terminally Sick DR TB Patients

- **Pain control and symptom relief**. The three Step WHO analgesic ladder should be utilized in the management of pain. Pain assessment should be done every visit.

  Paracetamol, tramadol or codeine with paracetamol, gives relief from moderate pain. For Severe pain stronger analgesics, including morphine, should be used to keep the patient pain free. *Refer to the Ethiopian pain management guideline.*
- **Relief of respiratory insufficiency**. Oxygen can be used to alleviate shortness of breath. Morphine also provides significant relief from respiratory distress and should be offered if available.
- **Nutritional support**. Small and frequent meals are often best for a person at the end of life. It should be accepted that the intake will reduce as the patient's condition deteriorates during end-of-life care. Nausea and vomiting or any other conditions that interfere with nutritional support should be treated.
- **Continuation of ancillary medicines**. All necessary ancillary medications should be continued as needed. Codeine and morphine help control cough, as well as pain. Other cough suppressants can be added. Bronchospasm symptoms can be

controlled with a meter-dosed inhaler with a spacer or mask. Depression and anxiety, if present, should be addressed. Antiemetics may still be needed. Treat fever if the patient is uncomfortable.

- **Regular medical visits**. When therapy stops, regular visits by the treating physician and support team should not be discontinued. This is particularly important if palliative care is provided at home.
- **Hospitalization, hospice care, or nursing home care** may not be feasible in Ethiopia but admissions for treatment of acute exacerbations or complications may be sometimes needed
- **Preventive measures**. Oral care, prevention of bedsores, bathing, and prevention of muscle contractures are indicated in all patients. Regularly scheduled movement of the bedridden patient is very important. Encourage patients to move their bodies in bed, if able. Keeping beds dry and clean are also important.
- **Infection control measures**. The patient who is taken off anti-TB treatment because of failure often remains infectious for long periods of time. Infection control measures should be continued, including both environmental controls and personal protection. Health care workers and family members at high risk who are providing close patient care should use N95 particulate respirators (N95 masks).
- **Respect patient's beliefs and values at the end of life.**

16.3 Management of complications of MDR-TB

A. Respiratory insufficiency

Differential diagnosis of sudden shortness of breath during M/XDR-TB treatment

Diagnosis	Signs	Treatment
Bronchospasm	Wheezing and increased expiratory phase on physical examination; X-ray unchanged. It may look like COPD or severe asthma.	• Mild wheezing: Beta-agonist inhaler. • Severe wheezing: Nebulized beta-agonist, oral or IV corticosteroids.
Pneumothorax	New pneumothorax on X-ray.	• Consider chest tube placement.

PCP	New infiltrates in an HIV-positive patient not on CPT, with CD4 count usually less than 200.	• Co-trimoxazole: two double-strength tabs three times daily x 21 days for adults. • Prednisone may be needed in severely ill patients.
Systemic infections and complications	Systemic symptoms in HIV-positive patient, such as altered mental status.	• Check serum electrolytes, creatinine, and urea. • Consider CSF analysis.

Notes

1) Bacterial pneumonia is rare during MDR-TB treatment because of the broad-spectrum activity of Levofloxacin /moxifloxacin that is generally part of MDR-TB regimens.
2) Pneumothorax is common in TB patients.
    - In MDR-TB patients with chronically scarred lungs, partial pneumothorax is common.
    - Conservative therapy (supplemental oxygen and close monitoring) is often the best choice, because of the risk of secondary infection with chest tube placement.
    - Indication for chest tube placement in pneumothorax:
        - Tension pneumothorax.
        - Large pneumothorax with significant respiratory compromise.
        - Significant pneumothorax that does not reinflate after several days of conservative therapy.

B. Hemoptysis

Blood-stained sputum

- Generally not serious and requires only reassurance.
- Can continue for months after MDR-TB treatment is started, especially in chronically ill patients with significant lung damage.

Large-volume hemoptysis (greater than 200 cc, or a small cup)

- Caused by a cavitary lesion eroding into a vein.
- Since it is a sign of advanced disease, massive hemoptysis is most common before starting treatment or early in the treatment course.

- Effective MDR-TB treatment is the most important treatment for large-volume hemoptysis.
- Patients with massive hemoptysis generally die of asphyxiation, not blood loss.

Large-volume hemoptysis should be considered a medical emergency and the patient should be hospitalized.

Table: Management of Hemoptysis

If vital signs are stable:	**If vital signs are unstable, start resuscitation:**
• Strict bed rest. • Oxygen at bedside. • Check hemoglobin and transfuse if necessary. • Consider codeine-containing cough suppressant or morphine suspension.	• Oxygen via nasal cannula. • Place two large IV catheters. • Ringer's lactate or normal saline running wide open. • Urgent blood transfusion. • Consider surgical resection if available.

C. Pleural effusion and empyema

Pleural effusions in MDR-TB are common

- Pleural effusions that are not empyemas usually do not need to be drained if the patient is clinically stable. These are usually chronic and have developed during multiple retreatment episodes.
- Small, loculated effusions may not be easily drained by a chest tube. Even if the effusion is large and free-flowing, there may not be recuperable lung tissue.

Empyema

- Empyemas are caused by large amounts of bacteria in the pleural space.
- There are usually associated symptoms such as fever, productive cough, or chest wall pain.
- Diagnostic thoracentesis is simple and will quickly determine if a pleural effusion is an empyema (yellow/green thick fluid, pH < 7.2, etc.).
- Empyemas need to be drained, but the underlying cause of the empyema needs to be addressed.

- An empyema that occurs during MDR-TB treatment is usually caused by the formation of new bronchopleural fistula that allows oral flora to enter the pleural space.
- Bronchopleural fistula can be diagnosed by asking the patient to cough after the chest tube is placed. A large air leak is diagnostic of a bronchopleural fistula.
- An MDR-TB patient who develops a new empyema should be carefully evaluated for possible treatment failure, including culture and DST. If the treatment regimen is not adequate, placement of a chest tube will lead to a chronic bronchopleurocutaneous fistula unless the treatment regimen is changed.

17. INFECTION CONTROL IN THE CONTEXT OF DRUG RESISTANT-TB

- Transmission of tuberculosis is an important problem in health facilities with weak Infection Control measures and is a major concern in settings like Ethiopia with high TB, MDR TB and HIV prevalence.
- TB IC has become a key challenge in the era of MDR and XDR-TB because these are serious conditions with limited treatment options.
- The largest source of M. tuberculosis transmission is the contagious patients with respiratory tuberculosis not yet diagnosed and put on treatment.
- There is a similar risk of transmission DR TB strains. Since M/XDR TB patients are likely to be sick for a longer time before diagnosis and treatment the number persons infected per M/XDR TB patient may in fact be higher than by a drug susceptible TB patient.

Therefore, tuberculosis infection control (TB IC) relies heavily on:

- **Early diagnosis** (active case finding through cough surveillance at all service points and use of rapid diagnostics like Xpert MTB/RIF test), and
- Prompt implementation of **effective treatment**.

With effective treatment, contagiousness decreases **after a few days (<3 days)** and may be considered **nil after 2 to 3 weeks of treatment**.

It is essential treatment is '**effective**', as MDR TB patients that are placed on first-line anti-TB drugs are likely to remain contagious.

This calls for **treating MDR TB patients as outpatients** to decrease the risk of transmitting to other patients and also to decrease their risk of acquiring XDR TB by keeping these patients in MDR TB wards for longer times.

17.1 Set of TB Infection Control Measures for Health facilities

TB infection control is a combination of measures aimed at minimizing the risk of TB transmission within populations (from an infectious case to other patients, visitors or family members and health care workers in health facility, congregate and community settings).

***High-risk areas for TB transmission include**:*

- TB and medical wards
- Outpatient departments, radiology department and waiting areas to which infectious TB patients and potentially infectious TB suspects are referred
- Spaces reserved for aerosol generating procedures (e.g. sputum collection areas, bronchoscopy rooms)

There are four **components of TB infection control**: Managerial, Administrative, Environmental control measures and Personal Respiratory Protective measures.

1. <u>Managerial control measures</u>

Managerial control measures provide the managerial framework for the implementation of TB infection control in health-care facilities, congregate settings and households.

***Managerial Measures for facility-level TB infection control include**:*

1. **Identify and/or strengthen TB Infection control/IP Committees** and **develop a facility plan** based on periodic **facility risk assessment** for implementation (including human resources, and policies and procedures to ensure proper implementation of the controls).
   A **TB IC focal person should be assigned**. The TB IC focal person will coordinate TB infection control measures in the hospital (or HC). The specific roles and responsibilities should be clear and be part of his/her job description.
   The plan should be agreed upon by the committee and presented to the management and approved and disseminated to all staff in the health facility. The IC plan should be **written** down and each health-care worker should know and understand it. A staff member should be specifically assigned to each of the above actions and charged with follow-up. These staff members' names should be noted next to each action/set of actions in the TB IC plan (See Annex 4 and 5).

2. **Rethink the use of available spaces and** consider **renovation of existing** facilities or **construction of new** ones to optimize implementation of

controls.

3. **Conduct on-site surveillance of TB disease** and **HIV infection among health workers** and assess the facility.
4. **Address advocacy, communication and social mobilization (ACSM)** for health workers, patients and visitors.
   Patients, staff and visitors should understand the risks involved before entering a facility with a high risk of TB and especially MDR- or XDR-TB. Both verbal and written information should be made available to visitors at every visit. Posters depicting basic TB IC measures should be displayed in waiting areas and wards. Administrative IC measures should also be followed in emergency services, medical and other wards where PLH and patients with DM may be admitted.
5. **Monitor and evaluate the set of TB infection control measures**. The TB IC plan serves as the basis for monitoring and evaluating TB IC interventions. Implementation of the IC plan should be monitored on a daily basis to ensure that all activities are being carried out. Each activity within the IC plan should have a staff member assigned to monitor implementation. Planned activity implementation should be evaluated and a reassessment of the level of risk of the health facility should be conducted to determine if the activities are appropriate or if there is a need to revise the plan to further reduce the risk of TB transmission. The effectiveness of the IC plan should be evaluated annually under the responsibility of a designated staff member.
6. **Participate in research efforts**. Operational research is essential for evaluating the effectiveness of all interventions implemented to control TB infection. Operational research is therefore recommended as an integral component of the TB infection control package.

2. Administrative controls

Administrative control measures are the first line of defense against TB transmission. It aims at preventing the **generation of and exposure to infectious droplet nuclei**. They require that people with TB symptoms be promptly identified, separated and treated.

This strategy includes the following:

- Prompt identification of potentially infectious cases (**triage**);
- **Separate** infectious cases and fast track their service;
- Control the **spread of** pathogens (cough etiquette and respiratory hygiene) and
- Minimize **time spent** in health-care facilities.

A) Administrative controls for Outpatient Units

- Patients should be screened for cough as they enter into the health care facility and receive basic education about TB.
- Patients with a cough of over two weeks or with confirmed TB and DR TB should be sent to a separate, well-ventilated waiting area and fast-tracked to sputum examination or other services in the health facility.
- All coughing patients should receive piece of cloth or tissues or surgical masks, and should be asked to cover their mouth and nose when they cough or sneeze.
- Early TB diagnosis should be facilitated and treatment should be started fast

B) Administrative controls for Inpatient Units

- Patients should preferably be treated as outpatients. Hospitalization should be limited and reserved for clinically unwell patients.
- Do not hospitalize patients for diagnosis of TB or DR TB unless absolutely indicated. Never put a patient who is not receiving TB medications in a TB ward.
- The circulation of visitors, patients, and their attendants in the hospital needs to be strictly controlled.
    - Have visible signage on entry doors to TB wards that forbid visitors to enter
    - Patients should be encouraged to spend as much time as possible outdoors.
    - Visiting areas should be well-marked with signage.
    - Before any visit, the nurse should provide information on transmission risk.
    - Encourage visits outside the building, in open air.

    - Limit visitation duration, particularly for contagious patients.
    - Adjust patient flow, avoiding unnecessary passage of susceptible persons through TB risk areas and vice versa
- The facility should be located away from the other wards with preferably a separate passage for the patients to access the toilets.
- Ideally, patients may be placed in single rooms. If single rooms are not possible, cohort isolation must be implemented.
- The distance between 2 adjacent beds should be optimal (at least 1.8 meters).

Isolation protocol for Inpatients

Patients are separated by degree of contagiousness (smear/culture status), DST pattern, and immune status.

When admitting patients separate:

- Sputum smear-positive patients from Smear-negative pulmonary TB, extra-pulmonary TB and Smear converted patients.
- DR TB patients and presumptive DR TB patients from drug-susceptible Patients
- XDR-TB patients from MDR-TB patients.
- Immunosuppressed patients (such as HIV-positive patients) from contagious TB patients.
- Presumptive TB cases from TB patients or other patients

Cough etiquette and respiratory hygiene

In order to minimize the generation of droplet nuclei, any coughing patient and TB/DR-TB patients should be educated on cough etiquette. That is, cover their nose and mouth when sneezing, coughing or talking. They can use a piece of cloth, a tissue, a surgical mask or the bend of the arm placed in front of the mouth and nose.

This also applies to health workers, visitors and families in health-care or congregate settings. Information, Education and Communication activities should strongly focus on cough etiquette.

Cough Hygiene:

- Display sign boards in the ward demonstrating cough hygiene.
- All DR TB patients admitted in the ward should be issued surgical masks.
- Adequate measures for safe collection and disposal of sputum
- Sputum cups with lead should be used for spitting directly into it.

3. Environmental controls

The second level in TB Infection control is the use of environmental or engineering controls. The environmental measures aim in **reducing the concentration** of infectious droplet nuclei in the air and to **control airflow**.

TB and MDR TB wards must be separated from the other wards and should be well-ventilated.

A) Ventilation as TB infection control measure

- Ventilation is replacement of inside air with outside air.
- Ventilation is the most effective means for reducing the concentration of *M. tuberculosis* suspended in the air and as a result the risk of transmission.
- Areas where TB transmission might occur should have a minimum ventilation rate of 12 air changes per hour (ACH).
- Natural ventilation relies on the movement caused by the wind and convection in order to achieve dilution and renewal of air.

- Natural ventilation can be very effective, especially when **cross-ventilation** (windows/doors in opposite sides of the room) is achieved at all times day and night in all seasons. This can be ensured only when there are fixed unrestricted openings.
- Create shady spaces so that patients, attendants, and visitors can stay outside during the day.

- If natural ventilation alone is not sufficient, other mechanical devices can be used to augment it:
  - **Simple propeller fans**. Propeller fans mix the air in a room, diluting infectious particles by spreading them throughout the room. This dilution effect should be combined with a mechanism that continuously allows new air to enter the room and old air to leave it. Replacement of room air with fresh air can be accomplished by keeping windows or doors open.
  - **Wind-driven roof turbines** (Whirly birds). Warm air rises up and roof turbines easily remove this air.
  - **Chimneys type of design** by directing room air towards the exterior .

B) Optimal arrangement of patient and staff should be implemented in all settings.

Health care staff should be mindful of the direction of airflow to ensure they are closest to the clean air source, and that patients are closest to the exhaust. This involves arranging patients and staff so that contaminated air is not likely to cross directly into staff/patient spaces. The natural direction of air flow should be between patients and staff, and not across patients and staff.

C) Architectural considerations

- TB infection control should be considered during the planning stages of new health structures and those being modified.
- Building layouts and designs should maximize natural ventilation.
  - Waiting areas should be open on three sides.
  - Avoid internal hallways with doors from the rooms and wards opening into them.
  - Doors should open to outside hallways that are open-air.

- Service areas with a high risk of *M. tuberculosis* transmission (e.g., waiting rooms) and procedures (e.g., sputum collection, sputum induction, X-ray department.) should be relocated into more isolated, better ventilated areas.
- Layouts should allow patient flow to be manipulated to reduce exposure of at-risk patients to infectious patients (e.g., separate waiting rooms for different cohorts, one patient per room).
- For TB wards, spaces incorporating plenty of single rooms or small rooms with two to four beds allow for easier separation of different patient cohorts.
- General hospitals should also have isolation rooms available for TB suspects and contagious patients.
- Sputum collection and sputum induction areas may be established outside in open air where bacilli will naturally be dispersed by wind. Proper waste disposal system should be followed for Sputum Cups, used GeneXpert cartridges, slides and other waste.
- Laboratories must have easy to clean working surfaces (avoid wood) to allow proper disinfection. Furthermore, they should also have large windows (well positioned to the sun) to allow good ventilation and sunlight.
- X-ray departments should provide separate waiting areas for infectious TB/MDR-TB suspects and patients where possible.

D) Ultraviolet germicidal irradiation (UVGI)

- *M. tuberculosis* is sensitive to germicidal radiation of UV found in the UV-C portion of the ultraviolet spectrum. The UV-C radiation in natural light does not inactivate the TB bacillus, but UVGI lamps can provide an appropriate germicidal dose.
- UVGI lamps are reserved for high-risk areas (sputum collection, sputum induction areas, poorly ventilated spaces with less than 6 ACHs, etc.) where other environmental measures are not sufficient due to climatic (hot arid or cold regions) or structural constraints.
- UVGI is not currently a major TB IC intervention in Ethiopia due to cost of installation and maintenance.

4. Personal Respiratory protection

Personal respiratory protection is considered the third line of defense for TB control and useful only when TB risk cannot be adequately reduced by administrative and engineering controls.

Respirators

- Respirators (also known as high-filtration masks, N95 Respirators, or FFP2 masks) provide a bacterial filtration efficiency of greater than 95 percent if challenged with 0.3-05 micrometer particles.
- If fitted and used properly to prevent facial seal leaks, a respirator (U.S certified N95 or EU certified FFP2 respirator masks) has been found to greatly reduce the chance that inhaled air will contain infectious tubercle bacilli.


N95 respirator

- *M. tuberculosis* is trapped in the filter of a mask, which will not be released with shaking or other physical movements of the mask. It eventually dies once outside the human body.

Respirators should be worn:

- When providing care to infectious MDR-TB and XDR-TB patients
- When collecting and examining sputum samples and when collecting and disposing of sputum containers of DR TB patients in TB culture facilities.
- During bronchoscopy, intubation and Surgery of DR TB patients

- Respirators classified as disposable can be reused by the staff as long as they are not wet, or damaged in any way, and provided they do not have loosened straps. The filter materials remain functional for weeks or months, however, the fitting may decrease with frequent wearing.
- If the filter material is damaged or the mask has loose straps, the respirator should be discarded. There is no set limit of days of use, but if a respirator is used

extensively for seven days, it may be discarded. If it is only used a few hours two to three times per week, it can be kept and reused for several weeks. Storage should not crush or damage the mask.

- Respirators can be disposed in normal waste and do not need to be incinerated. Respirators should never be shared between staff.
- In all facilities training on the correct use of the respirators including putting them on and removing them, there must be procedures for:
  - Selecting respirators for use in the facility.
  - Storing and re-use of the respirators.
  - Evaluating the effectiveness of the use of respirators.
  - Fit testing to ensure correct fit of respirator.

Surgical masks

- Surgical masks are meant to prevent the spread of micro-organisms from the person wearing the mask to others by trapping large wet particles near the source, which in this case is the mouth.
- They do not provide adequate protection to the wearer from inhaling infectious droplet nuclei in the air. Masks usually have limited filtration capacity and are loosely fitted over the mouth and nose, allowing free entrance of aerosolized mycobacteria.
- Although not the highest priority intervention, disposable masks can be used to reduce aerosols generated from potentially infectious DR-TB patients. They should therefore be considered for use by presumtive and confirmed DR-TB patients.

General Hygiene:

- Hand washing facility (Universal Precaution) shall be in place for doctors, health care workers and patients.
- Running water, soap and alcohol hand rub solution shall be provided.
- Frequent wet mopping of the ward shall be undertaken.
- Lavatory shall be kept clean.

Summary of recommendations for MDR-TB Wards

- Located away from the other wards, with adequate facilities for hand washing and good maintenance and cleaning.
- Adequate ventilation (natural and/or assisted ventilated) to ensure >12 ACH at all times.
- Adequate space between 2 adjacent beds, at least 1.8 meter.
- Cough hygiene should be promoted through signage and practice ensured through patients and staff training, ongoing reinforcement by staff.
- Adequate sputum disposal, with individual container with lid for collection of sputum.
- All staff should be trained on standard precautions, airborne infection control precautions, and the proper use of personal respiratory protection.
- A selection of different sizes of re-usable N95 particulate respirators should be made available for optional use by staff.

17.2 Minimum Package of TB infection control interventions for DR TB treatment facilities

Which TB IC measure for Health-care facilities?

- ❖ Implementation of controls as a combination of measures reduces transmission of TB in health-care facilities.
- ❖ Administrative controls should be implemented as the first priority because they have been shown to reduce transmission of TB in health-care facilities.
- ❖ Administrative controls are needed to ensure that people with TB symptoms can be rapidly identified and, if infectious, can be separated into an appropriate environment and treated promptly.

Which set ups should implement TB IC measures?

- ❖ All health-care facilities, public and private, caring for TB patients or persons presumed of having TB should implement the measures described in this policy.

Getting started with TB IC Implementation

1. Establish or strengthen a TB IC/IP committee
2. Assign a TB IC focal person
3. Do TB IC risk assessment
4. Develop a do-able TB IC plan
5. Monitor progress regularly

TB IC plans can be developed in phases & the components can be implemented based on realities at each facility level.

TB IC activities can be scaled up from easier to implement activities to more complex components step by step where staffs follow their progress before adding on more components.

Refer to Annex 4 to see the minimum recommended package of TB IC interventions at DR TB treating Health facility level.

17.3 Infection control in the community and home level

Awareness on reduction of TB/MDR-TB transmission in the community should be enhanced through early identification of presumptive TB/MDR-TB cases and referral for early diagnosis and early initiation of effective treatment and follow-up in the health care setting and later at community level.
Health education should be given to the 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 development and spread of DR-TB.

A) Administrative measures

- In assessing the home of an MDR-TB patient, information on the number of people that live in the house, number of rooms, etc., should be collected.
- HIV testing of family members is very important. Family members who are HIV-positive should not care for infectious MDR-TB patients.
- Advise patients on cough hygiene, such as covering their mouths with tissues, handkerchiefs, or surgical masks when coughing.
- When mothers with infectious TB are with their infants, this common time should be spent in well-ventilated areas or outdoors. The mother should use a surgical mask while visiting with the baby until she becomes sputum smear-negative. Until the mother is smear-negative (and ideally culture-negative also) the bulk of the infant care should be done by other family members if possible.

- Advise patients to minimize contact with infants and children during the initial months of treatment.
- Advise patients to collect their sputum in a plastic bag or jar and teach them how to bury or dispose of it.
- Regular household contacts screening every three months with particular emphasis to under 5 year old children, symptomatic individuals and immunocompromised (e.g. HIV infected) household members.

B) Environmental measures

- Improve natural ventilation and exposure to sun within the home.
- Advise patients to sleep in a separate, well-ventilated room during the initial months of treatment if possible.
- Communal spaces should be well-ventilated (often done by keeping windows/doors open at all times).

C) Personal protective measures

- If culture-positive, the patient should wear a cloth or surgical mask when in contact with family members.
- Any person attending to the patient in enclosed spaces should use a respirator (N95 mask). A fit test should be performed and the person should be educated on the proper use of masks.
- Environmental and personal protective measures should be followed at least until patient's smear status is negative, ideally until culture conversion for close contacts.

17.4 Infection Control during Patient Transport

When transporting DR-TB patients, the following infection control measures should be observed:

- Use compartmentalized vehicles separating the airspace of the driver from that of the passengers (if transporting the patient is mandatory);
- Open vehicle windows;
- Provide surgical mask for the patient;

- Provide N95 masks for medical staff and driver; and
- Educate patient about cough etiquette and respiratory hygiene.
- If the patient is forced to stay in a hotel during travel, he/she should sleep alone and ensure the room he/she stays in doesn't have openings that connect with adjacent rooms.

17.5 Care of the health care worker

- HCWs need to be educated on TB, MDR and TB IC at recruitment and at least annually.
    - This must be considered before MDR-TB service initiation to gain support and avoid misconceptions from health care workers
    - Should be repeated once a year (updating, sensitizing new staff)
    - Written infection control policies, procedures and job aids should be made available to health care workers assigned in MDR-TB wards/MDR-TB clinics
- All health-care workers should be screened for TB symptoms at the time of recruitment and at least annually.
- Health-care workers that have symptoms of TB should be examined without delay. Sputum microscopy examination should be done, followed by chest X-ray, molecular diagnostic testing (like GeneXpert) and other tests, as necessary.
- Healthcare workers diagnosed with TB disease should be started on TB treatment according to national guidelines and supported in treatment adherence.
- All health care workers working in MDR-TB wards, managing MDR-TB in ambulatory basis should be provided with respirators i.e. N95 masks.
- Staff should be encouraged to go for periodic TB screening and to know their HIV status
- 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 MDR-TB wards, medical wards, outpatient TB/MDR-TB clinics which take care of PTB/MDR-TB suspects or patients.

18. LEGISLATIVE FRAMEWORK AND PUBLIC HEALTH ETHICS IN DR TB

What ethical values are particularly important to TB care and control?

A comprehensive TB strategy should seek to protect individuals and communities through the proper treatment of infected individuals and the prevention of new infections. Fundamental ethical principles should be followed in fulfilling these tasks.

18.1 Guidance on Ethics of Tuberculosis Prevention, Care and Control

a) The obligation to provide access to TB services:

- The FDRE government has an ethical obligation to provide universal access of TB services of high quality and free of charge.

b) Information, counselling and informed consent:

- Patients have a right to be fully informed about the risks, benefits and alternatives available to them.

c) Supporting adherence to TB treatment:

- People with TB have a duty to complete therapy; providers have an obligation to support the patient's ability to adhere to treatment.

d) Universal access to M/XDR TB treatment:

- All eligible patients should undergo drug susceptibility testing to enable appropriate and effective drug therapy.
- There is a fundamental ethical obligation to provide palliative care and end-of-life-care to all M/XDR TB patients. It is also unacceptable to deny treatment based on the prediction about non-adherence by particular patients.

e) Health care workers' rights and obligations:

- Health care workers have an ethical obligation to care for patients, even if this involves some degree of risk. However, they should not be expected to assume risks that could be avoided by the adoption of basic infection control measures, or to assume risks when there is no reasonable possibility of benefit (curative or palliative) for those for whom they are providing care. Thus, any discussion of HCWs' obligations must also consider the reciprocal obligations of governments and health-care facilities to provide minimum standards of safety.

However HCWs who are unduly at risk of TB and MDR TB like HIV infected HCWs should be excused from working in such service points.

- TB is an occupational disease. HCWs who are not themselves in good health will not be able to properly look after their patients. For these reasons, health-care systems have an obligation to:
  - provide training, equipment, and protection to those who are in charge of TB patients;
  - give HCWs the skills and information necessary to assess their risks so that they can take proper precautions;
  - provide access to TB diagnosis, including TB screening, for HCWs living with HIV;
  - identify and treat HCWs with active TB, using the best proven treatment (including HIV counseling and testing, antiretroviral therapy, and chemoprophylaxis for TB if indicated);
  - clearly articulate their expectations about the working conditions of HCWs, the specific roles they are expected to assume, and the risks inherent in those situations; and
  - Appropriately compensate HCWs for their services; this may include risk allowance and insurance for themselves and their families and disability pay for those who become ill with TB or M/XDR TB.

f) Involuntary isolation and detention:

- In general, TB treatment should be provided on a voluntary basis, with the patient's informed consent and cooperation. As explained above, engaging the patient in decisions about treatment shows respect, promotes autonomy, and improves the likelihood of adherence. Indeed, non-adherence is often the direct result of failure to engage the patient fully in the treatment process.
- Detention should never be a routine component of TB Programmes. However, in rare cases, a patient may refuse treatment, leaving involuntary isolation or detention as the only means of safeguarding the public.

g) Research in TB care and control

- There is a need to for further research on TB prevention, diagnosis, treatment and support. It is crucial that research be guided by the ethical principles articulated in international guidelines for biomedical research involving

human subjects and national ethical guidelines. In general, research should always ensure the dignity of the research subjects, and results should lead to a benefit for the affected.

18.2 Patient Management Related Challenges in M/XDR TB

A number of factors need to considered and addressed when managing patients with DR-TB.

a. Community concerns

Implications of continued employment for infectious patients, discharging patients who failed treatment back to communities and disclosure of patients' condition to family, employer and close contacts need to be discussed with all affected parties. This requires that infection control strategies are implemented in the community to ensure protection of vulnerable groups (e.g. children, HIV-positive people) and intensive community mobilization to increase awareness and address stigma.

b. Work

TB and DR-TB mostly affect patients who are in their most productive age. Nearly all TB and DR-TB patients contribute to their family income. The stress of needing income often means that many patients work until their health has completely deteriorated.

- Patients should be sputum culture negative before returning to work.
  - Patients should be encouraged to resume work as soon as their sputum is culture negative. This allows patients to reintegrate into society and earn money for their families. Sick leaves should be arranged until sputum culture conversion.
  - Some patients will not want to return to work even if they are in good health, for fear of falling sick again. These patients need counseling and psychological support to facilitate their return to the workforce.
- Those without skills or jobs should be involved in Economic strengthening activities.

19. MANAGEMENT OF SECOND-LINE ANTI-TB DRUGS AND OTHER COMMODITIES

Programmatic management of DR TB requires drug supply system for the procurement of quality assured second line drugs with effective distribution system to treatment centers to meet the needs for designing effective regimen. This includes all the processes starting from product selection, placing order, arranging for its arrival, timely distribution to the appropriate drug stores, and monitoring the drug stock to avoid stock-outs and ensure the use of the drugs well before their expiration date.

The national TB control program takes the overall responsibilities establishing reliable system and handling the process with relevant stakeholders. The purpose of this chapter is to provide information and guide on second-line anti-TB drugs management in Ethiopia.

19.1 Selection Quantification and placing Second-Line Drugs order

The selection process for second-line medicines has to consider the recommended second line drugs for standardized, alternate and individualized regimens in Ethiopia, availability of WHO pre-qualified suppliers, cost of individualized drugs, toxicity profile and suitability for storage & distribution, and ease of administration by patients.

The national annual quantification and distribution should be made by the national program in collaboration with regional programs and PFSA. Quantification of second-line drugs is important to prepare and justify the program budget for MDR-TB treatment and resupply the program with subsequent orders. The quantification should take in account: shelf life of the drugs, Length of intensive and continuous phase, lead time before procurement, Consumption report and experience of previous cohorts, the distribution of the centers and patients and the annual enrollment plan.

19.2 Procurement

Procurement of second-line TB medicines is peculiar as often not immediately available in international markets, has limited suppliers and their seldom use in the

market with quality approval products. The procurement of SLDs for Ethiopia shall be managed by direct procurement using Global Drug Facility (GDF) mechanism. At point of importation, no drugs shall have shelf life shorter than 75% of the pre-defined shelf life of the specific drug by the manufacturer. It is recommended to ship the drugs in intervals to secure delivery of fresh products. 15% Buffer stock levels at national and 5% at peripheral levels should be considered to avoid losing products due to wastage.

19.3 Registration and importation

Importation of any product in to the country requires the fulfillment of the following national regulatory standards; i.e. the product has to be included in the 'List of Drugs for Ethiopia' (LIDE), or registered by Food Medicine health Care Administration and Control authority of Ethiopia (FMHACA), and WHO approval certificate. However, as some of these drugs used in the management of DRTB are relatively new or not commonly used, they might not be yet registered. FMOH/FMHACA should waiver system for such products considering the public health significance, international recommendation on the use of the product, and the complexity of the registration process. PFSA shall be responsible for clearance and in-country distribution of the products as per the national system.

19.4 Quality Assurance and Quality Control and Shelf life

All Second-line anti TB drugs are procured from WHO prequalified companies through the GDF approval by current GLC/GDF procuring agent. In country quality control activities are the responsibilities of FMHACA; onsite physical inspection before port clearance and sampled laboratory analysis shall be conducted according to the rules and regulations of FMHACA.

19.5 Distribution to treatment centers

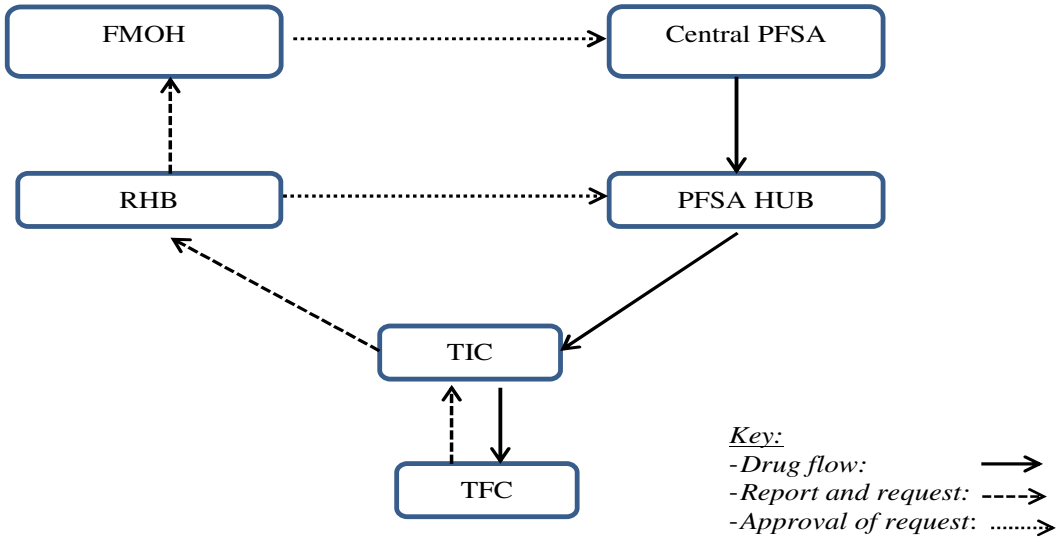
Second line drugs at the country level are managed by NTP in collaboration with RHB and PFSA due to the limited amount stock available at country level. Hence, the National stock of SLDs will be maintained at central PFSA warehouse and will be distributed periodically to respective treatment centers through regional PFSA hubs.

The storage of second line anti-TB drugs at all levels in the supply chain shall be

follow the appropriate recommendation indicated for each item by the manufacturer. PFSA and selected MDR TB treatment centers are responsible for the proper storage, inventory and monitoring of second line anti TB drugs while TB control program and FMHACA shall conduct supportive supervision and provide technical support to ensure proper storage practices at every level.

SLDs to TFCs within the catchment area shall be dispensed from TIC every three months, and TFCs shall collect SLDs from the catchment TIC till the centers have reasonable number of patients to collect directly from PFSA hubs. At all levels, first-expiry first-out (FEFO) procedure shall be followed irrespective of the chronological order of receipt of drugs.

SLDs Distribution flow from the national level to treatment centers



N.B.: Distribution to federal hospitals shall be managed by national TB program at FMoH level while distribution to regional treatment centers in the regions shall be handled by regional Health Bureaus in collaboration with the PFSA hubs.

19.6 Inventory Control

Second-line anti-TB medicines require a strong inventory management as serious health consequences could occur due to stock out of products and wastage due to expiry. Therefore, all staff working at the different levels of the supply chain should

be aware of the need for strong inventory management and act accordingly.

19.7 Rational use

DR-TB products should be used with caution and under close patient monitoring by clinicians, considering the toxicity of some of these products. Measures should be put in place to avoid misuse of these products, thereby avoiding loss of susceptibility to the DR-TB medicines and production of strains that will be extremely difficult to cure with currently available medicines. Use of fluoroquinolones should be limited to the treatment of DR-TB. Information on medicines and their side effects should be made available to clinicians who treat patients with DR-TB, along with training in appropriate regimen prescriptions that include these medicines. Drug information resources should be available for health care providers for reference. Medicines to deal with side effects should also be made available with the DR-TB medicines.

19.8 Distribution of Ancillary medicine and consumables

TB control program shall handle the quantification, procurement and distribution of Ancillary medicines, personal protective equipment and other necessary commodities on regular basis for effective program implementation and case management.

19.9 Pharmacovigilance

Adverse drug reactions (ADRs) can lead to a TB patient interrupting treatment before completion, and thus contribute to morbidity, treatment failure, reduced quality of life, or death. Pharmacovigilance, or the surveillance of adverse effects of treatment, is expected to become more relevant to programmatic management of DR-TB. National scale-up in MDR-TB treatment will expose more people of different ages and diverse ethnic mix to complex combinations of second-line anti-TB drugs. HIV and other co-morbidities necessitate the concomitant use of other medications increasing the risk of drug interactions. New classes of TB drugs are in pipeline and they will be used in combination with existent second-line anti-TB drugs, creating a potential for previously unrecognized ADRs.AS a result, pharmacovigilance needs to be given attention and results of surveillance system be assessed and interpreted to guide the TB control program.

20. MONITORING AND EVALUATION OF DR-TB PROGRAM

20.1 Introduction

The information system for treatment of DR-TB is based upon, and is an extension of, the basic DOTS information system. The forms have therefore been designed to be as similar as possible to the standard forms used in DOTS program.

The DR TB information system should be consistent across settings to permit comparison; so that it allows the managers at different levels to monitor program performance. It does not include all of the detailed information that treatment units may need to manage individual patients; that information should be contained in clinical records and other forms used in the wards or clinics.

20.2. Recording and Reporting formats and Registers

Good recordkeeping, regular reporting and critical assessment of data should be given high priority, as these are the bases for improvement of drug-resistant tuberculosis (DR-TB) management and guide policy development; therefore, service providers should use the standardized recording and reporting formats availed for the program. All the forms and registers developed to monitor the program are in line with international standard with customization to the national context. The updating, printing and distribution of all forms and registers are the responsibilities of NTP/HMIS. The reporting and recording formats that are used for MDR TB program implementation includes:

DR-TB forms and registers	DR-TB Reporting forms
• MDR TB Treatment Card (Form 1); • MDR TB Register (Form 2); • TB Bacteriology request form (Form 3); • Laboratory Register for culture & DST (Form 4); • MDR TB suspects register	• MDR-TB case finding report (Form 5) • MDR-TB Enrolment report (Form 6) • MDR TB treatment interim result report (Form 7) • MDR-TB Final treatment outcome report (Form 8), and

• MDR TB treatment follow up register • Treatment supporter card • Patient identity card	• Monthly DR TB treatment follow up report

20.3. Description of DR-TB Recording and Reporting Tools

I. MDR TB Treatment Card (Form 01)

MDR TB Treatment Card is a key instrument/information source for health staff administrating drugs daily to the patient. This form should be completed when a patient is started MDR-TB treatment and should be updated daily. It is also the source to complete and periodically update date onto the MDR-TB register (form 2). This form required to be prepared in two copies, one for TIC and the other for TFC, and keep updated. If the patient transferred out permanently to other TIC, the copy of DR-TB Treatment Card must be prepared and sent with the patient.

II. MDR TB Register (Form 02)

MDR TB Register is a valuable source of information on the clinical aspects of patient management, Smear and culture results. MDR TB Register is filled based on information in the MDR TB treatment card (form 1). Patients should be recorded in the register consecutively by date of registration. The register should be updated daily as new patients are registered and should be filled as completely as possible during every patient visit. This registration form will help to facilitate quarterly report including analysis of case finding and treatment outcome.

III. TB culture and DST request form (Form 03)

Sputum examination request paper has three portions. The top of the form is like the form used in DOTS programs, while the middle part is used for requesting microscopy, culture and DST and other WHO approved rapid diagnostics (WRD). The bottom part is used for reporting the results. The same form is returned to the requesting facility/unit with the results.

IV. Laboratory registers for culture and DST (Form 04)

This is the standard laboratory register, to be kept at any TB laboratories where culture and/or DST are performed; it must be maintained by the laboratory personnel. The register records culture and DST results of any MDR-TB/MDR-TB suspects. The Culture and DST Register must be compared regularly with the MDR-TB Register to ensure that all MDR-TB cases eligible for treatment are properly entered in both registers and accordingly reported.

NB: Laboratories should have a registers for smear microscopy and GeneXpert, and a separate register for culture and DST.

V. MDR TB case finding reporting form (Form 05)

MDR TB case finding/detection is reported by Culture and DST diagnostic laboratories on monthly/quarterly basis to respective higher level(NRL). This report gets compiled centrally by national referral laboratory and reported to NTP regularly. This monthly/ quarterly report records how many "suspect MDR-TB" patients were tested and how many confirmed MDR-TB cases (or confirmed RR-TB) identified. This report is used for program managers for planning, to assess how well the diagnostic centres are doing, their capacity and to address challenges on time.

VI. MDR TB Enrollment reporting form (Form 06)

This report is prepared by the treatment initiating centres (TICs). It is mainly used to assess the number of MDR TB cases who start treatment among those detected. The report should be made quarterly. MDR TB Register (Form 2) is the main source of the information to produce this report.

Remember:

- One cohort is all patients started treatment with DR-TB regimen in three month period or in a quarter. Always use Ethiopian calendar of the fiscal year to define a cohort and generate all DR-TB reports.

VII. MDR TB treatment Six-Month interim result report(Form 07)

This six month report evaluates the interim outcomes after six months of MDR-TB treatment, which is helpful for tracking progress since final treatment outcomes are only available two to three years after the start of treatment.

The interim results will be reported nine months past the closing date of the reported cohort patients. This allows culture information at 6 months of treatment to be included in the cohort.

Cohort patients are all patients enrolled in MDR TB program at reporting location who started treatment on any MDR tuberculosis regimen during the specified year (and quarter/month if specified).

Six Month interim result helps to assess:

- Culture conversion (for confirmed pulmonary cases)
- Death by six months
- LTFU by 6 months.
- How many patients started on second-line drugs for MDR turned out not to be MDR; and likewise for XDR.

Generally, Six month interim result (Culture conversion and death) is widely used as a proxy of final outcomes. The six month Interim outcome report is prepared by using data from the MDR-TB Register kept at the TICs.

VIII. MDR TB patients final treatment outcome (Form 08).

This report shows the final treatment outcomes for patients enrolled in the MDR-TB Program showing overall success of the program over a full treatment regimen cycle. The annual report should be completed 24 and 36 months after the last patient in the cohort starts treatment. Most of the patients will have finished treatment by 24 months and this allows preliminary assessment for one of seven outcomes: Cured; Treatment Completed; failed; lost follow up; Died; and not evaluated. Since a few patients may be on treatment for longer than 24 months, the form is completed again at 36 months after the last patient in the cohort starts treatment. The 36-month evaluation will then considered the final result.

The annual report is prepared by using data from the MDR-TB Register kept at the TICs.

IX. MDR TB suspects register

This register is to be kept in all DOTs clinics to capture presumptive MDR TB cases including Laboratory results and related patient information. This register can also be used to register patients waiting treatment after confirmation.

X. MDR TB treatment Follow up register

This register is basically a copy of MDR TB treatment card (form 01) to be kept in TFCs for the purpose of registering patient on follow up coming from TICs.

XI. Monthly MDR TB treatment Follow up reporting format

This report is on the treatment status of MDR TB patient. The format is designed to be reported on the status of follow up patient from TFCs to TICs on monthly basis with a copy to be submitted woreda, town, or sub city health office.

XII. Treatment supporter card

This card is to be given for the MDR TB patient supporter to monitor daily drug intake by the patient. It is translated into three languages (Amharic, Oromiffa, Tigrigna)

XIII. MDR-TB Patient Identity Card

This card contains all the general information related to the MDR-TB patient, such as the name and address, disease classification, patient registration category and treatment regimen. The HCW in-charge in the MDR TB Unit marks the next appointment date on this card, which is kept at all times with the patient.

20.4. Key Indicators in PMDT

The DR-TB indicators are used in tracking the achievements of the program. The indicators are grouped into four classes:

Table: Key Indicators in PMDT

Indicator Group	Indicator/s
1. Screening	• Proportion of presumed DR-TB patient tested using DST.
2. Detection	• Proportion of presumptive DR TB cases for whom DST performed • The Number of MDR/RR-TB cases Detected during the reporting period • Number of XDR TB cases detected •
3. Enrolment	• Number of MDR/RR-TB cases started on second-line anti-TB treatment regimen
4. Interim results	• RR-/MDR-TB cases on MDR-TB treatment regimen with negative culture by six months • RR-/MDR-TB cases on MDR-TB treatment regimen who died by six months • RR-/MDR-TB cases on MDR-TB treatment regimen who LTFU by six months
5. Final outcomes	RR-/MDR-TB cases on MDR-TB treatment regimen with an outcome : • Cured • Completed • Died • Failed • LTFU • No Outcome Assigned (Transferred, Still On Treatment Or Unknown).

20.5. Recording and Reporting in PMDT

The respective treatment centers are responsible to handle data recording, entry, reporting of the activities to the program at the regional and national level through the data clerk of the unit /HMIS focal points on monthly/quarterly basis.

Case notification of DR-TB confirmed cases from the total sputum samples processed for TB culture and DST tests should be registered by all DST laboratories (public and private) and should be reported quarterly to National Reference TB laboratory for central compilation.

The national TB program has developed and introduced an electronic DR-TB database to be used at Treatment Initiating Center level to facilitate patient registration , monitoring and report generation.

20.6. Data management and information dissemination

The national level data management will be handled by the National TB program and HMIS. Report of DR-TB activities shall be collected through the routine surveillance reporting system which will be later integrated to the national HMIS.

The steps involved in the quarterly MDR-TB data management are:

- MDR-TB notification and cohort analysis of treatment outcome are compiled by the Health facility(TICs) every quarter send to zonal/regional HMIS unit.
- The Region MDR-TB focal person in coordination with HMIS unit verifies that the reports for data quality in terms of completeness of the information and accuracy and compiles cohort analysis reports on all patients in the Region.
- The Region submits quarterly and annual reports to the central unit of the NTP.
- The central unit of the NTP compiles the MDR-TB notification and cohort analysis reports on all MDR-TB patients registered nationally.
- The quarterly reporting at the each level should be linked with the quarterly collection of Drugs and supplies from the PFSA. The SLD consumption report should be compiled and submitted regularly to next higher level along with MDR TB report.

20.7. Supportive Supervision

Regular Biannual supportive supervision will be conducted using nationally standardized Pre-prepared supervision checklist. The supervision will be conducted by a Joint team comprised of experts from FMoH, RHBs , ZHDs, Sub-city/ Woreda HOs and partner organizations. Feedback must follow in both verbal and written form to the respective visited facility based on the findings. Follow up on the agreed action points will be conducted and cross-checked on the subsequent visits.

20.8. Program Monitoring

The Quality of the implementation of the national DR-TB program will be monitored regularly using the quarterly/monthly activity reports coming from the treatment sites, regular quarterly supportive supervisions and review meetings and annual

review meeting involving implementers and team of experts from respective RHB and developmental partners.

NB: Treatment initiating centers are responsible in providing quarterly support on DR- TB program recording and reporting to Treatment Follow up Centers(TFC) as part of regular mentoring and programmatic support to TFC in their catchment area.

20.9 Program Evaluation

The national MDRTB program shall be reviewed and evaluated annually by external reviewers preferably by GLC consultants to assess the program performance, achievements and challenges and document the lessons learnt. Hence further scale up of the service will be guided by the assessment outcomes. The area of support from the GLC mission will be identified by the country team to address all the critical areas where the program should be monitored and evaluated against the international and regional standards and experiences to assist the country's progress towards delivery of quality services. Additionally, the program performance will be measured against the internationally agreed up on standard MDR-TB indicators which are accepted by the program.

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ANNEXES

Annex 1: Weight-based oral anti-TB drug daily dosing in adults ≥ 30 kg

Drugs	Daily dose	30-35 kg	36-45 kg	46-55 kg	56-70 kg	> 70 kg
Isoniazid	4-6 mg/kg once daily	150 mg	200 mg	300 mg	300 mg	300 mg
Rifampicin	8-12 mg/kg once daily	300 mg	450 mg	450 mg	600 mg	600 mg
Pyrazinamide	20-30 mg/kg once daily	800 mg	1000 mg	1200 mg	1600 mg	2000 mg
Ethambutol	15-25 mg/kg once daily	600 mg	800 mg	1000 mg	1200 mg	1200 mg
Rifabutin	5-10 mg/kg once daily	300 mg	300 mg	300 mg	300 mg	300 mg
Levofloxacin	750-1000 mg once daily	750 mg	750 mg	1000 mg	1000 mg	1000 mg
Moxifloxacin	400 mg once daily	400 mg	400 mg	400 mg	400 mg	400 mg
Ethionamide	500-750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Prothionamide	500-750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Cycloserine	500-750 mg/day in 2 divided doses	500 mg	500 mg	500 mg	750 mg	750 mg
p-Aminosalicylic acid*	8 g/day in 2 divided doses	8 g	8 g	8 g	8 g	8-12 g
Bedaquiline	400 mg once daily for 2 weeks then 200 mg 3 times per week					
Clofazimine	200-300 mg (2 first months) then 100 mg					
Linezolid	600 mg once daily	600 mg	600 mg	600 mg	600 mg	600 mg
Amoxicillin/clavulanate (875/125mg)	80 mg/kg/day in 2 divided doses	2600 mg	2600 mg	2600 mg	2600 mg	2600 mg
High-dose isoniazid	16-20 mg/kg once daily	600-1000 mg	1000-1500 mg	1500 mg	1500 mg	1500 mg
Imipenem/cilastatin	1000 imipenem/1000 mg cilastatin twice daily					
Meropenem	1000 mg three times daily (alternative dosing is 2000 mg twice daily)					

Weight-based injectable anti-TB daily dosing in adults ≥ 30 kg

Drugs		30-33 kg	34-40 kg	41-45 kg	46-50 kg	51-70 kg	> 70 kg
Streptomycin	12-18 mg/kg once daily	500 mg	600 mg	700 mg	800 mg	900 mg	1000 mg
Kanamycin	15-20 mg/kg once daily	500 mg	625 mg	750 mg	875 mg	1000 mg	1000 mg
Amikacin	15-20 mg/kg once daily	500 mg	625 mg	750 mg	875 mg	1000 mg	1000 mg
Capreomycin	15-20 mg/kg once daily	500 mg	600 mg	750 mg	800 mg	1000 mg	1000 mg

*Adapted from *Tuberculosis: Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries*. Médecins Sans Frontières and Partners In Health; 2013

Annex 2. Pediatric dosing of second-line medications

Group	Drug	Daily dose	Maximum daily dose
1	isoniazid (H)	10-15 mg/kg once daily	300 mg
	rifampicin (R)	10-20 mg/kg once daily	600 mg
	ethambutol (E)	15-25 mg/kg once daily	2000 mg
	pyrazinamide (Z)	30-40 mg/kg once daily	2500 mg
2	amikacin (Am)	15-22.5 mg/kg once daily	1000 mg
	kanamycin (Km)	15-30 mg/kg once daily	1000 mg
	capreomycin (Cm)	15-30 mg/kg once daily	1000 mg
3	ofloxacin (Ofx)	15-20 mg/kg in 2 divided doses	800 mg
	levofloxacin (Lfx)	< 5 years 5-10 mg/kg twice daily > 5 years 10 mg/kg twice daily	1000 mg
	moxifloxacin (Mfx)	7.5-10 mg/kg once daily	400 mg
4	ethionamide (Eto)	15-20 mg/kg once daily	1000 mg
	protionamide (Pto)	15-20 mg/kg once daily	1000 mg
	cycloserine (Cs)	10-20 mg/kg once daily	1000 mg
	PAS (4 g sachet)	300 mg two or three times daily	12 g
5	clofazimine (Cfz)	1 mg/kg once daily	200 mg
	co-amoxiclav (Amx/Clv)	80 mg/kg in 2 divided doses	4000 mg of Amx and 500 mg Clv

Annex 3. Specimen for analysis of presumptive TB in children

Specimen	Brief description of sample collection procedure	Recommended age group	Recommended *minimum* volume for studies*	Optimal collection time	Comments/ tips
Spontaneous sputum	Expectoration of sputum without prior saline nebulization	>7 y.o.	3 mL	Early morning	If child is unable to produce sputum of sufficient quantity and quality, consider sputum induction.
Induced sputum/ laryngopharyngeal aspirate	Expectoration of sputum preceded by hypertonic saline nebulization	Any age	3 mL	Early morning	If child is unable to expectorate, consider laryngo-pharyngeal suctioning.
Gastric aspirate (GA)	Nasogastric aspiration of gastric juice containing swallowed sputum	<7 y.o.	5 mL	Early morning before child gets out of bed	Upon awakening and sitting and standing, peristalsis begins, and stomach gradually empties, consequently compromising volume.
Gastric lavage (GL)	Nasogastric instillation of solution to "wash off" and recover sputum adhered to walls of stomach	<7 y.o.	10 mL	Early morning	Recommended only when 3 mL of gastric aspirate cannot be obtained.
String test	Esophagogastroduodenal nylon yarn that can absorb swallowed sputum	>4 y.o.	N/A	Unknown, but probably more a factor of duration in which it is left in place	Consider when good quality or quantity sputum and aspirates are not obtainable.
Nasopharyngeal aspirate	Nasopharyngeal suctioning of the nasopharynx to collect secretions from URT, but may also collect secretions from LRT if cough reflex is stimulated	≤5 y.o.	2 mL	Unknown, but probably higher yield in morning	The bacteriologic yield of naso-pharyngeal aspirate tends to be similar to or lower than that of induced sputum or GA/GL.

* These values are the minimum recommended amount; larger volumes tend to have higher bacteriological yields.

Annex 4: Minimum Package of TB IC Interventions at Health facility level

I. Managerial Measures for facility-level TB infection control:

1. **Identify and/or strengthen TB Infection control/IP Committees**
   - Develop TOR and establish or strengthen IP/TB IC Committee
   - Assign TB IC focal person with clear Job description
   - Do facility TB IC risk assessment
   - Develop annual plan (plan should include What to do, when, who will do and how)
2. **Rethink** the use of available spaces and consider **renovation** of existing facilities or **construction** of new ones to optimize implementation of controls.
3. Conduct on-site **surveillance of TB** disease among health workers and assess the facility.
4. **Address advocacy, communication and social mobilization (ACSM)** for health workers, patients and visitors. Use both audiovisual, Verbal and written communication materials.
5. **Monitor and evaluate** the set of TB infection control measures: Implementation should be followed daily, IP/TB IC committee should meet at least quarterly and the whole TB IC plan should be evaluated at least annually.

II. Administrative controls:

1. Promptly identify people with TB symptoms (**triage**).
2. **Separate infectious patients** (fast track services for outpatients and keep them separate from others in inpatient),
3. **Minimize time spent** in health-care facilities.
   - Rapid diagnosis of TB and DR TB using available diagnostic tests (Smear Microscopy or if available Xpert MTB/RIF test).
   - Put patients on Effective treatment based on DST status.
4. **Control the spread of** pathogens (cough etiquette and respiratory hygiene) and
5. Provide a package of prevention and care interventions on TB and HIV for **health workers**

III. Environmental controls:

Maximal utilization of natural ventilation systems

- Opening doors and windows to attain at least **12** Air Change per Hour
- Utilization of additional measures like propeller fans and whirly-birds in places where natural ventilation is inadequate
- Proper Client-HCW sitting arrangement.
- Build waiting areas with good natural ventilation (open on three sides)
- Encouraging DR-TB patients to stay out-door, as much as possible.

IV. Personal protective equipment: **Use particulate respirators.**

- Availing N-95 respirator for health care workers who are involved in care of DR-TB patients
  - Use Quality assured N-95/FFP2 respirator (NIOSH/CDC/CEN approved).
  - Ensure correct use by doing facial seal check every time Respirators are used.
  - A respirator can be worn for at least 15 days, as long it is intact and properly handled.
- **Surgical masks for DR-TB patients until culture conversion.** Other materials like piece of cloth or tissue paper can be used when surgical mask is not available.

Annex 5: Simplified TB IC Plan for Health care facility

Name of Health Facility_____ Date_____

TB IC Intervention	TB IC activity	Responsible person/body *(write the name)*	Frequency	Indicators	Remark
Managerial	IP/PS & TB IC committee establishment and functionality	Facility manager	Monthly meeting	Documented minutes	
	Assign TB IC Focal person	Facility manager	Annually	Assigned and working	
	TB IC Risk assessment	IP/PS & TB IC committee	Annually	Documented assessment	
	Develop TB IC plan	IP/PS & TB IC committee	Annually	Documented plan	
	TB and TBIC awareness creation , training and education for staffs and visitors	Focal person/ IP/PS & TB IC committee	Daily	List and dates of topics provided	
	Ensure provision and posting of Client education material on TB in every service outlets	Focal person/Unit heads	Monthly	Posted materials	
	Monitoring of IP/PS & TB IC activities	Focal person/ IP/PS & TB IC committee	Monthly	Evaluation document	
Administrative	Triaging: Identify those have cough lasting for ≥ 2 weeks or Confirmed TB and MDR TB patients	Triage /card room officer/ Facility Manger	Daily	Documented suspects in logbook	
	Separating coughing patients from others and Fast tracking services	Assigned provider/ TB IC focal person	Daily	Observed practices	
	Cough Etiquette and respiratory hygiene	Focal person/ unit heads/ HCW	Daily	Observed practices	
	Monitor sputum AFB result turnaround time.	Laboratory head/ TB IC focal person	Daily	Result provision within 36 hrs	
	Monitor inpatient stay of presumptive and confirmed TB or MDR TB Patients.	focal person/ TB IC focal person	Daily	Admitted for clear indications and stay < 7 days	
Environmental	Opening clinic windows (all Service outlets)	Service outlet heads	Daily	Observed practices	
Personal Protective Equipment	-Ensure N95 respirator used according to guidelines -Avail piece of cloth or handkerchief or tissue paper for M/XDR TB Patients	MDR TB focal person	Daily	Observed practices	

Annex 6: MDR TB Patient Socioeconomic and Home assessment tool

Issues	Assess	Score	
Social	• How many people are sharing the household with the patient?		
	• How many are HIV positive or suffer from another chronic disease?		
	• How many are below 5 or above 50 years of age?		
	• Is this the patient's only residence?		
Economic	• Does the patient have a source of income (employed, self employed, getting aid)?	Yes	No
	• From what material is the patient's residence constructed?		
	• What is the ratio of employed persons versus unemployed persons in the household?		
Habits	• Does the patient smoke?	Yes	No
	• Does the patient drink alcohol or chew Khat?	Yes	No
	• Does anyone else in the household drink or chew Khat?	Yes	No
TB Knowledge	• Do the patient and the family understand how TB is transmitted?	Yes	No
	• Does the family understand the need to be screened for TB?	Yes	No
Infection control	• Does the house have enough windows?	Yes	No
	• Does the patient have several visitors?	Yes	No
	• Does the patient sleep in a separate room?	Yes	No
	• Does the patient socialize in outdoor spaces while on treatment?	Yes	No
Hygiene	• Is the patient able to demonstrate good cough hygiene?	Yes	No
	• Does the patient know how to safely dispose of sputum?	Yes	No

(adapted from TBCARE II)

Final Assessment:

_____

_____

Recommendations:_____

_____

_____

Annex 7: Stepwise introduction New TB drugs for use in DRTB patients

Steps towards responsible use of Bedaquiline in Ethiopia

1. Organizing the process and governance
    - National oversight committee to ensure planning and coordination of the introduction process:
        - National and international stakeholders (including lab side)
        - National pharmacovigilance center
    - Implementation taskforce to prepare and support all practical implementation steps (including NRL)
2. Coordination with national drug regulatory authority
3. Dialogue with pharmaceutical company
4. Develop implementation strategy:

    Suggestions:
    - Use Bdq for pre-XDR and XDR
    - Under supervision of one national MDR treatment center with active pharmacovigilance operational research experience
    - Ambulatory care (if clinically possible) under good patient support and infection control conditions, integrated into routine MDR treatment system with direct monitoring of all drug intakes
    - Informed patient consent
5. Preparation of implementation plan (training, M&E, diagnostic needs, drug procurement, patients management and support, pharmacovigilance, operational research, participation in international reporting/coordination)
6. Approval of implementation plan by MOH Ethical committee
7. Mobilize funding for all elements
8. Initiation of use of the drugs as per the national protocol
9. Regular supervision of the implementation, documentation and occurrence of unprecedented events observed by HCWs or encountered by patients
10. Document all the process and experience for future use.

Annex 8: Sample Transportation SOP

Standard Operating Procedure (SOP) for Collection , Handling , Packaging and Transportation of Sputum Sample for TB

***Title*: Collection , Handling , Packaging and Transportation of Sample for TB**			
Written by: Lab Quality officer	**si**gnature	Effective Date:	
Approved by: TB Lab Head	signature	Revised Date:	
		Laboratory area	

PURPOSE

This standard operating procedure (SOP) provides the general technical requirements and Operational guidelines for the proper collecting, packing, and shipping of sputum specimen samples to a culture and drug susceptibility testing (DST) laboratory for analysis for MDR TB. This SOP includes the guidance and regulatory requirements that ensure proper collecting, packing, and shipping of sputum samples classified as "hazardous material"

GENERAL CONSIDERATION

Potential hazards associated with the planned tasks are thoroughly evaluated prior to conducting laboratory activities. The laboratory safety manual provides a description of potential hazards and associated safety and control measures. Personnel wear gloves while performing the procedures described in this SOP. Specifically, gloves are worn while preparing, handling and packing samples. Protocols for sample temperature maintenance and sample packing are applicable to collection of samples. The intent is to ensure that samples arrive at the laboratory in good condition both physically intact and appropriately preserved.

MATERIALS

- Falcon Tube
- Cetylpyridinium chloride
- Triple package
- Absorbent cotton swab

SAMPLE TYPE: Sputum
AMOUNT: 3-5 ml*

COLLECTION:

- two purulent /muco purulent early morning and spot sputum specimen for culture and DST
- one purulent /muco purulent (Non bloody) spot sputum specimen for Xpert MTB/RIF

STORAGE: Store the sputum specimen at 2 to 8^{o}C up to 5 days

TRANSPORT: Use triple packaging and the sample must reach to the testing site within 5 days after collection

STABILITY: Cold chain must be maintained using Ice pack and the Ice pack must be changed at the transit site after 12 hours.

SPECIMEN REJECTION:

- Specimen is unlabeled or mislabeled.
- Specimen without request form.
- Specimen name and request form does not match.
- Specimen container breakage or leakage.
- Specimen not collected in an appropriate container

*Ideally a sputum specimen should have a volume of 3- 5ml, although smaller quantities are acceptable if the quality is satisfactory

SAFETY PRECAUTIONS

- Patients should produce sputum in sputum coughing designated area
- Avoid shaking of the tube
- Wear gown and glove when handling the sputum

PROCEDURES

SPUTUM SPECIMEN COLLECTION PROCEDURE

Instruct the patient

- To collect in a separate, ventilated room or preferably outdoors/ produce sputum in sputum coughing designation area/
- To Keep both hands on hips, cough forcibly and collect sputum in the mouth
- To spit the sputum carefully into a wide-mouthed, unbreakable, leak proof container and close the lid tightly. Example Falcon tube.
- To collect 3–5ml in volume, although smaller quantities are acceptable if the quality is satisfactory.
- To collect two sample for culture or one sputum sample for GeneXpert

Consider the following for collection

- Sample containers are pre-labeled before sample collection, and the labels are protected from the sample matrix by using water proof labels or by covering with clear tape

- Laboratory personnel should label each specimen container with the unique identification number and date of collection
- Give labelled falcon tube to the patient
- Check the quantity, quality and cross check the number with the request form when receive
- Keep in the refrigerator or at room temperature until transport (depending on the time /date transport)

SPUTUM SAMPLE PACKAGING AND SHIPMENT

- Obtain samples in the laboratory-specified containers and verify the completeness of the sample identification information on the label and keeping record.
- Verify custody seals on sample containers and/or bags are intact and have been initialed and dated.
- If packaging aqueous samples or using wet ice for temperature preservation, place a garbage bag or liner in the cooler.
- Place samples in re-sealable plastic bags and then into the cooler. If appropriate, place a temperature blank in the center of the cooler.
- Place ample amounts of wet ice contained in doubled re sealable bags inside the garbage bag/liner in cooler. As needed, place bubble wrap or other inert packing material around the garbage bag/liner in the cooler. **Note**: Blue Ice is used for temperature maintenance for particulate matter sample media.
- Seal the garbage bag/liner with duct tape. This is to ensure that if the contents were to spill that the garbage bag/liner would contain the spill.
- Permanent marker to write number on the label.
- Sample custodian or designee relinquishes the samples on the COC record by signing their name and providing the date and time that the samples were packed.
- Write the shipper's tracking number (such as courier and courier air bill number) on the COC form when a commercial courier is used.

Triple Packaging Materials

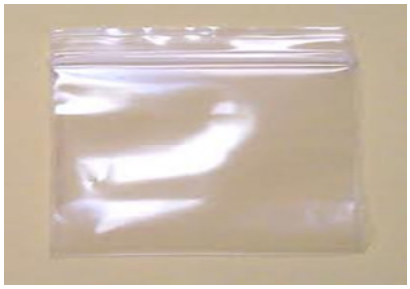
All specimens should be appropriately packaged within a triple packaging system: primary, secondary and outer packaging and should contain all relevant documentation:

a) Primary Receptacle:

A primary watertight, leak-proof receptacle containing the specimen. The receptacle is packaged with enough absorbent material to absorb all fluid in case of breakage.

A second durable, watertight, leak-proof packaging is used to enclose and protect the primary receptacle(s).

b) Secondary Packaging:



c) Outer packaging.

Secondary packaging is placed in outer shipping packaging with suitable cushioning material. Several cushioned secondary packages may be placed in one outer packaging. Outer packaging protects their contents from outside influences, such as physical damage, while in transit. Each completed package is normally required to be marked, labeled and accompanied with proper documentation.

Safety warnings to be written on the tertiary container

- Sputum and other specimens presumed to contain infectious Mycobacteria or other infectious agents are classified as **"Infectious substance, Category B".**
- The shipping name labeled on containers with such specimens is **"BIOLOGICAL SUBSTANCE, CATEGORY B".**

- Infectious substances in Category B are assigned to a specific UN number: **UN 3373.**
- Label the safety box with the words **"BIOLOGICAL SUBSTANCE, CATEGORY B"** and the UN number: **UN 3373**