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MINISTRY OF HEALTH - ETHIOPIA
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FDRE Ministry of Health National TBL Control Program

Clinical and Programmatic Management of Drug Resistant TB in Ethiopia

Participants' Training Manual for Health Care Workers

September 2020

Addis Ababa

FDRE Ministry of Health National TBL Control Program

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ACKNOWLEDGMENT

Drug Resistant TB remains a global and national health threat. Ethiopia is among the high TB, TB/HIV and MDR-TB burden countries globally. Cognizant of the burden and the deleterious health impacts of drug-resistant TB in the country, the FDRE Ministry of Health (FMOH) has begun responding to the emergence of DR-TB by conducting the first Drug Resistant TB survey (DRS) in 2005 followed by the establishment of the first DR-TB treatment center in Addis Ababa in 2009 to treat the first cohorts of DR-TB patients under programmatic conditions. This was followed by the introduction of ambulatory model of DR-TB and massive expansion of the DR-TB diagnostic and treatment centers, development of national PMDT guidelines consistent with global recommendations, and training of health care workers on the clinical and programmatic management of DR-TB. Substantial gains have been made as the result of the significant investments on Programmatic management of DR-TB (PMDT).

The global policies on Clinical and Programmatic management of DR-TB has been changing quite frequently with the development of new drugs and novel regimens as well as advances in TB/DR-TB diagnostics. These changes in global policies necessitate the revision of the national guidelines and training manuals. In line with this, FMOH has developed this training manual to support the implementation of the national guidelines and help the health workers provide highest standards of DR-TB care in accordance with the latest guidelines. The Federal ministry of Health strongly believes that this material would be of paramount importance to train and equip general health workers with the latest knowledge on the clinical and programmatic management of RR/MDR-TB. This training manual reflects the latest national policies on the clinical and programmatic management of DR-TB.

The development of these national MDR-TB modular training materials is the great efforts of several experts in the field and FMOH would like to express its heartfelt thanks to the following individuals for their contributions in the preparation of the training materials:

Hiwot Solomon (FMOH), Taye Leta (FMoH), Atlabachew Liaulseged (FMoH), Dagim Damitew (FMOH), Dr Yohannes Molla (USAID/challenge TB/KNCV), Dr Andargachew Kumsa (FMOH/USAID), Dr. Endale Berta (FMOH/WHO-E), Dr Anteneh Kassa (USAID), Dr Eshetu Kebede (FMoH/WHO-E), Addisalem Yilma (FMoH/WHO-E), Abayneh Admase (FMOH), Dr Daniel Meressa (St Peter's Specialized hospital/GHC), Dr Amsalu Bekele (Addis Ababa university college of health sciences), Dr Aschalew Worku (Addis Ababa university college of health sciences), Dr Tewodros Haile (Addis Ababa university college of health sciences), Dr. Tewodros Tsegaye (Gondar Universty Hospital), Dr Emawayish Tessema (ALERT/USAID/Challenge TB), Dr Fraser Wares(USAID/challenge TB/KNCV -TA), Kassech Sintayehu(USAID/challenge TB/KNCV), Dr Fikireselam Dessalegn (Mekele Hospital), Dr Ermias Ergette (Gondar Universty Hospital), Dr Dinkye Abebe (Yirgalem Hospital), Dr Girum Bayissa (Bishoftu Hospital), Dr Tamiru Aseffa (St Peter's Specialized Hospital), Dr Bezamariam Fisseha (Boru Meda Hospital), Dr Kalkidan Yae (Boru Meda Hospital), Dr Addisu Belay (Bishoftu Hospital), Dr Eyerusalem Negussie (FMOH), Dr. Seid Hassen (Borumeda Hospital), Shewuki Moga (EPHI), Dr.Workabeba Abebe (Addis Ababa University College of health sciences).

The 2020 Updates to this training manual to reflect the latest WHO and national guidelines was made by *Atlabachew Liaulseged (FMOH) and Dr Andargachew Kumsa (FMOH/USAID)*. FMOH would like to acknowledge their dedication.

1. BURDEN AND BASIC CONCEPTS OF DRUG RESISTANT TB

LEARNING OBJECTIVES

By the end of this unit, participants will be able to:

- Describe the global and national epidemiology of Drug resistant TB.
- Discuss the basics of Drug-Resistant TB
- Discuss causes of inadequate treatment as risk for DR-TB
- Discuss the national MDRTB control strategic framework

EPIDEMIOLOGY AND BASICS OF DRUG RESISTANT TUBERCULOSIS

Epidemiology

Drug-resistant TB threatens global TB care and prevention and remains a major public health concern in many countries. According to the Global TB Report 2019, 10.0 million people are estimated to have fallen ill with TB in 2018 while an estimated 1.3 million people died of TB. An estimated 3.5% of these new TB cases and 18% of the previously treated cases had Drug resistant- TB with an estimated 558000 cases of multidrug-resistant TB (MDR-TB) emerging in 2018. Ethiopia is among the 30 High TB, TB-HIV and MDR-TB Burden Countries, with annual estimated TB incidence of 151/100,000 populations and death rate of 22 per 100,000 populations in 2018. An estimated 0.71% of these new TB cases and 7.2% of previously treated TB cases had drug resistant TB in 2018 and an estimated 1600 MDR/RR-TB cases emerging in 2018.

Basics of Drug Resistant TB

TB is considered drug-resistant (DR) when the organism (mycobacterium tuberculosis) is not killed by anti-TB drugs. And this can be confirmed by a laboratory test called drug susceptibility test (DST).

Development of Drug Resistance in Tuberculosis:

Drug resistance in tuberculosis is the result of selection of resistant mutants in the bacterial population, due to killing of susceptible bacilli by anti-TB drugs. The problem is greatly exacerbated by inadequate treatment such as direct or indirect mono therapy, resulting from intake of a single anti-TB drug from intake of several drugs with suboptimal concentrations. Susceptible bacilli are killed rapidly and resistant mutants are then able to multiply.

Mycobacterium tuberculosis has the ability to undergo spontaneous, slow but constant mutation, resulting in resistant mutant organisms. This natural phenomenon is genetically determined and varies from drug to drug.

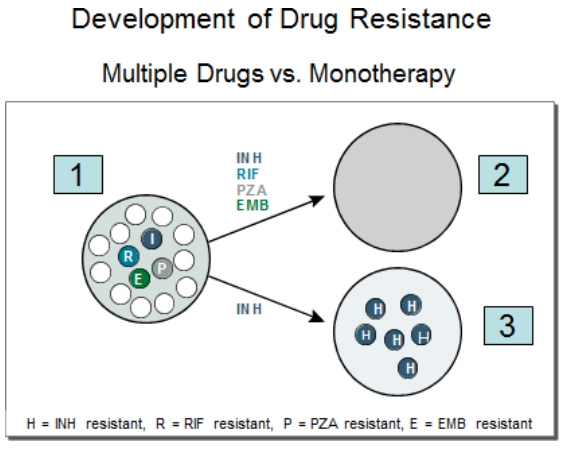
The probability of spontaneous resistance to individual first-line anti-TB drug is as follows:

- Isoniazid: 1 in every 1 million cell divisions
- Rifampicin: 1 in every 1 billion cell divisions
- Streptomycin: 1 in every 1 million cell divisions
- Ethambutol: 1 in every hundred thousand cell divisions
- Pyrazinamide: 1 in every hundred thousand cell divisions

Since resistance to various TB drugs is not genetically linked, it is uncommon for a bacillus to be resistant to more than one TB drug. For instance, one would require bacillary load of 2.56*108 x 2.25*1010 = 5.76*1018 to find one bacillus that is resistant to the combination of INH and RIF.

The chance for an untreated individual to develop either mono or poly resistant form of TB from the naturally occurring wild type resistant bacillary strains is extremely rare indicating other causes for the development of resistant form of clinical TB.

Drug resistance in tuberculosis, in programmatic settings, is the result of selection of resistant mutant bacilli in the bacterial population by administering an ineffective anti-TB treatment that kills all the susceptible bacilli and leaves the resistant ones behind to multiply and predominate. The problem is greatly exacerbated by inadequate treatment such as direct or indirect mono therapy, resulting from intake of sub-optimal regimen.

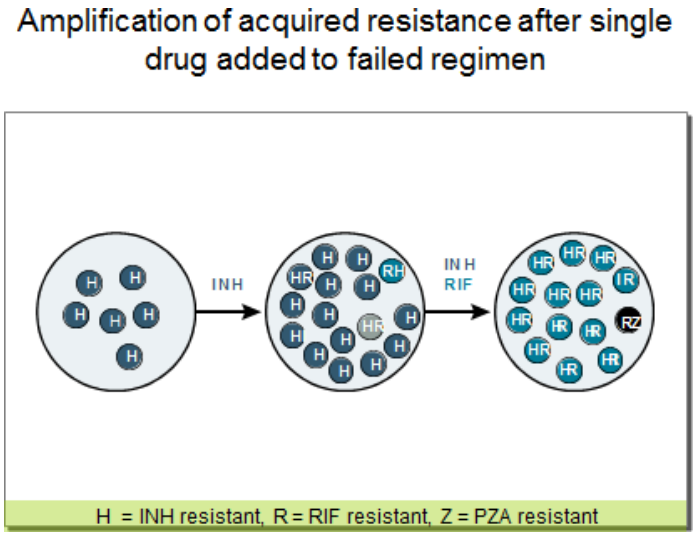


The figure above shows:

- Culture media 1‖ is the pre-treatment colonies of TB where there is random naturally present wild resistant strain with majority susceptible colonies.
- Culture media 2‖ is the post treatment media with multiple anti-TB drugs, RHZE, where both the susceptible and all forms of wild-type mutants are killed as no bacilli is resistant to more than one drug and hence can be killed by the other drug to which the bacillus is susceptible.
- Culture media 3‖ is the post-treatment media with INH mono-therapy where all bacilli susceptible to IHN get killed and leave those resistant to IHN, which will then multiply and predominate the colony.

This is why combination chemotherapy is so important for TB. Treatment with both isoniazid and rifampicin together is likely to kill all TB bacilli, including drug-resistant mutants.

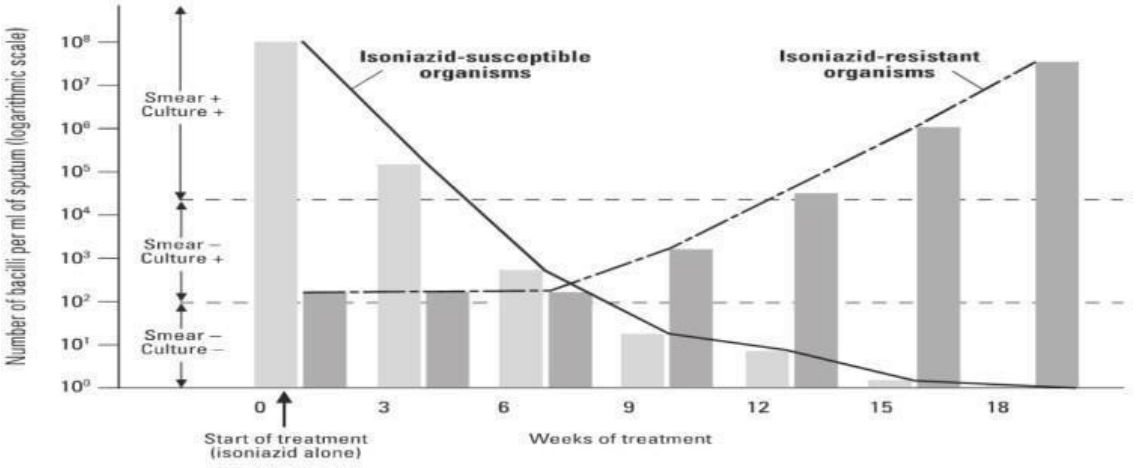
Retreatment and Amplification of resistance: is a phenomenon where patients develop additional resistance due to in-adequately constructed TB treatment regimen. Previously treated TB cases may often be re-treated with first line TB drugs while having drug resistant strains, and further subjected to amplification of resistance.



As shown above, the initial colonies of bacillary population were resistant to INH and if continued to be treated with INH, the population with INH-resistant strain will grow in number and predominate the bacillary population. If a single drug is added to the existing failed treatment with RH as shown for treatment of the second media, then sequential mutations to rifampicin develops, on the already existing INH-resistant bacillus, to result in DR-TB resistant to both INH and rifampicin.

"**Fall and rise" Phenomenon in TB treatment**: this phenomenon is encountered when TB patients are treated with an inadequate regimen where patients initially respond bacteriologically and clinically. The bacillary load decreases and the patient may become smear- or even culture- negative. At the same time, the symptoms of TB may also improve — the fever may come down, and the appetite and weight may increase. But, as the remaining resistant bacilli in the sputum start to increase, the patient clinically deteriorates. The term "fall and rise" refers to a fall followed by a rise in the bacillary load. "Fall and rise" is the classic pattern showing the connection between treatment failure and development of drug resistance.

The graph below shows that when INH mono therapy is started, the dominant strains (INH susceptible strains) are rapidly killed, the smear and culture convert negative, but after few weeks of treatment, the INH-resistant strains, that were not killed initially, started to re-populate and become the dominant strain when the smear and culture revert to positive. This demonstrates the role of mono therapy in the generation of DR-TB.



Note that, evidences show that INH resistant TB cases are the precursor for the subsequent development of MDR-TB in most programs.

Transmission of DR-TB:

Both the drug susceptible and resistant MTB spread in the same manner, M.TB is carried in airborne particles, also called droplet nuclei, which can be generated when persons suffering from pulmonary tuberculosis disease sneeze, cough, laugh or speak. 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 DR-TB.

Picture: Sneezing liberates many organisms

The probability that a person who is exposed to a case of DR-TB become infected depends primarily on:

- The concentration of infectious droplet nuclei in the air, which is influenced by the number of organisms generated by TB patient & the amount of ventilation in the area of exposure.
- Duration of exposure to the infectious droplets nuclei
- Proximity to source of infectious droplet nuclei

The risk of transmission and infecting a susceptible individual is therefore highest in close, prolonged, indoor exposure to a person with sputum smear-positive pulmonary TB.

DEVELOPMENT OF DR-TB UNDER PROGRAMMATIC CONDITION

Under programmatic conditions, two main reasons are believed to drive the emergence of DR-TB:

A. On-going person to person transmission of resistant strains in the community:

Person to person transmission is the result of circulating drug resistant strains of the TB bacilli in the community.

The main source cases for DR-TB transmission include:

- those patients with DR-TB who are missed or late to be detected, or
- TB cases not receiving effective and adequate treatment.

Question: Discuss and propose interventions that need to be in place to detect RR/MDR-TB cases among patients with no prior exposure to TB treatment?

Community/House level	Care provider level	Programmatic level

B. Inadequate treatment leading to direct or indirect mono-therapy:

The potential causes of inadequate treatment can be broadly categorized into:-

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

Table 1.1summarizes the common causes of inadequate treatment although DR-TB can then spread from one person to another.

Table1.1 Causes of inadequate Anti- tuberculosis treatment

Health provider/program related factors:	**Drug related factors**	**Patient- related factors: inadequate drug intake**
• 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 of TB medicines • Unavailability of certain drugs due to stock-outs/delivery disruptions • Poor storage conditions • Wrong doses or combinations (manufacture related)	• Poor adherence/default • Lack of or inadequate patient information • If Treatment not given for free • Lack of transportation money or support • Drug adverse effects/interaction, • Social barriers • Mal-absorption • Substance/alcohol dependence

Discuss which causes of inadequate treatment applies to your setting and explain why?	Suggested Possible solutions
1. 2. 3.	1. 2. 3.

PREVENTION OF DEVELOPMENT OF DR TB:

Knowing the complexity of programmatic, clinical and laboratory management of DR-TB, strengthening of recommended TB prevention strategies in Ethiopia could have pivotal effect in further control of DR-TB with emphasis on five major ways.

There are five major 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.
iii. Health system strengthening and regulation: integration of services strengthens lab capacity, strengthen TB Infection Control and Drug regulation.
iv. Addressing underlying risk factors and social determinants: Poverty, Vulnerable groups (Refugees, Prison), HIV, Diabetes, Malnutrition, Substance abuse.
v. Ensuring patient adherence and supervision of therapy and Patient support.

National TB Control Strategy and DR-TB Implementation Framework

Ethiopia has achieved the Millennium Development Goals for TB in 2015 and now adopted the new END TB strategy. The national TB control program has endorsed the END TB strategy and aligned it with the National HSTP document and national strategic plan for tuberculosis, TB/HIV, DR-TB, and leprosy prevention and control.

The END TB Strategy aims to end the global TB epidemic, with targets to reduce TB deaths by 95% and to cut new cases by 90% between 2015 and 2035, and to ensure that no family is burdened with catastrophic expenses due to TB.

Furthermore, the national TB program has also re-prioritized the key strategic interventions in the five-year National TB strategic plan that paves towards achieving the END TB 90-(90)-90 targets set for 2020:

- Ensure 90% of all people with tuberculosis, including DR-TB diagnosed and treated.
- Ensure 90% of the key populations in the country are diagnosed and treated
- Ensure 90% of people diagnosed successfully complete treatment with services to ensure adherence and social support, for drug-susceptible and drug-resistant TB combined.

The national DR-TB Control framework is a subset of the national TB control strategy. The National TB strategic plan is customized to address the additional needs of DR TB as shown in the box below:

National MDR-TB Implementation frame work:

1. Reinforce Bold Policies & Supportive Systems
   - Governance, Leadership and Multi-sectoral Collaboration and Accountability to end TB
   - Engage all care providers (PPM-TB)
   - Universal Health Coverage and Social Protection
   - Strengthen TB Laboratory Services
   - Enhance Supply Chain Management to ensure Uninterrupted supply of quality-assured SLDs
   - Active drug safety monitoring and pharmacovigilance
   - HRH for TB/DR-TB
   - Strategic Information and Research
2. Promote care seeking and TB/DR-TB prevention in the community
   - Targeted and differentiated approach to reach high risk groups
   - Addressing the factors leading to the emergence of MDR-TB
3. Accelerate TB screening and diagnosis including universal DST
   - Targeted systematic screening of population at risk of TB/DR-TB
   - Expand engagement of all care providers in TB diagnostics
   - Increase DST coverage, both First and Second Line Anti-TB Medicines with expansion of quality assured mWRD, DST and TB Culture Lab services
   - Rational triage of patients into DST and the DR-TB control programme
   - Relationship with supranational TB reference laboratory
4. Early treatment of all types of TB including DR-TB with efficacious medicines
   - Treatment with new drugs and regimens in accordance with latest global recommendations
   - Strengthen quality of DR-TB Care services
   - Maximize health outcomes by addressing comorbidities.
   - Empower patients through education, technologies and support.
5. Prevent Infection and Active Disease
   - TB infection and control in healthcare and congregate settings
   - TPT

Summary points

- Drug resistant TB is becoming an emerging global threat.
- Development of either Mono- or poly- resistant TB cases is mainly the result of selective pressure due to repeated treatment with in-adequate regimen.
- Direct and indirect monotherapy are common causes for development of resistance.
- Control of DR-TB costs more and its program implementation is complicated

2. DIAGNOSIS OF DR-TB IN ETHIOPIA

LEARNING OBJECTIVES

By the end of this unit, participants will be able to:

- Describe laboratory methods for diagnosis of cases of Drug resistant-TB
- Identify clinical manifestations of cases of Drug resistant-TB
- Discuss the case finding strategies for DR-TB
- Describe diagnostic algorithms for drug resistant TB diagnosis
- Arrange and utilize TB specimen referral services

INTRODUCTION

The definitive diagnosis of Drug resistant TB is reached on laboratory based confirmation of bacilli that are resistant to treatment with the TB drugs, which require establishing quality assured TB laboratories.

Over recent years, the national program has progressively expanded the national capacity to perform DST by using Xpert machines which also improved the accessibility of FL-DST service to the peripheral health facilities.

With the aim towards a "universal DST" strategy to all T B patients, systematic triaging of all TB patients for drug resistance at time of evaluation for TB diagnosis, and also before or at time of registration for drug Susceptible TB treatment remains to be the main case finding strategy.

Universal DST is defined as universal access to rapid DST for at least rifampicin among all patients with bacteriologically confirmed TB, and further DST for at least fluoroquinolones and second-line injectable agents among all TB patients with rifampicin resistance.

LABORATORY METHODS FOR DIAGNOSIS OF DRUG RESISTANT-TB

Smear Microscopy (ZN/FM): Direct smear microscopy is one of the diagnostic methods for drug-susceptible pulmonary TB. However, it fails to distinguish drug-susceptible from drug- resistant M. Tuberculosis. Therefore, the main uses of direct sputum microscopy in drug- resistant TB are limited to monitoring of treatment response, along with culture and to assess infectiousness of patients.

TB Culture: The current gold standard method for the bacteriological confirmation of TB is culture using commercially available liquid media. However, culture is not used as a primary diagnostic test because of the cost, infrastructure requirements (biosafety level 3 [BSL3] or TB containment laboratory) and long time required to generate results (1–3 weeks for a positive result and up to 6 weeks for a negative result). Nonetheless, conventional culture remain necessary to monitor a patient's response to treatment. It permits detection of a minimum of 10 to 100 viable bacilli per ml of sputum. It allows to perform drug susceptibility testing (DST) for TB from the isolates.

There are two types of TB culture techniques:

- **Solid culture:** Löwenstien-Jensen (LJ) media is culture media which with ease of preparation, low cost, and low contamination rate. Solid culture may take several weeks, 21-42 days, to detect growth and produce results. It is the gold standard for diagnosis of MTB.
- **Liquid culture:** Mycobacterial Growth Indicator Tube (MGIT) is highly enriched media for growing mycobacteria with added 10 % more sensitivity than LJ media, and can produce positive results rapidly. However, the method is prone to higher contamination rate and expensive.

The rapid identification of Mycobacterium tuberculosis complex is done using an immune-chromatographic assay to differentiate MTB from Non-Tuberculosis mycobacterium (NTM) isolates grown on MGIT or LJ AFB medium.

Advantage of Mycobacterial culture:

- Detects small numbers of organisms (as few as 10 bacilli)
- More sensitive (than smear microscopy) in diagnosing TB
- Allows species identification and drug susceptibility testing

Limitations of TB Culture:

- Slow growth of MTB(weeks to months) especially for solid culture media
- High installation and maintenance cost

Drug susceptibility testing (DST): is a technique that is used to screen for susceptibility of the TB bacilli for various Anti-TB drugs using either phenotypic or genotypic means:

a) Phenotypic DST methods:

- The conventional method for detecting resistance to anti-TB drugs relies on culture-based phenotypic DST using liquid or solid media. However, phenotypic testing is time consuming (taking from weeks to months to generate results), primarily because of the slow growth rate of M.tuberculosis. This is often too late to inform therapy, stop the acquisition or spread of additional resistance, or prevent mortality.
- Another issue is that culture-based phenotypic DST requires sophisticated laboratory infrastructure, qualified staff and strict quality control.
- Also, reliable phenotypic DST methods are not available for some first-line and second-line anti-TB drugs, and for certain drugs (e.g. pyrazinamide), it is technically difficult to generate reliable DST results.
- Despite the disadvantages, culture-based phenotypic DST remains essential for those drugs for which there are no reliable molecular tests at present, but for which there are accurate and reproducible phenotypic methods (e.g. Bedaquiline). In addition, phenotypic DST may be needed even for drugs for which there are reliable and accurate molecular tests, if there is a need to investigate discordant results, or to perform further testing in the case of unexpected molecular test results (either resistance or susceptibility).
- Phenotypic DST of M. tuberculosis can be determined either by observation of growth or metabolic inhibition in a medium containing antituberculosis drug. The standard methods using Löwenstein–Jensen medium include the proportion method, the absolute concentration method and the resistant ratio method, which are fairly well standardised with clinical samples, for the major antituberculosis drugs like Rifampicin, Isoniazid (high and low), Ethambutol, Pyrazinamide, Streptomycin, Amikacin, Kanamycin, Capreomycin, Ethionamide, Ofloxacin, Moxifloxacin and levofloxacin.
- Among conventional methods, the proportion method is the most preferred choice; the proportion method calculates the proportion of resistant bacilli present in a strain. Two

appropriate dilutions of the bacilli; 10-2 and 10-4, are inoculated on drug-containing and drug-free media, in order to obtain countable colonies on both media. The ratio of number of colonies observed on the drug-containing media to drug-free medium indicates proportion of resistant bacilli present in the strain. Below a certain proportion (critical proportion = 1%), the strain is classified as sensitive; above, as resistant.

- Growth not more than 14 days old is used for conventional phenotypic DST. The first reading of drug susceptibility test results is done at 4 weeks of incubation. At this time, all strains showing drug resistance can be reported as drug resistant. The last reading of drug susceptibility test results is done at 6 weeks of incubation. Reading at 6 weeks is done because some (especially multidrug-resistant) strains grow very slowly; a further 2 weeks of incubation are needed before reporting susceptibility.

b) Genotypic/ Molecular DST techniques:

- The genotypic methods employ DNA PCR technologies that are specifically designed to detect/confirm genetic mutations associated with drug resistance.
- These techniques produce rapid results if DST is performed directly from sputum samples but may take weeks if done from culture isolates. Their role is mainly limited to diagnostic purpose and cannot help to monitor patient's treatment response as they don't distinguish between live and dead bacilli.
- The techniques may not detect uncommon mutations for which the technique is not designed; hence, are not definitive test to exclude resistance in some patients.
- Molecular tests are not recommended for treatment monitoring.

NATIONALLY RECOMMENDED MOLECULAR RAPID DIAGNOSTICS FOR TB/DR-TB

At present, the national TBL Control Program recommends the following molecular DST techniques for use in Ethiopia (Both Xpert MTB/RIF and LPA tests are currently available in country and there is a plan to introduce the other molecular tests):

- Xpert MTB/RIF Assay and Xpert MTB/RIF Ultra assays,
- Line Probe Assays (GenoType® MTBDRplus and GenoType® MTBDRsl)
- Truenat™ MTB, MTB Plus and MTBRIF Dx tests

Xpert MTB/RIF assay

- The Xpert MTB/RIF assay is a cartridge-based automated test that uses real-time polymerase chain reaction (PCR) on the GeneXpert® platform, to identify MTBC and mutations associated with RIF resistance directly from sputum specimens in less than 2 hours.
- It is fully automated for sample processing, DNA extraction, amplification and detection, making it possible for molecular testing to be implemented closer to the service delivery points with medium level professionals and biosafety precautions similar to AFB microscopy.
- Xpert MTB/RIF assay detects more TB cases in patients likely to be missed by smear microscopy.

The national TBL Control Program recommends using the Xpert MTB/RIF test in the following situations:

- In adults with signs and symptoms of pulmonary TB, Xpert MTB/RIF should be used as an initial diagnostic test for TB and detection of rifampicin resistance rather than smear microscopy/culture and phenotypic drug-susceptibility testing;
- In children with signs and symptoms of pulmonary TB, Xpert MTB/RIF should be used in sputum, gastric aspirate, nasopharyngeal aspirate, or stool specimens as the initial diagnostic test for TB and rifampicin-resistance detection rather than smear microscopy/culture and phenotypic drug-susceptibility testing;
- In adults and children with signs and symptoms of TB meningitis, Xpert MTB/RIF should be used in cerebrospinal fluid (CSF) as an initial diagnostic test for TB meningitis rather than smear microscopy/ culture;
- In adults and children with signs and symptoms of extrapulmonary TB, Xpert MTB/RIF may be used in lymph node aspirate, lymph node biopsy, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid or urine specimens as the initial diagnostic test for the corresponding form of extrapulmonary TB rather than smear microscopy/culture;
- In adults and children with signs and symptoms of extrapulmonary TB, Xpert MTB/RIF should be used for rifampicin-resistance detection rather than culture and phenotypic drug-susceptibility testing;
- In HIV-positive adults and children with signs and symptoms of disseminated TB, Xpert MTB/RIF may be used in blood, as a diagnostic test for disseminated TB.

Table: Advantages and Limitations of Xpert MTB/RIF Assay

Advantages of Xpert MTB/RIF Assay	Limitations of Xpert MTB/RIF Assay
• Simultaneous detection of both *M.tb* and rifampicin resistance • More sensitive to detect *M.tb* even in smear negative cases, especially in HIV positive patients and among children • Useful to confirm diagnosis of TB and RR-TB from extrapulmonary sites • Produce results in two hours • Does not require sophisticated bio-safety precautions	• Requires continuous electrical supply. • It is not designed to detect susceptibility or resistance to H.

Xpert MTB/RIF Ultra assay

- The Xpert MTB/RIF Ultra assay (hereafter called Xpert Ultra) uses the same GeneXpert® platform as the Xpert MTB/RIF test, and was developed to improve the sensitivity and reliability of detection of MTBC and RIF resistance.
- To address sensitivity, Xpert Ultra uses two multicopy amplification targets (IS6110 and IS1081) and a larger PCR reaction chamber; thus, Xpert Ultra has a lower LOD than Xpert MTB/RIF (16 colony forming units [cfu]/mL and 131 cfu/mL, respectively).
- Furthermore, the use of analysis based on melting temperature instead of real-time PCR analysis allows Xpert Ultra to better differentiate silent from resistance-conferring mutations, and minimizes false results on RIF resistance, especially in samples with a low bacterial load.

The Xpert Ultra test is recommended in the following situations:

- In adults with signs and symptoms of pulmonary TB without a prior history of TB or with a remote history of TB treatment (> 5 years since end of treatment), Xpert Ultra should be used as the initial diagnostic test for TB and for rifampicin-resistance detection rather than smear microscopy/culture and phenotypic DST;
- In adults with signs and symptoms of pulmonary TB and a prior history of TB with an end of treatment within the last five years, Xpert Ultra may be used as the initial diagnostic test for TB and for rifampicin-resistance detection rather than smear microscopy/culture and phenotypic DST;
- In children with signs and symptoms of pulmonary TB, Xpert Ultra should be used as the initial diagnostic test for TB rather than smear microscopy/culture in sputum or nasopharyngeal aspirates;
- In adults and children with signs and symptoms of TB meningitis, Xpert Ultra should be used in cerebrospinal fluid (CSF) as an initial diagnostic test for TB meningitis rather than smear microscopy/ culture;
- In adults and children with signs and symptoms of extra-pulmonary TB an Xpert Ultra may be used in lymph node aspirate and lymph node biopsy as the initial diagnostic test for the detection of lymph nodes TB, rather than smear microscopy/culture;
- In adults and children with signs and symptoms of extrapulmonary TB, Xpert Ultra should be used for rifampicin-resistance detection rather than culture and phenotypic drug susceptibility testing;
- In adults with signs and symptoms of pulmonary TB who have an Xpert Ultra trace positive result on the initial test, repeated testing with Ultra may not be used;
- In children with signs and symptoms of pulmonary TB in settings with pretest probability below 5% and an Xpert Ultra negative result on the initial test, repeated testing with Xpert Ultra in sputum or nasopharyngeal aspirate specimens may not be used.
- In children with signs and symptoms of pulmonary TB in settings with pretest probability 5% or more and an Xpert Ultra negative result on the first initial test, repeated one Xpert Ultra test (for a total of two tests) in sputum and nasopharyngeal aspirate specimens may be used.

Truenat MTB, MTB Plus and MTB-RIF Dx assays

- The Truenat MTB and MTB Plus assays use chip-based real-time micro PCR for the semi-quantitative detection of MTBC directly from sputum specimens, and can report results in less than an hour. The assays use automated, battery-operated devices to extract, amplify and detect specific genomic DNA loci.
- The assays are designed to be operated in peripheral laboratories with minimal infrastructure and minimally trained technicians.
- If the MTB or MTB Plus assay result is positive, an aliquot of extracted DNA is run on the Truenat MTBRIF Dx assay to detect mutations associated with RIF resistance.

The use of Truenat MTB, MTB Plus and MTB-RIF Dx tests are recommended in the following situations:

- In adults and children with signs and symptoms of pulmonary TB, the Truenat MTB or MTB Plus may be used as an initial diagnostic test for TB rather than smear microscopy/culture.
- In adults and children with signs and symptoms of pulmonary TB and a Truenat MTB or MTB Plus positive result, Truenat MTB-RIF Dx may be used as an initial test for rifampicin resistance rather than culture and phenotypic DST:
    1. These recommendations apply to the use of the test with sputum specimens from people living with HIV (PLHIV), based on extrapolation of the data on test performance with smear-negative sputum specimens.
    2. These recommendations apply to the use of the test with sputum specimens from children, based on extrapolation of the data from adults, although the test is expected to be less sensitive in children.

Line Probe Assays (LPAs)

- LPAs are a family of DNA strip-based tests that detect mutations associated with drug resistance directly, through binding DNA amplification products (amplicons) to probes targeting the most commonly occurring mutations (MUT probes); or indirectly, inferred by the lack of binding the amplicons to the corresponding wildtype probes.
- First-line LPAs (FL-LPAs) such as GenoType MTBDRplus and NTM+MDRTB Detection Kit allow the detection of resistance to RIF, INH and ETO.

FL-LPAs are recommended in the following situations:

- For persons with a sputum smear-positive specimen or a cultured isolate of MTBC, commercial molecular FL-LPAs may be used as the initial test instead of phenotypic culture-based DST to detect resistance to RIF and INH:
    - These recommendations apply to the use of FL-LPAs for testing smear-positive sputum specimens (direct testing) and cultured isolates of MTBC (indirect testing), from both pulmonary and extrapulmonary sites.
    - These recommendations are particularly important to detect Hr-TB cases among TB patients.
    - Conventional culture-based DST for INH may still be used to evaluate patients when the LPA result does not detect INH resistance. This is particularly important for populations with a high pre-test probability of resistance to INH.
- FL-LPAs are not recommended for the direct testing of sputum smear-negative specimens for the detection of Mycobacterium tuberculosis complex (MTBC).
- Second-line LPAs (SL-LPAs) allow the detection of resistance to FQs and AMK.
- SL-LPAs are recommended for use in the following situations:
    - For patients with confirmed MDR/RR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to FQs and AMK
    - These recommendations apply to the use of SL-LPA for testing sputum specimens, irrespective of the smear status and cultured isolates of MTBC from both pulmonary and extrapulmonary sites.
    - Culture-based phenotypic DST may be useful in evaluating patients with negative SL-LPA results, particularly in populations with a high probability for resistance to FQs or AMK.
    - SL-LPA tests are also useful for detecting FQ resistance before starting therapy for both RR/MDR-TB and Hr-TB.

Advantages and Limitations of LPAs

Advantages	Limitations
○ Performed directly on smear positive sputum samples for FLDs, and from both smear positive and negative samples for SLDs. ○ Rapid test and gives results into 2 days' time when performed on sputum ○ Capacity to perform large volumes of tests per day	○ requires well-trained staff ○ requires at least three rooms in the laboratory ○ Infection control precautions requires sophisticated biosafety level ○ Not suitable for peripheral laboratories

DST SERVICES IN ETHIOPIA:

Xpert MTB/RIF is the preferred method for detecting RR-TB cases considering the suitability for use at peripheral health facility level, the rapid turn-around-time of results, and minimal need for expertise & infection control precautions. However, Line probe Assays and conventional culture and DST techniques will continue to be used at reference laboratories for difficult cases (see table 3.1).

Table 3.1.Options for DST Service in Ethiopia:

DST techniques	Turn-around time		DST results	Recommendation
	MTB Detection	DST		
Xpert MTB/RIF Assays	2 Hours	2 Hours	R-Only	Preferred for use at Health facility level with minimal Biosafety requirements and less experienced professionals
Xpert MTB/RIF Ultra Assay	2 Hours	2 Hours	R-only	Same as Xpert MTB/RIF assay, higher sensitivity and reliability of detection of MTBC and RIF resistance compared to Xpert MTB/RIF Assay. Uses analysis based on melting temperature to differentiate silent and resistance conferring mutations.
FL-LPA	NA	48hrs (smear +ve), 21-42 days (indirect, smear -ve)	R and H	Preferred for use at reference Labs, and when information on H susceptibility is required*.
SL-LPA	NA	48hrs (Direct), 21-42days (Indirect, if invalid	FQs and SL Injectable agents	Preferred for use at reference Labs.
Truenat MTB, MTB Plus and MTB-RIF Dx assays			R-Only	Can be used at peripheral labs
Phenotypic DST from Liquid culture Technique (MGIT system)	8days (smear +ve) 16days (smear –ve)	4 weeks	R,H,E,S, FQ, SLI, Bdq, Lnz, Cs, etc	Preferred for use at Reference Labs
Phenotypic DST from Solid culture Medium (LJ)	16days (smear +ve) 29 days	6 weeks	R,H,E,S, FQ, SLI, Bdq, Lnz, Cs, etc	Preferred for use at reference Labs as gold standard, and when information on full DST

CLINICAL PRESENTATION OF PATIENT WITH DR-TB

Patients with Drug resistant form of TB present with similar clinical manifestations as those with the drug susceptible TB. Cough, fever, weight loss, night sweating etc are the usual clinical presentation.

Moreover, conventional AFB microscopy test or Chest X- ray imaging does not differentiate patients with drug resistant TB from the susceptible form.

Hence, Individuals with presumptive or confirmed diagnosis of Tuberculosis should regularly be evaluated for risk of contracting drug resistant form of Tuberculosis.

Presumptive DR-TB case refers to any presumed or confirmed TB cases with risk for harboring bacilli strains resistant to one or more of the standard TB drugs.

Diagnosis of Drug Resistant Tuberculosis

Case finding strategy of Drug resistant TB relies mainly on systematic identification of patients, either with presumed or diagnosed TB, with increased risk of contracting resistant forms of TB(see table on DR-TB risk), and perform confirmatory laboratory-based first and second line drugs susceptibility testing (DST) for core TB drugs using rapid molecular techniques. Besides, TB program is scaling up the laboratory capacity to ensure universal DST for core drugs at time of diagnosis or registration to treatment.

Diagnosis of resistance to first line TB drugs

Individuals with presumptive or confirmed diagnosis of TB should be evaluated for risk of contracting drug resistant forms of TB. Patients diagnosed to have TB should have their susceptibility information known for at least for Rifampicin and preferably for Isoniazid, using mWRDs (e.g. Xpert MTB/RIF assays) or FL-LPA to ensure effectiveness of the treatment regimen.

TB patients with extra-pulmonary sites involvement should also be assessed for risk of drug resistant TB and appropriate specimen should be obtained for DST whenever possible.

First Line DST is recommended for

- Presumptive/confirmed TB patients with prior TB treatment history for one or more month
- Patients with presumed or confirmed TB with contact history with RR/MDR-TB
- Presumptive TB in patients from health care settings or congregated settings or other known high MDR-TB prevalent settings
- TB patients who remain smear positive at end of second months or later on TB treatment.
- All bacteriologically confirmed TB patients at time of registration to TB treatment if not done as initial diagnosis.
- FL-DST including for INH using FL-LPA or Trunat is also indicated for all TB patients who are smear positive at the end of second month of treatment or later and in whom RIF resistance is ruled out (see section under Hr-TB for details). The tests are also indicated for all presumptive TB cases or confirmed TB cases who are close contacts of confirmed Hr-TB cases.

If the patient meets the criteria for the risk of drug resistant TB, Rapid DST techniques with Xpert should be performed to screen at least for Rifampicin resistance (see National algorithm below):

Table 2.1. Approach in the management of presumptive DR-TB cases based on risk level and availability of FL-DST results:

Risk for DR TB	Risk group	Action
High risk (40-80%)	• Failure after 2nd course of TB treatment • Symptomatic close contacts of confirmed/presumed DR TB case • Failure after treatment for INH resistant TB	• Perform rapid DST/GeneXpert • If not clinically stable, consider RR/MDR-TB treatment regimen by the MDR TB panel team decision while awaiting DST
	• Failure of new TB	• If clinically stable, wait for DST Result • If DST result Delays > 1 week restart FLD. • If not clinically stable, consider SLD treatment by the MDR TB panel team decision while awaiting DST,
Medium risk (10-20%)	• Relapse(including repeated episodes of Relapse) • Return after lost to follow up • Sputum smear positive at the end of 2nd month of TB treatment • 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 with Xpert • Wait the DST result for a maximum of one week if patient is stable, • Treat with first line anti-TB regimen if clinically not stable till DST result is available

	• Patient receiving inadequate TB treatment outside of TB program such referred from abroad or private sector outside of PPM sites • Other previously treated case (EPTB, clinically diagnosed cases)	

Diagnosis of resistance to Second line anti-TB drugs

- All confirmed RR-TB or MDR-TB patient require baseline DST for SLDs at least for FQs using molecular DST techniques from sputum collected before or within one week of treatment with second line TB regimen.
- In addition, RR-/MDR-TB patients may require second line DST during the course of second line treatment based on the response to second line treatment.
- SL-LPA is nationally recommended initial screening test for resistance to the core second line drugs using the national algorithm for RR/MDRTB patients.

Second line DST is recommended under the following conditions:

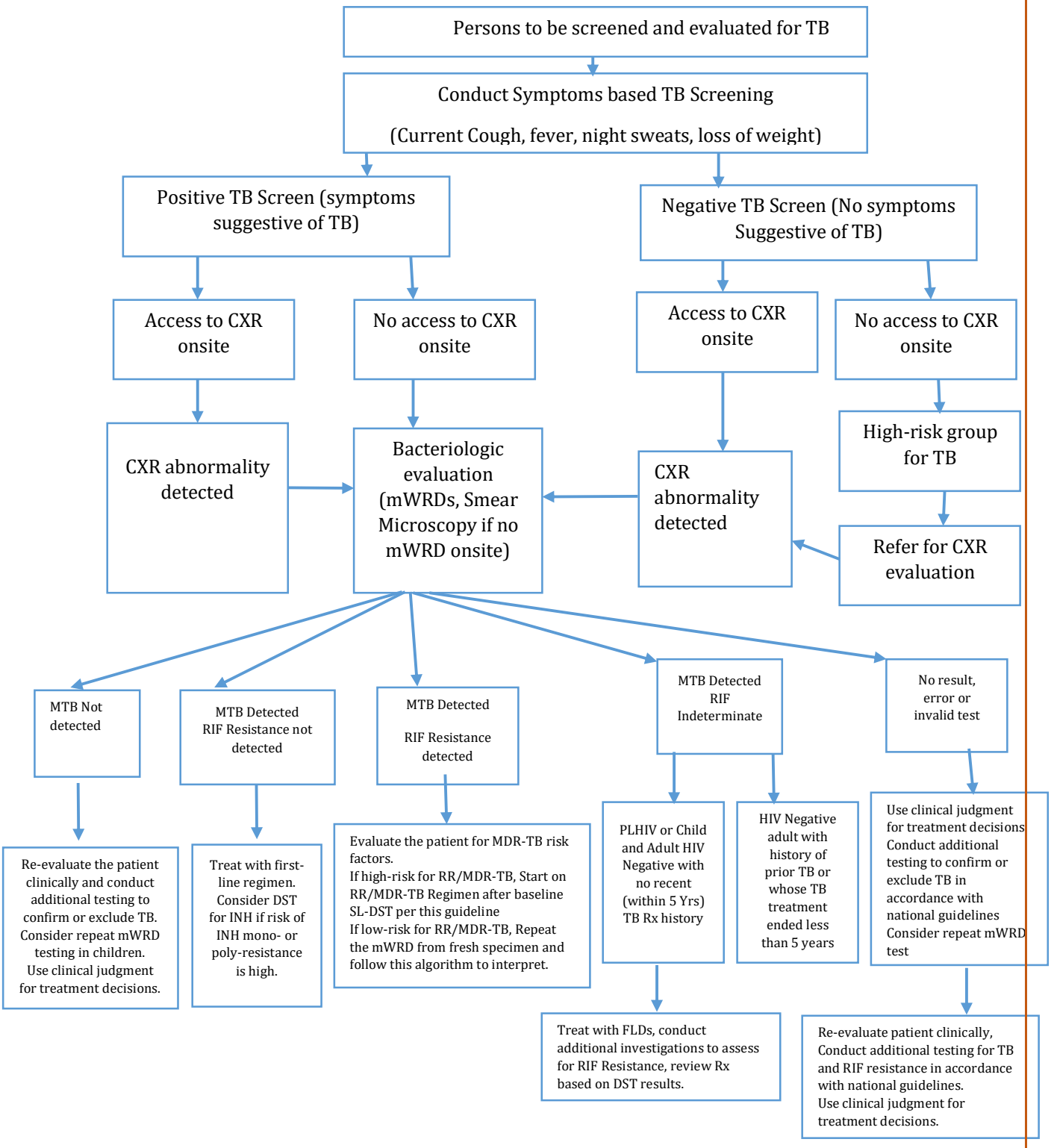
- All bacteriologically confirmed RR/MDR-TB patient at baseline, before initiation of RR/MDR-TB regimens
- All Hr-TB patients at baseline, before initiation of treatment.
- Confirmed TB patients who are contacts of patients with documented RR/MDR-TB
- Symptomatic contacts of patients with documented RR/MDR-TB
- Smear/culture positivity at the end of 4th month of treatment or later for patients on RR/MDR-TB regimens
- Smear/culture reversion to positive after initial conversion in a patient on RR/MDR-TB Regimen.
- Patient in whom the current SL regimen is seriously compromised because of drug intolerance
- All patients being evaluated for treatment after loss to follow up from RR/MDR-TB regimens for more than one month.
- All RR/MDR-TB patients coming from areas with high rates of second line drug resistance or unfavorable treatment outcomes
- All RR/MDR-TB patients with clinical and radiological deterioration/none-response despite adequate RR/MDR-TB regimens

NATIONAL TB/DR-TB DIAGNOSTIC POLICIES AND ALGORITHMS FOR TUBERCULOSIS

Rational use of TB diagnostics and drug susceptibility tests for TB drugs should consider the potential benefits of the test and patient-centeredness. The national algorithm for TB diagnosis, drug susceptibility testing and patient management expresses the following policy recommendations:

- All presumptive pulmonary TB cases should submit sputum for bacteriologic examination with Xpert MTB/RIF assay or sputum microscopy.
- If Xpert service is accessible on same day, Xpert MTB/RIF test is recommended as the initial diagnostic test for all persons with presumptive TB.
- If Xpert service is not readily available on same day, sputum microscopy should be used the primary diagnostic test for tuberculosis in the interim to avoid diagnostic delay. In the meantime, a sputum specimen should be sent for Xpert testing for Eligible populations group including HIV positives, children, and previously treated or other DR-TB risk group patients to detect additional cases of TB and/or screen for possible RR-TB.
- All individual diagnosed with TB should undergo drug resistance screening test at least for rifampicin at baseline using rapid DST technique preferably by Xpert or FL- LPA.
- Patients with unexplained finding on CXR should submit sputum for confirmatory test preferably by X-pert MTB/RIF test.
- For all patients with confirmed RR/MDRTB, send sputum for SL-DST using LPA for core Second line drugs before or within one week of treatment initiation with DRTB regimen.
- DR-TB Patients with reported resistance on SL-LPA, also need culture and phenotypic DST.
- In patients in whom the diagnosis of TB remains in doubt despite negative results on AFB and/or Xpert tests; additional investigations may be performed as needed.
- Individuals with presumptive or confirmed TB should be offered rapid HIV test.

Figure 2.1: National TB/DR-TB Diagnostic algorithm in Ethiopia



Interpretation of sputum results:

Interpretation of test results and decision to treat for TB should be made carefully to avoid mismanagement.

1. Results of Sputum AFB microscopy:

a) When Sputum microscopy shows one or two positive AFB results:

- Register the patient as bacteriologic confirmed TB cases, and initiate first line anti-TB
- Collect and refer sputum specimen for GeneXpert MTB/RIF testing or other molecular DST

b) When Sputum microscopy report says two negative AFB results:

- Collect and refer sputum specimen for GeneXpert MTB/RIF testing or other molecular WRDs (mWRDs).
- Give broad spectrum antimicrobials treatment while awaiting Xpert MTB/RIF test results
- Follow results of the Xpert MTB/RIF test or other mWRDs and decide based on results
- Re-evaluate patient after 10-14 days: If the Patient improves; rule out TB
- If the patient did not improve and diagnosis remains in doubt: consider repeat Xpert MTB/RIF test, conduct additional testing (CXR if not done already, pathology), consult experienced clinicians and decide based on clinical parameters.

2. Results of Xpert MTB/RIF Assay:

a) When Xpert MTB/RIF detects MTB without RIF resistance:

- Start or continue patient on first line Anti-TB regimen

b) When Xpert MTB/RIF detects MTB with Rifampicin resistance:

- If Patients carry high or moderate risk for MDR-TB; Link the patient to TIC, register as Bacteriologically confirmed RR-TB, and start on Nationally recommended regimen for RR-TB; Send sputum for DST for core SLDs
- If RR-TB is reported in a patient considered to have low risk for DR-TB (i.e. below 5% risk of acquiring RR-TB); repeat Xpert MTB/RIF test immediately or refer the patient to the nearby TIC to avoid delay in the initiation of effective treatment;
    - if repeat test result shows RR TB again, treat with Second line drug;

- If second test result shows MTB but susceptibility to Rifampicin, treat with FLDs; monitor response Clinically & Bacteriologically. Culture & DST for discordant results if available.

c) When Xpert MTB/RIF does not detect MTB:

- If patient is seriously sick or HIV positive or TB diagnosis is still in doubt; refer to hospital for further investigation with CXR, ESR, histopathology
- Consider repeat Xpert MTB/RIF test
- Use opinion of a senior clinician to decide on ―clinical diagnosis of TB‖ and treatment with full course of anti-TB,
- Antibiotic trial is not recommended in HIV positives and under-five children

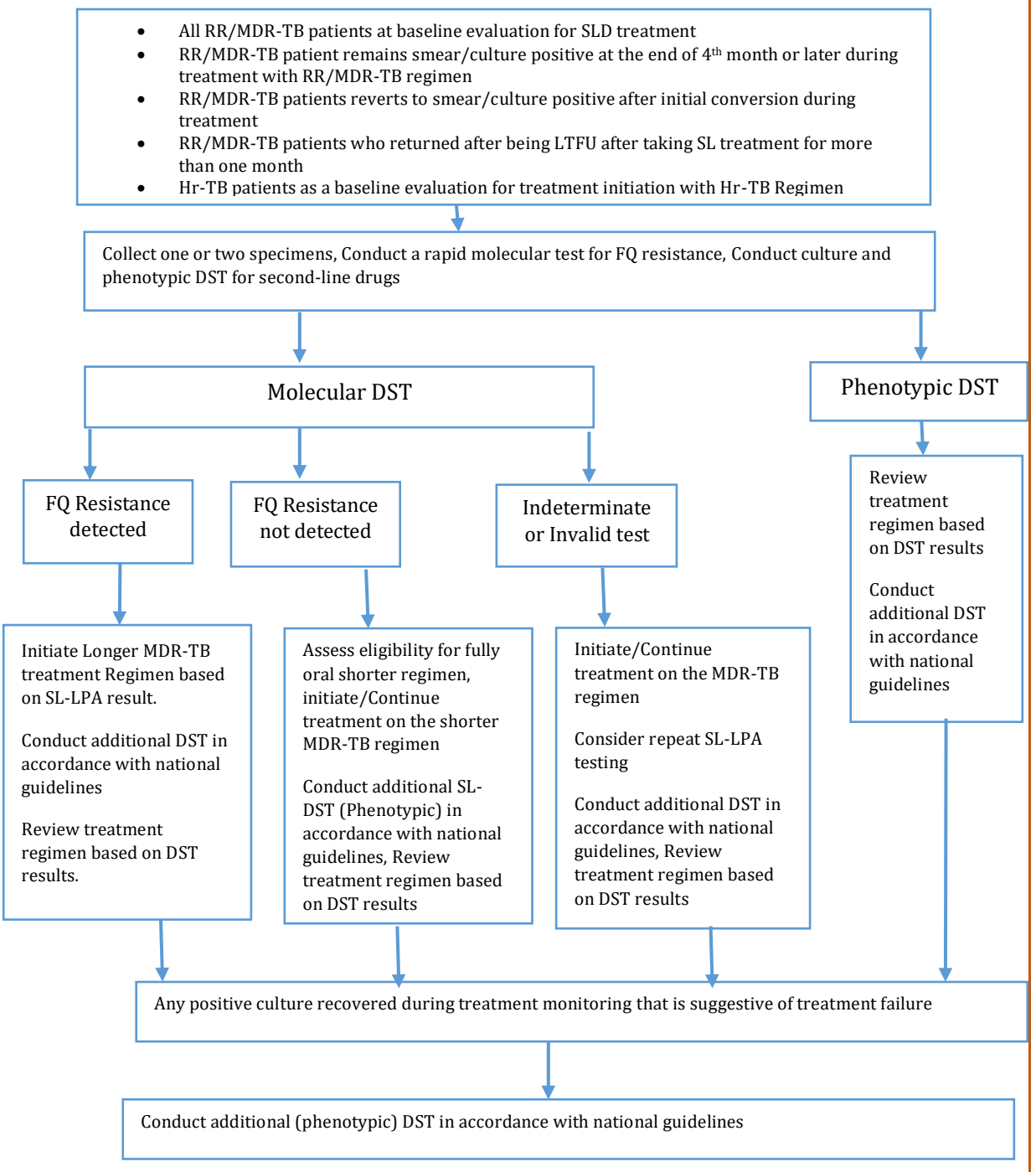
d) When Xpert MTB/RIF tests become invalid/ error/ indeterminate:

- Repeat Xpert test on fresh sample (spot/morning) and decide based on the second result.

e) When Xpert MTB/RIF shows MTB but RR indeterminate result:

- Repeat the Xpert on fresh morning sample.

National Algorithm for DST for SLDs among RR/MDR-TB Patients



DIAGNOSIS OF DR-TB IN CHILDREN:

DR-TB case-finding strategy for children mainly relies on the systematic contact tracing and 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 intensive phase of treatment
    - History of previous TB treatment interruption, treatment failure or retreatment case or
    - History of contact with a TB patient who has poor outcome

ii. Features in a child suggestive of having drug resistant TB
    - Contact with a known case of MDR-TB
    - Failure to improve clinically after intensive phase of FLD treatment despite good adherence, including persistent smear positivity, persistence of symptoms, and failure to gain weight
    - Child with TB recurrence after completing TB treatment

When DR-TB is suspected, every effort should be made to confirm diagnosis by obtaining specimens for culture and drug susceptibility testing (DST).

In all cases of confirmed RR/MDR-TB, second line DST should be performed to exclude FQ Resistance and to help establish an effective treatment regimen.

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 and confirmation of Drug resistant TB among presumptive cases using nationally recommended diagnostic algorithms.

Opportunities to detect presumptive cases of DR TB:

All attempts must be made not to miss opportunities to identify TB cases who are also presumed MDRTB cases. Table presents opportunities to identify presumed DR TB and send sample DST.

Opportunity	**Action to be taken**
At time of clinical evaluation at outpatient/inpatient departments	Assess all presumptive TB cases for risk of DR-TB: - previous TB treatment history, - History of close contact with DR-TB patient, and - Assessment of socio-demographic factors.
At time of patient preparation and registration and treatment initiation	Check all diagnosed TB patients for DST eligibility as per national guidance
At time of recording of follow up results	Make sure all smear positive results during treatment warrants attention and DST
At time of treatment outcome Evaluation	Remember that failure cases carry high risk for DRTB and require urgent DST
During supportive supervision	Check that DST is performed for all Eligible and results are communicated, and patients are linked up or managed as per the national guidance.

Collection and referral of specimen:

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 the national Standard procedure for biological transport (See SOP for sample collection and referral Annex 6).

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,

Filling out the TB laboratory request form

Culture and DST request form, see below, to be used to request for either diagnostic or follow culture and DST or DST alone. The section above the solid horizontal line is to be filled by the requesting HCW while the part below the solid line will be filled by lab professionals at culture and DST center. Note that, not filling out this request properly may results in loss or delay of results, failure to capture information at laboratory and failure of prompt initiation of DR-TB.

Task: Please review the TB Lab Request forms.

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 possible to avoid delay. SMS printer machines, SMS messages, emails, or postal system can be applied to minimize the turnaround time of results and expedite the treatment decision. The laboratory, together with the TB program, has to arrange reliable and fast mechanism to return results to the provider.

DR-TB PATIENT REFERRAL AND LINKAGE TO DR-TB TREATMENT CENTERS

Once the confirmatory DST result is received, 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
- Basic information on the nature of the disease,
- Treatment modality and duration of treatment, and
- Inform and Arrange linkage with the nearest TIC

RECORDING PRESUMPTIVE DR-TB CASES AND TREATMENT OUTCOMES

Presumptive DR-TB cases identified from the TB unit register should be recorded on either the remark column or in the dedicated column for recoding of DST screening results.

Defining treatment outcome will depend on months of treatment completed when diagnosis of RR/MDR/XDR-TB is made. The outcome will be assigned as:

- Moved to MDR-TB register if the patient has completed less than 5 months of TB treatment with first line Anti-TB.
- Failure if the patient found to harbor RR or MDR-TB after completion of the fifth months of Anti-TB treatment. However, some patients may have other outcomes e.g. died or defaulted prior to the DST result being available. Those would be left unchanged.

Summary points

- All Presumptive TB with same day access to Xpert result, Presumed DR-TB and confirmed TB cases in facilities with no same day access to Xpert result has to be evaluated for Drug resistance
- Universal DST (at least for Rifampicin among all bacteriologically confirmed TB cases and SL-DST at least for FQs among all RR/MDR-TB cases) needs to be implemented
- HCW must use different opportunities to identify and screen cases who are suspected to have DR-TB
- DR-TB algorithms should be followed in all Health facilities to diagnose DR-TB cases
- Rapid molecular techniques for DST must be opted for screening of drug resistance.
- Whenever accessible use Xpert MTB/RIF test for screening for drug susceptibility
- If sample is to be sent to testing site, follow the SOP for Sample collection, packing and transporting(See Annex 4)
- Turnaround time (TATs) needs to be determined for all samples sent to testing sites and all testing sites are required to adhere to the TATs.

- Linkage of confirmed DR-TB case must be ensured at all levels of care
- All confirmed DR-TB cases should start treatment with the appropriate RR/MDR-TB regimen without delay.
- Linking confirmed DR-TB cases is the joint responsibility of the sender and the diagnostic sites, and the respective TB program officer.

Case Studies

- Do Part I: Identification of Presumptive DRTB
- Instruction: Use the case booklet.
- Time allocated: 30 minutes

3. DR-TB CONTACTS INVESTIGATION AND MANAGEMENT

LEARNING OBJECTIVES:

By end of this module, participants are expected to:

- Identify definitions of terminologies for contact management
- investigate Symptomatic DR TB household contacts
- manage DR TB Contacts as per national protocol

INTRODUCTION AND DEFINITION O F TERMS

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 systematic reviews in 2012 WHO 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.

Definition 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.

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.

IDENTIFICATION AND MANAGEMENT OF CONTACTS O F DR-TB CASES

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 RR/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 RR/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.

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

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

A household contact with any symptoms suggestive of active TB should receive all of the following:

- Evaluation by a physician, including history and physical examination.
- Chest X-ray to look for signs of active TB (e.g., infiltrates, cavities) or inactive TB (e.g., scarring, granulomas).
    - 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.

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

- Bacteriological investigations of sputum or other samples:
  - Xpert MTB/RIF is the recommended initial diagnostic test because it provides diagnosis of TB and MDR-TB rapidly.
  - Culture and DST may be sent if Xpert MTB/RIF is negative and suspicion of active TB or MDR-TB remains high.

Management of Symptomatic Contacts

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

- Household contacts of MDR-TB patients who develop active TB 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.
- If rapid molecular DST is not available, household contacts with active TB 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 (EPTB)

- EPTB 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.
- 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.

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**, special 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.*

3 .4 CHEMOPROPHYLAXIS OF CONTACTS O F 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 every 3month for a period of at least two year.

In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification. Preventive therapy can be considered in the following high risk household contacts of MDR-TB index patients after careful consideration of cons and pros as per the following parameters: capacity to rule out active TB, capacity to perform (have access to) quality-assured testing for drug susceptibility (in the presumed source case), capacity to deliver the necessary medications and to monitor closely for adverse events and for the emergence of active disease.

Preventive treatment for MDR-TB requires a different approach using a fluoroquinolone or other second-line agents. The regimen of preventive treatment of MDR-TB contacts should be individualized and based on reliable information on the drug resistance profile of the presumed source. Later-generation fluoroquinolones (e.g. levofloxacin or moxifloxacin) may be used unless the strain of the presumed source shows resistance to these medicines. Pediatric formulations of levofloxacin can be used for this purpose. For strains showing additional resistance, other treatment regimens may be used based on local studies and literature review.

Contacts of people with rifampicin-resistant TB (RR-TB) are usually treated as for MDR-TB unless isoniazid-susceptibility in the index case is reliably confirmed, in which case IPT may be effective.

4. DEFINITION OF TERMS AND PATIENT REGISTRATION

LEARNING OBJECTIVES

By the end the session participants will be able to:

- Classify and categorize DRTB patients in a standardized fashion
- Assign patients to appropriate registration group
- Assign the MDR-TB patient into standardized treatment outcome

CASE DEFINITIONS

The definitions below are based on the level of certainty of the diagnosis and on whether or not laboratory confirmation is available and based on susceptibly status to standard TB drugs on DST:

i) Case definitions for Drug susceptible TB

Presumptive Tuberculosis case: Any person who presents with symptoms and/or signs suggestive of tuberculosis, in particular cough of two weeks or more duration is a presumed TB case. The most common symptom of pulmonary TB is a productive cough for more than 2 weeks, which may be accompanied by other respiratory symptoms (shortness of breath, chest pains, and hemoptysis) and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats, and fatigue).

Case of tuberculosis: refers to a patient in whom TB has been bacteriologically confirmed or diagnosed by a clinician decision:

ii) Case definitions for Drug resistant TB:

- **Presumptive DR-TB case:** refers to a person who presents with clinical features suggestive of TB or diagnosis of active TB and with known risk to harbor Drug resistant TB.
- **Bacteriologically confirmed DR-TB**: refers to those cases with documented laboratory DST (phenotypic or molecular) results for DR-TB or Rifampicin Resistant TB.
- **Clinically diagnosed DR-TB case**: refers to a person who is diagnosed to have DR-TB without documented DST result but the clinical panel team decided to empirically treat with SLD regimen. Mainly reserved for children as obtain specimen is not feasible.

CLASSIFICATION OF TB

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

i) Anatomical site of disease
ii) History of previous treatment
iii) Drug Resistance, and
iv) HIV status of the patient.

Anatomical site of TB disease

Pulmonary tuberculosis (PTB): refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. A patient with both pulmonary and extra pulmonary TB should be classified as a case of PTB.

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

Case definition of an EPTB case with more than one site affected will be based the site that carry the most severe form of disease.

History of previous treatment:

New: patients have never been treated for TB or have taken anti-TB drugs for less than 1 month.
Previously treated: patients who have received anti-TB drugs for one or more months in the past, again diagnosed with Tuberculosis.

Drug Resistance

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

Rifampicin resistant TB: resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs.

Multidrug-resistance (MDR): resistance to at least isoniazid and rifampicin.

Pre-XDR TB: resistance to at least one of the second line injectable or any of the fluoroquinolones.

Extensive drug-resistance (XDR): Resistance to isoniazid and rifampicin (i.e. MDR) as well as any fluoroquinolone, and any of the second line injectable Anti TB drugs (capreomycin, kanamycin, and amikacin).

HIV status of a Patient

HIV-positive TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB with documented evidence of HIV infection.

HIV-negative TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB with documented evidence of HIV negative result.

HIV status unknown TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrolment in HIV care.

REGISTRATION GROUP FOR DR TB PATIENT

New TB: patients that have never been treated for TB or have taken anti-TB drugs for less than 1 month.

Relapse: patients who were declared cured or treatment completed at the end of their most recent treatment course and is now diagnosed with a recurrent episode of TB regardless of duration.

Treatment after failure: refers to patients who came back for treatment after declared treatment failure in their most recent treatment course, as defined by the national guideline.

Treatment after loss to follow-up: refers to patients who were declared lost to follow-up at the end of their most recent course of TB treatment and is now decided to be treated with full course of TB treatment.

Others: refers to patients who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented, or patients that do not fit into any of the categories listed above.

Transfer in: A patient who is transferred to continue treatment at a given reporting unit after starting treatment in another reporting unit.

TB TREATMENT OUTCOME

The final result of treatment outcome of TB patients should be defined and recorded in the space provided on treatment register. These outcomes are mutually exclusive and only one outcome should be assigned to one per patient.

Definitions of treatment outcome for DR TB

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 or during the last 12 months of treatment for patients on longer regimens.
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 or during the last 12 months of treatment for patients on longer regimens.
Treatment failure	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
Died	A patient who dies for any reason during the course of TB treatment.
Lost to follow up(LTFU)	A patient who Started Anti-TB Treatment and Interrupted for 2 Consecutive months or more.
Not Evaluated	A TB patient for whom no treatment outcome is assigned. This includes transferred out cases with unknown outcome at reporting unit.
Moved to XDR-TB*	TB Patients who were found to have RR-TB or MDR-TB before end of intensive phase of treatment and who were moved to regimen beyond the standard RR/MDR TB regimen.

***Remark**: *This outcome definition might not be applicable with the current regimen changes*.

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 back to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. The purpose of defining treatment failed, reversion is considered only when it occurs in the continuation phase.

5 TREATMENT OF DRUG RESISTANT TUBERCULOSIS

LEARNING OBJECTIVES

By the end of this unit, participants will be able to:

- Assess and prepare patient for treatment
- Apply the principles of good chronic care in DR TB management
- Describe principles of DR-TB treatment
- Identify the national standard MDR-TB Treatment regimen
- Manage MDR-TB in especial conditions
- Management of MDR-TB and HIV co-infection
- Manage MDRTB in children

PRETREATMENT SCREENING AND PATIENT PREPARATION

PRE-TREATMENT EVALUATION

The pretreatment evaluation should include a thorough medical history, physical examination, and laboratory investigations:

Pre-treatment clinical history and assessment should be systematically conducted for each and every patient with RR-/MDR-TB diagnosis in order to develop a comprehensive individual care plan by determining/screening for:

- Details of past TB treatment and/or contact history with TB patients, if any
- The risk levels for acquiring additional resistances or developing treatment intolerance or, unfavorable treatment outcomes
- Baseline clinical and laboratory profiles to guide subsequent treatment monitoring
- Potential adherence, psychosocial and economic barriers
- Presence of co-existing or undiagnosed especial situations and co-morbid conditions that might affect the choice of initial treatment regimen and other important management decisions: HIV infection, Diabetes mellitus, Hypertension, cardiac conditions, renal insufficiency, chronic liver diseases, Thyroid diseases, Mental and seizure disorder, Drug or alcohol dependence, or Pregnancy etc.

Baseline laboratory and Clinical tests: All RR-/MDR-TB patients starting treatment should have the following tests:

- Sputum smear, culture, and SL-DST.
- Baseline potassium, renal function test, and liver function tests.
- Baseline audiometry
- ECG
- Visual Acuity and Color blindness tests
- Brief Peripheral Neuropathy Screen
- HIV rapid testing.
- Pregnancy test for women of child-bearing age.
- Thyroid-stimulating hormone (TSH).
- CBC
- Chest x-ray
- Serum Albumin

Patients co-infected with HIV should have additional tests:

- CD4 cell count (CD4 percent in children).
- HIV viral load testing
- See table on treatment response monitoring schedule

Patient Registration

Patients will be registered according to the standardized case definitions in the registration form and treatment card. Registration of the patient should include details of the patients and the treatment supporters' addresses. This is to be used for subsequent patient follow up and tracing.

Patient Counseling and adherence initiation

Patients should be counseled to understand the nature of the disease, its transmission and the treatment. Importance of treatment adherence for favorable outcome should be emphasized. It is also important to address the issues raised by the patient including the psychosocial conditions.

All the necessary information should be given to the patient with proper health education.

Patient education

The following are key elements of health education for MDR-TB patients:

- Nature of his/her illness (TB and MDR-TB)
- Mechanism of transmission; the need to evaluate contacts, and prevention of further spread.
- Medications and duration of treatment; expected follow up visits including necessary laboratory and radiological monitoring.
- Importance of adherence to treatment until completion.
- Importance of HIV testing and the implication of confection on treatment approach
- Information not to share medications, appropriate storage of medications.
- Expected drug side effects and their manifestations; availability of treatment to treat side effects, whom to report when such manifestations occur
- Implications if there is pregnancy and contraception (for women in child bearing age)
- Expectations from the treatment.
- Rights of the patient in relation to his/her treatment.
- All services related to the treatment of his/her illness (MDR TB) are free.
- Responsibilities of the patient including providing information on accurate contact details.
- Where to contact for his social problems and any information needed (provide information brochure, if any).

Principle of Good chronic care

Use the general principles of good chronic care

1. Develop a treatment partnership with your patient
2. Focus on your patients concerns and priorities
3. Use the 5 A's - Assess, Advise, Agree, Assist, Arrange
4. Support the patient education and self-management
5. Organize proactive follow-up
6. Involve "expert patients", peer educators and support staff at your health facility.
7. Link the patient to community-based resources and support
8. Use written information—registers, treatment plans, the patient calendars, treatment cards—to document, monitor, and remind
9. Work as a clinical team (and hold team meetings)

Adherence counseling with 5A's

The 5 A's of counseling are series of steps that can be used in adherence counseling of MDR TB patients. It has been shown that patients do better if their health worker or provider follows this process.

ASSESS: Questions asked initially about

- The patients understanding of anti-TB drug resistance, and how he/she developed DR-TB;
- His/her understanding of MDR-TB therapy;
- Whether the patient has demonstrated an ability to keep appointments, and to adhere to other medications;
- Whether the patient knows his/her HIV serostatus.
- Psychosocial and behavioral barriers of adherence (mental illness, substance abuse)

Example: "What do you know about drug resistance tuberculosis and its treatment?"

ADVISE: Information and recommendations given about their illness, coping mechanisms, treatment and adherence:

- Using non-judgmental language to give correct information about their illness
- Telling the benefits of treatments adherence
- Providing options for mechanisms of improving adherence

Example:

- Drug-resistant TB
  - is created when TB patients do not take anti-TB drugs regularly;
  - can be transmitted to family and friends;
  - Can be easily transmitted to people living with HIV.
- Offer HIV testing if the patient does not know their sero-status.
- Second-line anti-TB drugs must be taken regularly as per the recommendations of the treating physician. If not, there is a high chance that treatment may fail.
- The currently available SLD are the only option for treatment of MDR TB.
- Second-line anti-TB drugs have many adverse-effects, but these can be managed. The patients need to report any new feelings and inconveniences to the health worker and
- Advice on life style modification to avoid barriers to adherence – e.g. psychosocial or behavioral

AGREE: Consensus made between the health worker and the patient on the future steps to:

- Comply with the treatment schedule
- agree on the strategies that the patient prefers for his/her adherence

Examples: agree

- That the patient is willing to undergo full course of treatment with second-line anti-TB drugs;
- That the patient is willing to receive directly observed therapy;
- On who will observe the therapy? Community TB treatment supporter or a health worker at a nearby facility?
- That the patient is willing to come monthly to the MDR-TB initiating center clinic for follow-up.

ASSIST: Discussions made about how to manage difficulties by:

- Providing written information such as pamphlets and leaflets on MDR-TB treatment
- Predicting possible barriers to implement their plans
- Linking to available support

Example:

- By discussing how taking medications can be integrated into work and home routines;
- By giving food packages if needed;
- By giving support for transportation. If the patient lives in a remote area, discuss options such the patient moving closer to the clinic for a period of time;
- By referring the patient to an MDR-TB therapeutic support group

ARRANGE: Actions that the health worker takes, such as arranging another appointment, referring to care and support services, giving ancillary medications, and recording to:

- Arrange follow-up appointments
- Link to support groups
- Record what happened during the visit

Example: arrange

- For injections to be given at the health center nearest to the patient's home;
- To educate the treatment supporter about MDR-TB and how to observe MDR-TB therapy

TREATMENT OF DRUG RESISTANT TUBERCULOSIS

Learning Objectives

By the end of this session, participants will be able to:

- Describe principles of designing DR-TB treatment regimen
- Discuss DR-TB treatment regimens in Ethiopia
- Identify treatment recommendations in different conditions
- Monitor Treatment and follow up of DR-TB patient.

Now Discuss about TB drugs using the Medication factsheet on the Annex 1 for 10minutes

Principles of Drug resistant Tuberculosis treatment:

- Detect RR-/MDR-TB early and initiate effective treatment promptly,
- RR/MDR-TB diagnosis must be confirmed for rifampicin and if possible for isoniazid using rapid molecular DST techniques, to initiate treatment consisting of second line medicines,
- Bacteriologically confirmed RR/MDRTB TB patients are recommended to have baseline screening DST for core-second lines medicines, fluoroquinolones and injectable second line- Line probe Assay (SL-LPA),
- Pulmonary RR/MDR TB patients must submit sputum specimen for SL-LPA before or within seven days of treatment initiation with DR-TB treatment,
- SL-LPA must be performed directly from the sputum specimen,
- Never add a single TB medicine for TB patients receiving likely failing regimen,
- Any patient – child or adult – with RR/MDR-TB be treated with the recommended MDR- TB treatment regimen, either a longer regimen or a all oral Bdq containing regimen,
- In MDR/RR-TB patients who have not been previously treated for more than 1 month with second-line medicines used in the shorter MDR-TB regimen or in whom resistance to fluoroquinolones has been excluded, a shorter MDR- TB regimen of 9–12 months may be used instead of the longer regimens,
- Individualized regimen for eligible patients should be constructed at the level of clinical panel team in consultation with the national/regional clinical review committee (CRC).

- Develop comprehensive individual care plan in consultation with the patient and care takers, by identifying potential medical, psycho-social and economic barriers,
- Avoid or cautiously use drug(s) with known contraindication such as known drug-drug interactions, overlapping toxicities, history of severe allergy and/or pregnancy,
- Surgical interventions, as complimentary to chemotherapy, should be considered when indicated,
- For RR-/MDR-TB patients with documented HIV co-infection, initiate antiretroviral therapy upon tolerating anti-tuberculosis treatment as early as possible within 8 weeks period,
- Ambulatory model of care is recommended approach except for those with severe diseases and/or complication warranting in-patient care.

Nationally Recommended DR-TB treatment regimens in Ethiopia:

1. All-Oral Bedaquiline Containing Shorter MDR/RR-TB Regimen

2. All-Oral Longer MDR/RR-TB Treatment Regimen

3. Individualized longer treatment regimen (ITR):

4. Regimen for isoniazid-resistant TB

Table 5.1 Suggested MDR/RR-TB Regimen composition:

Regimen type	Regimen composition	Remarks on use
Shorter all-oral bedaquiline-containing RR/MDR-TB regimen	4–6 Bdq(6 m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto / 5 Lfx/Mfx-Cfz-Z-E	-Recommended for eligible patients -Add pyridoxine (VB6)
Longer regimen for MDR/RR-TB:	18 Bdq(6 m)-Lfx/Mfx-Lzd-Cfz-Cs	-Recommended for patients not eligible for full oral shorter regimen -Add pyridoxine (VB6)
Regimen for isoniazid-resistant TB	6 (H)REZ-Lfx	-Lfx is recommended for 6 month in any case -Add pyridoxine (VB6)
Individualized longer LTR, 18-20 months, but could be extended up to 24 months ***	At least 4-5 likely effective drugs can be used based on the drug availability and CRC decision.	Recommended when construction of all oral shorter regimen and all oral longer regimen with at least 3 group A and 2 group B drugs is not possible due to intolerance to

		the medicines, acquired additional resistance, any contra indication

** Due to potential side effects with Lzd and potential unknown FQ resistance at initiation of treatment (due to delay in getting the SL LPA result), Cs is routinely included at the start of treatment in the all-oral longer regimen.*

***Bdq is recommended for a total duration of 6 months, however, could be extended depending on the patient condition & clinician decision (off-label use),*

**** The individualized LTR composition depends on whether each of the medicines in the list could be used as an effective drug based on reliable DST result or likelihood of effectiveness as well as intolerance*

The shorter all-oral bedaquiline-containing regimen for MDR/RR-TB

Recommendation:

- A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed MDR/RR-TB who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month and in whom resistance to fluoroquinolones has been excluded.

Eligibility Criteria for shorter all-oral Bedaquiline contacting RR/MDR TB

When deciding whether the shorter all-oral bedaquiline-containing MDR-TB regimen can be offered, several eligibility criteria need to be considered.

The regimen is recommended for patients with confirmed MDR/RR-TB (with at least confirmed resistance to rifampicin), for whom resistance to fluoroquinolones has been ruled out, in the following situations:

- No resistance or suspected ineffectiveness of a medicine in the shorter regimen (except isoniazid resistance determined by phenotypic DST or mutations in either inhA or katG genes (not both). The presence of mutations in both the inhA promoter and katG suggests that isoniazid at high dose and thioamides are not effective, and that the shorter regimen should not therefore be used);
- No exposure to previous treatment with second-line medicines in the regimen for more than 1 month (unless susceptibility to these medicines is confirmed);

- No extensive TB disease and no severe extra-pulmonary TB;
- Not pregnant;
- Children 6 years old and above.

The decision on which regimen offers the best option for cure in a patient may also depend on other considerations (e.g. preferences of patients and clinicians). If the shorter all-oral bedaquiline-containing MDR-TB regimen cannot be used, the patient needs to be reassessed for a longer all-oral MDR-TB regimen. The health care provider may opt for a longer all-oral treatment regimen even in patients who are eligible for the shorter all-oral bedaquiline containing MDR-TB regimen. This could be motivated by uncertainty about drug susceptibility while the patient's condition requires an immediate start of treatment and cannot wait for DST results.

Assessment of extent of TB disease:

Extent of TB disease is important to determine the regimen options, in addition to the DST and other considerations mentioned above.

Extensive TB disease is defined as the presence of:

- Bilateral cavitary disease or extensive parenchymal damage on chest radiography.
- In children aged less than 15 years, the presence of cavities or bilateral disease on chest radiography.
- Severe extra-pulmonary TB is defined as the presence of:
  - miliary TB or TB meningitis.
  - In children aged less than 15 years, extra-pulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression)

DST results:

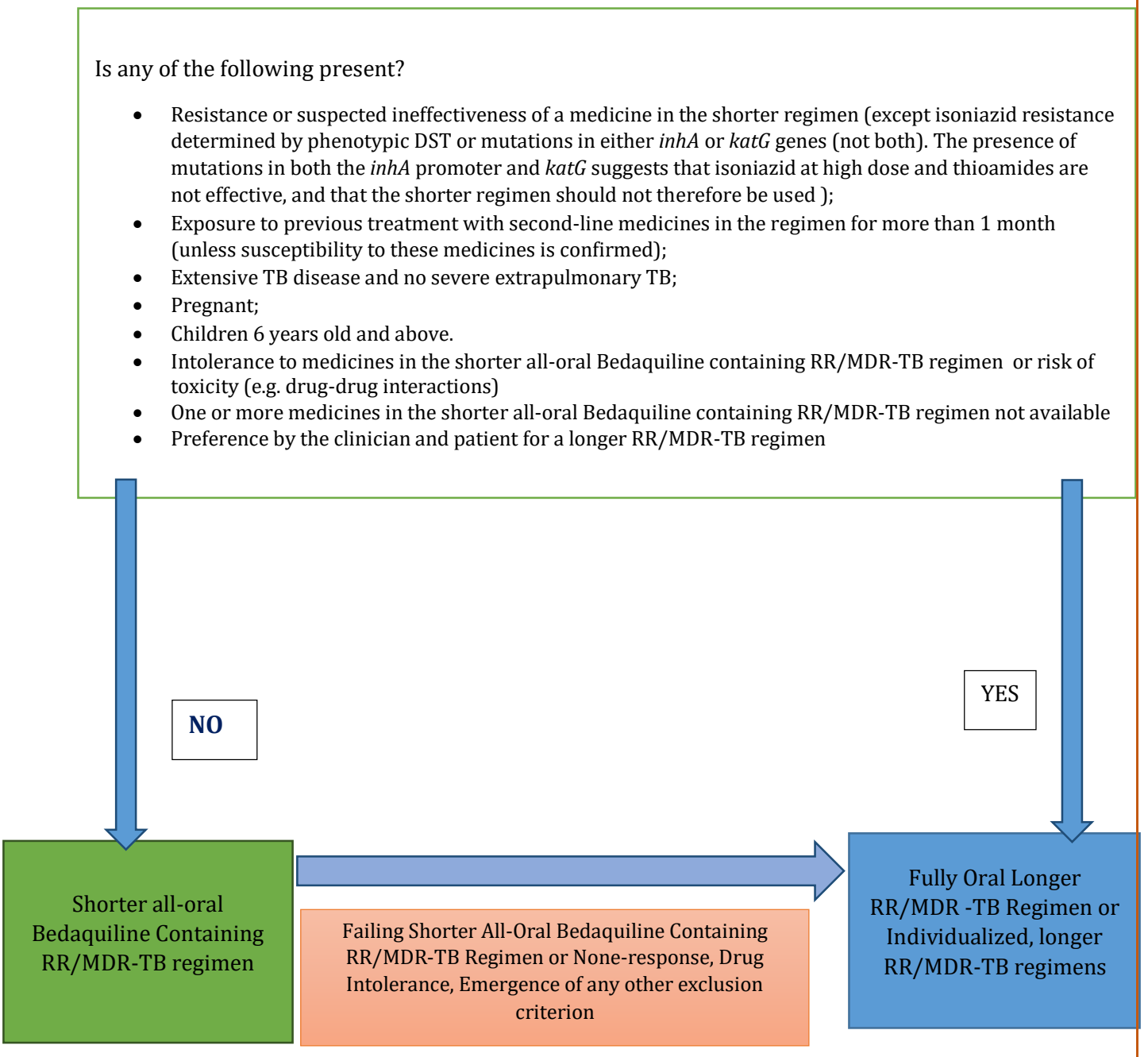
Testing for susceptibility to at least fluoroquinolones is recommended before the start of a shorter all-oral bedaquiline-containing MDR-TB regimen, to ensure exclusion of resistance to fluoroquinolones.

Isoniazid has been shown to be a key component of shorter regimens, despite the presence of resistance to the drug. The presence of both mutations (i.e. inhA promoter and katG) suggests that isoniazid at high dose and thioamides are not effective, and that the shorter regimen may therefore not be used.

There are no rapid methods to detect resistance to clofazimine and bedaquiline; Until the capacity for second-line DST – including for bedaquiline, linezolid and clofazimine – becomes available (preferably as a last resort and an interim measure), treatment decisions may need to rely on the likelihood of effectiveness of medicines, based on an individual patient's clinical history and surveillance data from the country or region.

There are some data on cross-resistance between clofazimine and bedaquiline, with the development of specific mutations in Rv0678 accounting for this cross-resistance; further evidence is needed to better understand the mechanism of this resistance and its clinical value.

Figure 5.1 Criteria to decide when the shorter all-oral Bedaquiline Containing RR/MDR-TB regimen is used



Composition and duration of the shorter all-oral bedaquiline containing regimen

The shorter all-oral bedaquiline-containing MDR/RR-TB regimen contains bedaquiline, levofloxacin/moxifloxacin, clofazimine, ethionamide, ethambutol, isoniazid (high dose) and pyrazinamide for 4 months (with the possibility of extending to 6 months if the patient remains sputum smear positive or culture positive at the end of the fourth month), followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide. Bedaquiline use in this regimen is for 6 months. The dosages proposed are outlined in Annex XX. All medicines were taken once a day on all days of the week, except for bedaquiline, which is taken every day for the first 2 weeks, followed by three times a week in the remaining 22 weeks.

The regimen is summarized as: 4–6 Bdq(6 m) -Lfx-Cfz-Z-E-Hh-Eto / 5 Lfx-Cfz-Z-E

Initial phase: 4–6 Bdq(6 m)-Lfx-Cfz-Z-E-Hh-Eto

Continuation phase: 5 Lfx-Cfz-Z-E

The shorter all-oral bedaquiline-containing MDR/RR-TB regimen needs to be implemented as a standardized package under programmatic conditions.

Thus, it is not advisable to change the composition or shorten the duration of the initial or continuation phase, or to prolong those phases in case of lack of response, other than making the following modifications:

- If the sputum smear or culture does not become negative by the fourth month, the initial phase is prolonged until the sputum smear or culture converts; however, the initial phase is not prolonged for more than 6 months in total. The duration of the later phase remains fixed at 5 months regardless.
- Bedaquiline is used for 6 months.
- Prothionamide may be used instead of ethionamide.
- Moxifloxacin may be used instead of levofloxacin.

Other changes to the regimen (e.g. removing ethionamide in the presence of the *inhA* promoter gene mutation or replacing ethionamide or clofazimine by linezolid) have not been studied and may have an unpredictable impact on the performance of the shorter regimen. Therefore, other changes are not currently recommended in programmatic use.

If a patient is started on the shorter all-oral bedaquiline-containing MDR/RR-TB regimen but is later found to be ineligible because of undetected resistance at the start of the treatment or emergence of additional resistance, it is assumed that further acquisition of resistance may have developed. Repeated DST at that point is necessary to guide the composition of the longer regimen.

Patients who are placed on a longer regimen and later found to be eligible for the shorter regimen can be switched, provided that treatment has not lasted for more than 1 month. However, there is little experience in changing regimens in this way. If patients are switched in this way, the shorter all-oral bedaquiline-containing MDR-TB regimen is given for the full duration, without any changes to its composition or duration.

Shorter All-oral Bedaquiline Containing MDR/RR-TB Regimen in Special Populations

1. PLHIV:

The shorter all-oral bedaquiline-containing MDR-TB regimen can be used in PLHIV, including those who are receiving ART. For PLHIV with pulmonary disease, there may be a potential for overlapping, additive toxicities or for drug–drug interactions between some antiretroviral medicines and TB drugs such as moxifloxacin and clofazimine, or efavirenz and bedaquiline. In addition, ritonavir may also increase the serum level concentration of bedaquiline , which could potentially increase the risk of bedaquiline related adverse reactions. Therefore, the combination of bedaquiline with ritonavir should be avoided or, if used, the combination should be administered with caution. Close monitoring of people on the two regimens is advised. Importantly, ART regimens need to be initiated early.

2. Children:

The shorter all-oral bedaquiline-containing regimen can also be used in children aged 6 years and above. Child-friendly (i.e. dispersible and palatable) formulations of the medications should be used whenever possible. Bedaquiline tablets suspended in water have been shown to have the same bioavailability as tablets swallowed whole, and can therefore be used to treat drug-resistant TB in children until a child-friendly formulation becomes available. In children below 6 years of age, bedaquiline is not yet recommended, mainly because of the lack of safety data and the absence of data on its use as part of the shorter all-oral regimens.

3. Pregnant and lactating women:

More compelling evidence on toxicity causes attributed to the use of specific anti-TB drugs during pregnancy and lactation is needed. Therefore individualized longer regimens can be designed to avoid known toxicities until better safety profiles are established.

5. Patients with extensive disease:

In patients with extensive disease, preference should be given to the all-oral longer regimen. The programmatic data on the shorter all-oral bedaquiline-containing MDR-TB regimen did not include patients with extensive disease; therefore, this recommendation could not be extrapolated to this subgroup.

6. Severe extra-pulmonary TB disease:

The evaluated all-oral bedaquiline-containing shorter regimen was also implemented in individuals with non-complicated forms of extra-pulmonary TB disease. Therefore, this regimen may be also used in these subgroups, but cannot be extrapolated directly to severe extra-pulmonary TB disease.

7. Patients with diabetes mellitus:

There are no data on the use of the shorter all-oral bedaquiline containing regimen among people with diabetes mellitus. Thus, although the shorter all-oral bedaquiline-containing regimen may be considered as an option, it may be prudent to monitor closely for hepatotoxicity among this patient group.

Dosages and dosing frequency of All-Oral Bedaquiline Containing Shorter Regimen

Table 5.2: Dosages for all-oral bedaquiline-containing shorter regimen for patients 15 years or older

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients older than 14 years					Usual Upper daily dose
				30-35 Kg	36-45 Kg	46-55 Kg	56-70 Kg	>70 Kg	
A	Bedaquiline		100 mg tab	4 tabs daily for first 2 weeks; then 2 tabs od M/W/F for 22 weeks					400 mg
	Levofloxacin		250 mg tab	3	3	4	4	4	
			500 mg tab	1.5	1.5	2	2	2	1.5 g
			750 mg tab	1	1	1.5	1.5	1.5	
B	Clofazimine		50 mg Cap or Tab	2	2	2	2	2	100 mg
			100 mg Cap or Tab	1	1	1	1	1	100 mg
C	Ethambutol	15–25 mg/kg	400 mg tab	2	2	3	3	3	
	Pyrazinamide	20–30 mg/kg	400 mg tab	3	4	4	4	5	
			500 mg tab	2	3	3	3	4	
	Ethionamide	15–20 mg/kg	250 mg tab	2	2	3	3	4	1 gm
Other medicines	Isoniazid	10–15 mg/kg (high dose)	300 mg tab	1.5	1.5	2	2	2	

Table 5.3: Dosages for all-oral bedaquiline-containing shorter regimen for patients <15 years

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients older than 14 years							Usual Upper daily dose
				5-6 Kg	7-9 Kg	10 - 15 Kg	16–23 Kg	24–30 Kg	31-34 Kg	>34 Kg	
A	Bedaquiline		100 mg tab	_	_	_	2 tabs od for 2 weeks; then 1 tab od M/W/F for 22 weeks		4 tabs od for 2 weeks; then 2 tabs od M/W/F for 22 weeks		
			20 mg dt	_	_	_	10 dts od for 2 weeks; then 5 dts od M/W/F for 22 weeks		20 dts od for 2 weeks; then 10 dts od M/W/F for 22 weeks		
	Levofloxacin	15–20 mg/kg	100 mg dt	1	1.5	2 or 3	3 or 4	(>14 y)	(>14 y)	(>14 y)	1.5 g
			250 mg tab	0.5	0.5	1 or 1.5	1.5 or 2	2	3	(>14 y)	1.5 g
B	Clofazimine	2–5 mg/kg	50 mg Cap or Tab	1 alt days	1 alt days	1 alt days	1	2	2	(>14 y)	100 mg
			100 mg Cap or Tab	M/W/F	M/W/F	1 alt days	1 alt days	1	>14 y	>14 y	100 mg
C	Ethambutol	15–25 mg/kg	100 mg dt	1	2	3	4	__	__	(>14 y)	
			400 mg tab	2	2	3	3			3	
	Pyrazinamide	30–40 mg/kg	150 mg dt	1	2	3	4 or 5	__	__	(>14 y)	_
			400 mg tab	0.5	0.75	1	1.5 or 2	2.5	3	(>14 y)	
			500 mg tab	0.5	0.5	0.75 or 1	1.5	2	2.5	(>14 y)	
	Ethionamide	15–20 mg/kg	125 mg dt	1	1	2	3	4	4	(>14 y)	1 gm
			250 mg tab	0.5	0.5	1	2	2	2	(>14 y)	1 gm
Other medicines	Isoniazid	15–20 mg/kg (high dose)	50 mg/5 mL soln	8–10 mL	15 mL	20 mL	_	_	_	_	
			100 mg tab	1	1.5	2	3	4	4	(>14 y)	

Medicines are taken once per day, on every day of the week. Bedaquiline should be taken every day for the first 2 weeks, followed by three times per day for the remaining 22 weeks.

Treatment monitoring for all-oral Bedaquiline containing MDR/RR-TB Regimen

At times, the shorter all-oral bedaquiline-containing MDR-TB regimen may need to be switched to a longer MDR-TB regimen; this is most likely to happen when:

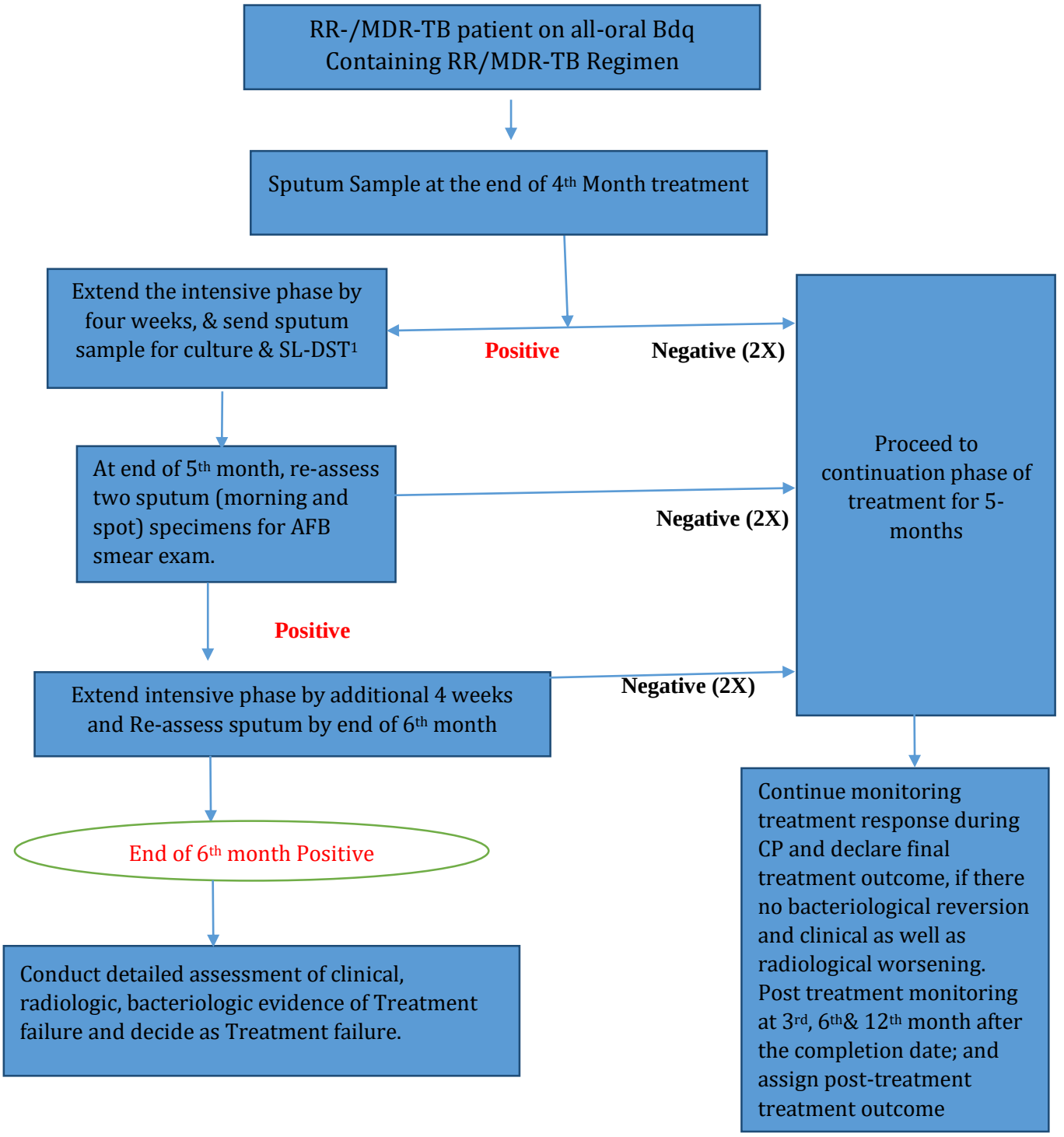
- reliable DST results show resistance to key medicines in the shorter all-oral bedaquiline-containing MDR-TB regimen: this may reflect the actual situation at the start of treatment (that was unknown at that time) or the acquisition of additional resistance during treatment;
- There is a lack of response to treatment (e.g. no sputum smear conversion from positive to negative by 6 months, or deterioration of clinical condition despite treatment);
- Treatment of a patient is interrupted for 2 months or more after being treated for more than 1 month; or
- Another disqualifying criterion emerges (e.g. pregnancy, intolerance or toxicity to a medicine in the regimen, or clinical deterioration).

If the patient is assessed for a longer MDR-TB regimen, the treatment should be designed on the basis of established algorithms. Patients need to be made aware of this before starting on the shorter all-oral bedaquiline-containing regimen. If the interruption is for less than 2 months, the clinician needs to decide whether the shorter MDR-TB regimen can be continued based on clinical condition and repeat laboratory test results, and whether the missed doses will be added to the rest of the treatment or a longer regimen should be started.

Monitoring treatment response and outcome assignment

Response to treatment is monitored on the basis of monthly sputum smear microscopy and culture. The treatment outcome definitions and reporting framework for patients on the shorter MDR-TB regimen are the same as those for patients on the longer MDR-TB regimens.

Figure 5.2: Treatment Response Monitoring Chart for patients on all-oral shorter MDR/RR-TB Regimen



Monitoring safety

Even though the shorter all-oral bedaquiline-containing regimen is well tolerated, the safety profile of some medicines used concomitantly may present its own concerns. Thus, for instance, concomitant use of clofazimine, bedaquiline and high-dose moxifloxacin – all of which prolong the QT interval – may make it more important to monitor for additive cardiotoxicity (using ECG) for these drug combinations than it is for other drug combinations. All details of the patient's diagnosis, DST, treatment, adverse effects and outcomes must be recorded in accordance with good practice. In addition, routine monitoring or regular surveys should be performed to assess for emerging bedaquiline resistance.

Longer regimens for MDR/RR-TB

All MDR/RR-TB patients who are not eligible for shorter all-oral regimens, including those with quinolone resistance are treated with longer regimens.

Medicines used in longer MDR-TB treatment regimens

TB medicines to be used for treatment of MDR/RR-TB are categorized into Groups A, B and C. This new classification is based on drug class, and level of certainty in the evidence on effectiveness and safety (i.e. balance between benefit and risk of harm). Groups A–C features the medicines to be used to compose longer MDR-TB regimens. Table 5.4 also indicates the overall approach to designing longer treatment regimens for adults and children based on the revised groupings. The regimen is designed by adding medicines, sequentially, going down to the three groups in Table 5.4. Therefore, Clinicians should be guided by these new recommendations in designing treatment regimen.

Table 5.4. Medicines used in the longer RR/MDR-TB regimens

Group	Name of medicine	Abbreviation
Group A: **Include all three medicines**	Levofloxacin Or	Lfx
	Moxifloxacin	Mfx
	Bedaquiline [2,3]	Bdq
	Linezolid [4]	Lzd
Group B: **Add one or both medicines**	Clofazimine	Cfz
	Cycloserine or	Cs
	Terizidone	Trd
Group C: **Add to complete the regimen and when medicines from Groups A and B cannot be used**	Ethambutol	E
	Delamanid [3,5]	Dlm
	Pyrazinamide [6]	Z
	Imipenem-cilastatin or	Ipm
	Meropenem [7]	Mpm
	Amikacin (or Streptomycin) [8]	Am (or S)
	Ethionamide	Eto
	or Prothionamide [9]	Pto
	Para-aminosalicylic acid [9]	PAS

Medicines in Group C are ranked by decreasing order of usual preference for use subject to other considerations.

[2] Bedaquiline is usually administered 400 mg orally once daily for the first 2 weeks, followed by 200 mg orally three times per week for 22 weeks (total duration of 24 weeks). New evidence on the safety profile of bedaquiline use beyond 6 months was available in 2019. The evidence supports the safe use of bedaquiline beyond 6 months in patients who receive appropriate schedules of baseline and follow-up monitoring. The use of bedaquline beyond 6 months still remains as off-label use, and in this regard best practices in off-label use still apply.

[3] New evidence on both the safety and effectiveness of concurrent use of bedaquiline and delamanid was made available in 2019. With regard to safety, the data suggested no additional safety concerns regarding concurrent use of bedaquiline and delamanid. Both medicines may be used concurrently among patients who have limited other treatment options available to them, and if sufficient monitoring (including baseline and follow-up ECG and electrolyte monitoring) is in place. The data on the effectiveness of concurrent use of bedaquiline and delamanid were reviewed, but due to the limited evidence and potential residual confounding in the data, a recommendation on effectiveness could not be made.

[4] Use of Lzd for at least 6 months was shown to increase effectiveness, although toxicity may limit its use. Using Lzd for the whole duration of treatment would optimize its effect.

[5] Evidence on the safety and effectiveness of Dlm beyond 6 months and in patients below the age of 3 years was insufficient for review. Use of Dlm beyond these limits should follow best practices in "off-label" use (8).

[6] Z is only counted as an effective agent when DST results confirm susceptibility.

[7] Every dose of Imp-Clv and Mpm is administered with oral clavulanic acid, which is only available in formulations combined with amoxicillin (Amx-Clv). Amx-Clv is not counted as an additional effective TB agent and should not be used without Imp-Cln or Mpm.

[8] Am and S are only to be considered if DST results confirm susceptibility and high-quality audiology monitoring for hearing loss can be ensured. S is to be considered only if Am cannot be used (unavailable or documented resistance) and if DST results confirm susceptibility (S resistance is not detectable with second-line molecular line probe assays and phenotypic DST is required). Kanamycin (Km) and capreomycin (Cm) are no longer recommended for use in MDR-TB regimens.

[9] These agents only showed effectiveness in regimens without Bdq, Lzd, Cfz or Dlm, and are thus only proposed when other options to compose a regimen are not possible.

Eligibility to Fully Oral Longer RR/MDR-TB Regimens

Any patient – child or adult – with MDR/RR-TB is eligible for treatment with either a shorter all-oral bedaquiline-containing MDR-TB regimen or, if this cannot be used, a longer MDR-TB regimen. Please refer to Figure 5.3 above regarding the patient triaging criteria to initiate either of the regimens.

Given the conditionality of the recommendation for the use of the shorter all-oral bedaquiline containing MDR-TB regimen, the health care provider and patient may agree to use a longer treatment regimen if the patient is eligible for the shorter all-oral bedaquiline-containing MDR-TB regimen based on that person's individual circumstances. If the shorter all-oral bedaquiline-containing MDR-TB regimen cannot be used, the patient needs to be reassessed, with a view to starting a longer MDR-TB regimen.

A patient started on the shorter all-oral bedaquiline-containing MDR-TB regimen can later be transferred to a longer MDR-TB regimen, should the need arise. However, once a patient is placed on a longer MDR-TB regimen for at least 4 weeks, normally that patient cannot be switched to the shorter all-oral bedaquiline-containing MDR-TB regimen because this 4-weeks treatment would represent an exposure to second-line medicines.

MDR/RR-TB alone or with additional resistance: Both shorter and longer regimens are more likely to be effective if the composition is guided by reliable DST. If rifampicin resistance is detected, rapid molecular tests for resistance to isoniazid and fluoroquinolones should be performed promptly, to inform the decision about which medicines to use for the treatment of MDR/RR-TB. Ideally, all MDR/ RR-TB patients are tested for resistance to fluoroquinolones as a minimum before starting MDR-TB treatment.

DST can be performed for anti-TB medicines for which there are now agreed reliable and reproducible methods (e.g. bedaquiline, linezolid, clofazimine, delamanid and pyrazinamide). Phenotypic DST for ethambutol, cycloserine/terizidone, imipenem/meropenem, ethionamid/ prothionamid and p-aminosalicylic acid is not reliable and is not routinely recommended. Hence, other approaches may be needed, to determine the likelihood of effectiveness of selected medicines.

If one or more agents are unlikely to be effective, then they need to be replaced (or, if they are included in the regimen, not counted as effective) in order to have at least four effective agents to start with.

The design of longer regimens for MDR-TB with additional resistance to fluoroquinolones or other second-line drugs follows a similar logic to that used for other MDR-TB patients.

Composition of Longer RR/MDR-TB Regimens

When designing Longer MDR/RR-TB regimens, a number of basic principles need to be respected. A stepwise approach guides the design of longer MDR-TB regimens. The treatment of patients with rifampicin mono-resistant TB, as well as those who have resistance to second-line agents in addition to MDR-TB (including XDR-TB), follows the same principles. The selection of agents follows a priority order based on the revised classification of regimen components, and a fully oral regimen is preferred.

- In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. If two agents from Group A are likely to be stopped before the end of treatment (e.g. bedaquiline stopped at month 6 and linezolid stopped early because of intolerance), then starting with five effective agents rather than four may be advisable. These provisions apply to most MDR-TB patients, including those with additional resistance to FQs or other medicines.
- Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens.
- Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens.
- Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more. Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years.
- Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens.
- Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens.
- Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens.
- Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens.
- Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens.
- Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens.
- Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions.
- Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible.
- P-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible.
- Clavulanic acid should not be included in the treatment of MDR/ RR-TB patients on longer regimens.

Group C is the group of less effective drugs, and a drug from Group C should not be considered an automatic replacement of a group A or B drug. The decision to use one or two Group C drugs should be informed by the likelihood of effectiveness, clinical condition, age of the patient and ease of administration of the drug or drugs for the patient. Some Group C drugs may require monitoring of additional adverse events, over and above those found using only Group A and B drugs.

The diagnosis of resistance additional to MDR-TB may present at baseline, or may be uncovered after MDR-TB treatment has started. The more information available at the start of the regimen the better; the aim is to protect the effectiveness of the component agents as much as possible, minimizing the need to replace medicines during treatment.

Most patients can be successfully treated with a regimen starting with four agents that are likely or confirmed to be effective. If bedaquiline is stopped at month 6, the regimen will still have three effective agents for the rest of the treatment duration. However, if another agent needs to be stopped because of toxicity, then that medicine would need to be replaced by another one, or bedaquiline could be continued throughout the treatment under “off-label” use. If the choice is to replace a medicine, instead of prolonging the use of bedaquiline, the replacement medicine would be chosen either from Group B (unless both clofazimine and cycloserine/terizidone are already included) or from Group C. The choice from Group C is usually determined by the order in which the medicines are ranked, and by the individual circumstances of the patient and setting.

Recent review of the observational data has shown no additional safety concerns when bedaquiline was used for longer than 6 months; however, no solid evidence was available to indicate whether longer use added efficacy. The clinicians may therefore consider continuing bedaquiline for longer than 6 months, and adding some flexibility for regimen design and the number of effective drugs.

To minimize the need to replace agents in the regimen, in addition to the option of prolonging the use of bedaquiline beyond 6 months, it is possible to start the regimen with five agents instead of four under the following conditions:

- Two of the four agents are likely to be stopped before the end of treatment (e.g. if bedaquiline is stopped at month 6 and linezolid is stopped early because of toxicity);
- Reliable DST is not available for one or more of the agents in the regimen but background resistance to the agent is known to be high; and
- The regimen cannot be constructed from at least four effective agents from Groups A and B medicines Due to intolerance, contra indications, drug drug interaction

Regimen composition may often need to be adjusted after the start of treatment once additional information from the clinical history or DST results emerges. However, if signs of non-response or impending treatment failure emerge, then the regimen should be reviewed completely rather than adjusted. The treating clinicians in the TIC are advised to consult the national or regional Clinical Review Committee in such cases.

A medicine may be avoided if there is high likelihood that the patient has developed, or will develop, a contraindication to it. Contraindications may depend on a history of severe reactions to the medicine or an allied substance, pregnancy or breastfeeding, co-administration of medicines that may cause interactions or have overlapping toxicities (e.g. QT interval prolongation) and problems with end-organ function (e.g. kidney or liver dysfunction).

Steps in longer MDR/RR-TB Regimens Design

Table 5.5: Step-by-step directions in longer MDR/RR-TB Regimen design

Steps	Group	Drugs
Step 1: Include all the three Group A medicines (unless they cannot be used): ▪ Avoid Mfx if possible when using multiple QT-prolonging drugs. If there is only low-level resistance to the FQ, the use of high-dose Mfx can be considered; in this case, this drug should not be counted as effective. ▪ Because of their excellent activity against MDR-TB and their relatively good side effect profile, FQ may still be used in patients when effectiveness is uncertain, but not counted as an effective drug. ▪ Lzd is considered very effective, but has a high incidence of AEs. ▪ Bdq is the first choice in case of confirmed or suspected resistance to second-line drugs (e.g. XDR or pre-XDR) or intolerance or contraindications to other second-line TB drugs. ▪ Bdq and Dlm can be used in the same regimen. Consider using both Bdq and Dlm in all cases of FQ-resistant strains.	A	Lfx/Mfx Bdq Lzd
Step 2. Add one or both Group B medicines (unless they cannot be used) ▪ If Cs or Cfz have been used in the patient's regimen previously without success, they are rarely used due to high rates of adverse events and as they may also be ineffective. If they are used in such patients, they should not be counted as effective drugs.	B	Cfz Cs
Step 3. Add Group C medicines to complete the regimen and when medicines from Groups A and B cannot be used ▪ Use Dlm in the regimen for any patient with risk of a poor outcome. In some patients, Dlm may be added in the regimen in order to maximize the probability of having five effective drugs. ▪ Dlm is the first choice from group C medicines in case of confirmed or suspected resistance to second-line drugs (e.g. XDR or pre-XDR) or intolerance to other second-line TB drugs. Consider using Dlm in all cases of FQ-resistant strains. ▪ In many countries, the prevalence of Z resistance among MDR-TB strains is significant. In such situations, Z can be added to the regimen but not counted as one of the effective drugs. If DST demonstrates resistance to Z from a reliable laboratory, consider not adding it to the regimen. In such cases, it should not be counted as an effective drug. ▪ If Eto/Pto has been used in the patient's regimen previously without success, they are rarely used due to high rates of adverse events. If they are used in such patients, they should not be counted as effective drugs	C	E Dlm Z Ipm-Cln / Mpm Am (or S) Eto / Pto PAS

Selecting medicines for use in longer MDR/RR-TB Regimens

Factors to consider when choosing individual medicines for the longer MDR-TB regimens:

- Results of DST performed using approved genotypic or phenotypic methods.
- Clinical condition of the patient and form of TB (e.g. EPTB and its severity, particularly CNS TB).
- History of previous use of first-line or second-line medicines used to treat TB in that particular patient (if previously treated).
- Patient and clinician preference for a specific regimen.
- Current and historical use of medicines that are routinely used in the MDR-TB regimen in the country, or in the country of origin of the patient.
- Prevalence of drug resistance detected through routine or periodic surveillance in the country (e.g. through regular laboratory surveillance or through periodic drug-resistance surveys), stratified by new and retreated cases if no reliable DST can be done for individual patients.
- Known contraindications such as allergy, pregnancy or breastfeeding, and presence of comorbidities.
- If the patient is a close or household contact of a bacteriologically confirmed TB case, the drug-resistance profile of the index case.
- Operational considerations such as availability of the medicines, ability to monitor for adverse reactions, and availability of necessary tools for follow-up and monitoring.
- Potential for or past history of, toxicities, intolerance (other than allergy) and drug– drug interactions.
- In children, age of the child and formulations available.

The number of likely effective medicines to be used in a longer MDR/RR-TB regimen from each group will vary depending on the number of medicines to which there is confirmed/suspected resistance or contraindication of use from either group A or B or both.

More medicines may be added than the recommended minimum if there is limited confidence in the effectiveness of regimen components, if the patient was exposed in a setting where second-line TB drug resistance is frequent and longer MDR-TB regimens perform poorly despite good programmatic management of MDR/RR-TB.

For MDR-TB with confirmed FQ resistance no FQ is used and, if Group C agents are needed, the recommended grouping will be followed based on benefit versus risk and individual circumstances. The choice and number of Group C medicines to include depends upon the confidence in the effectiveness of medicines in this group and the other components of the regimen, thus:

- If 4 Group A and B agents are included and there is confidence in all of them then Group C agents are not needed.
- If 3 Group A and B agents are included and there is confidence in all of them then at least one

Group C agent is added.

- If 2 Group A and B agents are included and there is confidence in all of them then at least three Group C agents are added.

Table 5.6: Longer MDR/RR-TB Regimen composition under different situations of known resistance/contra-indication of use among group A and B medicines

Medicines to which there is resistance or contraindication of use		**Consider adding medicines likely or confirmed to be effective**			**Examples of Regimens**
		Group A	**Group B**	**Group C**	
1	None of the Group A and B medicines	All 3 medicines	2 medicine	Not usually needed	18 $Bdq_{(6\ m\ or\ longer)}$-(Lfx or Mfx)-Lzd-Cfz – Cs
2	One Group A medicine	Remaining 2 medicines	Both medicines	May be needed	18 $Bdq_{(6\ m\ or\ longer)}$-(Lfx or Mfx)-Cfz-Cs-($Dlm_{(6\ m\ or\ longer)}$ or Z or E) 18 (Lfx or Mfx)-Lzd-Cfz-Cs-($Dlm_{(6\ m\ or\ longer)}$ or Z or E) 18 $Bdq_{(6\ m\ or\ longer)}$-Lzd-Cfz-Cs-($Dlm_{(6\ m\ or\ longer)}$ or Z or E) If there is a suspected resistance to E or Z, replace with other group C drugs
3	Two Group A medicines	Remaining medicine	Both medicines	At least 1 medicine	18 $Bdq_{(6\ m\ or\ longer)}$-Cfz-Cs-$Dlm_{(6\ m\ or\ longer)}$ -(Z or E) 18 Lzd-Cfz-Cs-$Dlm_{(6\ m\ or\ longer)}$ -(Z or E) 18 Lfx-Cfz-Cs-$Dlm_{(6\ m\ or\ longer)}$ -(Z or E) If there is a suspected resistance to E or Z, replace with other group C drugs
4	One Group B medicine	All 3 medicines	Remaining medicine	May not be needed	18 $Bdq_{(6\ m\ or\ longer)}$-(Lfx or Mfx)-Lzd-Cfz/ Cs
5	Both Group B medicines	All 3 medicines	None	1 or 2 medicines	18 $Bdq_{(6\ m\ or\ longer)}$-(Lfx or Mfx)-Lzd – $Dlm_{(6\ m\ or\ longer)}$ -(Z or E) If there is a suspected resistance to E or Z, replace with group C drugs
6	One Group A and both Group B medicines	Remaining 2 medicines	None	At least 3 medicines	18 $Bdq_{(6\ m\ or\ longer)}$-(Lfx or Mfx)-$Dlm_{(6\ m\ or\ longer)}$ -Z-E 18 (Lfx or Mfx)-Lzd-$Dlm_{(6\ m\ or\ longer)}$-Z-E 18 $Bdq_{(6\ m\ or\ longer)}$-Lzd-$Dlm_{(6\ m\ or\ longer)}$ -Z-E If there is a suspected resistance to E or Z, replace with group C drugs
7	All Group A medicines	None	Both	3 or more medicines	18–20 Cfz-Cs-Dlm-Z-E or other combinations of Group C drugs depending on known or suspected resistance

Prolonged use of bedaquiline and concurrent use of bedaquiline and delamanid

One of the most common misunderstandings among clinicians is that bedaquiline and delamanid can only be prescribed for 24 weeks. In fact, these drugs should be prescribed for a *minimum* of 24 weeks, and may be extended until the entire length of treatment if required. There is no need to stop bedaquiline and delamanid if these are the only last safe and effective drugs.

Common reasons for extending bedaquiline or delamanid longer than 24 weeks include:

- Less than five effective drugs in the regimen if Bdq or Dlm is stopped.
- Late or slow response to treatment. For example, the patient is slow to sputum convert (still strongly smear or culture positive after month 2), has slow resolution of TB symptoms, or has extensive lung damage.

The concurrent use of bedaquiline and delamanid are also sparse, and there is no formal recommendation on this subject. However, both medicines may be used concurrently among patients who have limited treatment options, provided that appropriate treatment monitoring (including baseline and follow-up ECG and electrolyte monitoring) is in place.

Table 5.7: Examples of LTRs by patient type

Patient type	**Recommended Regimen**	**Examples of the regimens**
Patient is very sick in severe condition or with extensive lung damage but has never been treated for MDR-TB before (SLD resistance is unlikely)	All-Oral LTR	18 $Bdq_{(6m\ or\ longer)}$-Lfx-Lzd-Cfz-Cs
Patients coming from catchment areas that have poor MDR-TB treatment outcomes (e.g. sites with extensive SLD resistance background)	All-Oral LTR plus Dlm if extensive resistance is expected	18 $Bdq_{(6m\ or\ longer)}$-Lfx-Lzd-Cfz-Cs ▪ Mfx could also be used instead of Lfx ▪ Dlm to be added if extensive resistance is likely
Patient has resistance to injectables on DST or experiencing (or at high risk for experiencing) ototoxicity,	All-Oral LTR (with Bdq or Dlm substituted for the injectable) All-Oral Bdq Containing Shorter Regimen may be initiated if other criteria	18 $Bdq_{(6m\ or\ longer)}$-Lfx-Lzd-Cfz-Cs 18 $Dlm_{(6m\ or\ longer)}$-Lfx - Lzd-Cfz-Cs if Bdq could not be used due to drug-drug interactions etc. 4–6 $Bdq_{(6\ m)}$ -Lfx-Cfz-Z-E-Hh-Eto / 5 Lfx-Cfz-Z-E

or nephrotoxicity	are met for its use.	
Patient has FQ resistance on DST	All-Oral LTR **with no FQ,** with Dlm added. Add other group C drugs such as Pto, Z, or PAS if there is other additional resistance. High-dose Mfx can be used in case of low-level FQ resistance but should not be counted as an effective drug. Am may be used with very strict monitoring for toxicity if both Group A and Group B medicines could not be used.	18 $Bdq_{(6m\ or\ longer)}$-Lzd-Cfz-Cs- $Dlm_{(6m\ or\ longer)}$-(Pto-Z) $Bdq_{(6m\ or\ longer)}$-Lzd- (Mfx^{HD})-Cfz-Cs-(Pto-Z) $Bdq_{(6m\ or\ longer)}$- Cfz- Cs- $Dlm_{(6m\ or\ longer)}$-(Am)-Pto-Z (if Lzd could not be used).
Documented XDR-TB Or Patient failed treatment with typical MDR regimen and likely has resistance to injectables and the fluoroquinolones ("probable XDR").	Individualized LTR composed of Any Group A and B drugs thought to still be effective plus Group C drugs until 5 likely effective drugs are included. In the case of failure of an MDR regimen, drugs in the patient's failing regimen (e.g. Pto, Cs and Z) usually cannot be considered likely effective. High-dose Mfx can be used in case of low-level FQ resistance .	18 $Bdq_{(6m\ or\ longer)}$-$Dlm_{(6m\ or\ longer)}$-Lzd-Cfz-Cs-PAS 18 $Bdq_{(6m\ or\ longer)}$-$Dlm_{(6m\ or\ longer)}$-Lzd-Cfz-Pto-Cs 18 $Bdq_{(6m\ or\ longer)}$-$Dlm_{(6m\ or\ longer)}$-Lzd-Cfz-Cs-PAS-Mfx^{HD} 18 $Bdq_{(6m\ or\ longer)}$-$Dlm_{(6m\ or\ longer)}$-Lzd-Cfz-Pto-Cs-Ipm/Cln-Amx/Clv

Duration of longer MDR/RR-TB regimens

Recommendations

- In MDR/RR-TB patients on longer regimens, total treatment duration of 18-20 months is suggested for most patients, and the duration may be modified according to the patient's response to therapy.
- In MDR/RR-TB patients on longer regimens, a treatment duration of 15 to 17 months after culture conversion is suggested for most patients, and the duration may be modified according to the patient's response to therapy
- In MDR/RR-TB patients on longer regimens containing amikacin or streptomycin, an intensive phase of 6-7 months is suggested for most patients, and the duration may be reduced or increased according to the patient's response to therapy.
- Treatment duration for less than 18 months may be considered for children with non-severe disease:
    - No cavities or bilateral disease on chest X-ray
    - Smear negative at treatment initiation
    - No extrapulmonary forms of the disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression)
    - No advanced immunosuppression.

The all-oral longer MDR-TB regimens do not have intensive phase. The duration of use of different medicines will depend on their clinical indication (e.g. bedaquiline and delamanid have been marketed for use for 6 months, but this period may be prolonged), patient tolerability (e.g. linezolid used for as long as no serious adverse event emerges) and individual treatment response (e.g. culture negativity), until completion of the expected total duration of treatment or time after culture conversion.

The total length of treatment is expected to be about 18–20 months in most patients, although the duration may need to be modified based on the patients' response to treatment. The recommendation also applies to patients previously treated with second-line regimens and to fluoroquinolone-resistant TB patients. The duration of treatment may need to be longer than 18–20 months overall in MDR/ RR-TB cases with additional resistance, depending on the clinical response to the treatment.

Sub-group considerations for use of longer MDR/RR-TB Regimen

MDR/RR-TB alone or with additional resistance:

A longer regimen is more likely to be effective if its composition is guided by reliable information on drug susceptibility. The design of longer regimens for MDR/RR-TB patients

with additional resistance (including XDR-TB) follows a similar logic to that used for other MDR-TB patients.

All MDR-TB patients need to be tested for resistance to fluoroquinolones as a minimum before starting MDR-TB treatment. If amikacin is being considered in the regimen, then rapid testing for the second-line injectable agents should be performed.

In many settings DST for other medicines commonly used in MDR-TB treatment is not usually reliable enough to guide regimen composition. Because of this, other elements may be necessary to determine likelihood of effectiveness.

Use of Longer MDR/RR-TB Regimen in Children:

The national recommendations on longer MDR-TB regimens apply to children as well as adults. Most medicines that are used in the longer regimens have been part of MDR-TB regimens for many years, in similar combinations, for both adults and children.

The use of bedaquiline is recommended in children down to 6 years of age and delamanid down to 3 years of age. There are concerns that the adult Delamanid 50mg tablet may shatter if attempts are made to split it and its contents are exceedingly bitter and unpalatable. Bioavailability may further be altered when the 50 mg tablet is split, crushed or dissolved. Delamanid is susceptible to oxidation and heat and therefore retaining pill fragments for use at any time other than the time of administration will likely result in the delivery of lower than expected active compound and unspecified oxidation by-products. Therefore, clinicians are advised to use the pediatric 25 mg Dlm formulation which is becoming available for children and avoid the inappropriate use of adult 50 mg Dlm tablets.

The avoidance of an injectable-containing regimen is particularly desirable in children, especially those very young and with mild disease, as determined by the absence of malnutrition, serious forms of extrapulmonary disease, cavitation on chest radiography or HIV infection. Hearing loss can have a permanent impact on the acquisition of language and the ability to learn at school, and therefore should use of amikacin or streptomycin be resorted to in children regular audiometry will be critical.

In general, children with MDR-TB should be managed according to the same principles that guide adult therapy. For children, however, the following principles are recommended:

- Treatment should be based on the DST pattern of the most likely source case if the child does not have a DST of his or her own;
- Recommendations on MDR-TB treatment regimens for adults also apply to children with severe forms of extra-pulmonary MDR-TB.
- Treatment of MDR-TB meningitis should be guided by the medicines' ability to cross the blood-brain barrier.
- Regimen construction should prioritize Group A and B drugs, as well as delamanid in children aged more than 3 years of age. PAS is an alternative drug to use in children instead of injectable agents or in instances where Bdq or Dlm could not be used, although its association with worse outcomes in adults should be considered.
- In children with fluoroquinolone resistance or in whom there are limited treatment options, extension and combination of bedaquiline and/or delamanid could be considered on a patient-by-patient basis with careful monitoring.
- Although linezolid is a Group A drug with proven effectiveness, its use has been associated with frequent toxicity. Toxicity is duration dependent and although use throughout treatment is likely to improve efficacy, adverse events may limit the duration of use to the first few months
- The duration of therapy in children should depend upon the site and severity of disease: children with non-severe disease can be treated with All-oral Bdq containing shorter regimen for 9 to 12 months while children with severe disease will require at least 18 months of therapy depending on their clinical progress.
- Severe disease in children is defined as follows: "In children <15 years, severe disease is usually defined by the presence of cavities or bilateral disease on chest radiography or extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression). In children the occurrence of advanced malnutrition (defined by syndrome or by metrics) or advanced immunosuppression or positive TB bacteriology (smear, Xpert MTB/RIF, culture) may also be considered when determining treatment duration.
- Child-friendly formulations of the medications should be used whenever possible.

Table 5.8 Suggested longer MDR/RR-TB Regimen for Children:

Age	DST Profile	Background Regimen	Additional Drugs if needed
< 3 Years	FQ-Susceptible	18 Lfx-Lzdz-Cfz-Cs	$Dlm_{(off\ label)}$, PAS, Pto/Eto
	FQ-Resistant	18 Lzd-Cfz-Cs-$Dlm_{(6m\ or\ longer)}$	Add PAS or Pto/Eto
3-6 Years	FQ-Susceptible	18 Lfx-Lzd-Cfz-Cs	Add $Dlm_{(6m\ or\ longer)}$ or PAS if needed
	FQ-Resistant	18 Lzd-Cfz-Cs-$Dlm_{(6m\ or\ longer)}$	Add PAS or Pto/Eto
>6 Years	FQ-Susceptible	18 $Bdq_{(6m\ or\ longer)}$-Lfx-Lzd-Cfz	Add Cs and Dlm if needed
	FQ-Resistant	18 $Bdq_{(6m\ or\ longer)}$-Lzd-Cfz-Cs	Add $Dlm_{(6m\ or\ longer)}$ and PAS if needed

- For children who are age 6 years and over and who have fluoroquinolone susceptible TB, the core of the regimen should be Bdq-Lfx-Lzd-Cfz. If a fifth drug is needed, then a choice can be made between cycloserine (a Group B drug with potential for neurological toxicity) or delamanid (a Group C drug that is relatively safe but for which there is limited data on efficacy when used in combination with bedaquiline). Of note, ethambutol could be given if there is documented susceptibility to it and the same with pyrazinamide.
- For children with fluoroquinolone resistance, the risk of a poor outcome is increased and thus the use of both cycloserine and delamanid is justified. Some treating centers, however, report good clinical experience using PAS, and this drug could be considered for children with fluoroquinolone resistant disease. PAS was associated with worse treatment outcomes in adults, however, and this should be taken into consideration in regimen design.
- For children who are 3 to <6 years of age, the use of bedaquiline is not routinely recommended since there are not yet pharmacokinetic and safety data available in this age group. In children who need five drugs, delamanid is a preferred agent, although again, some clinical centers have reported good results with PAS.
- In children who are ages 3 to <6 years and who have fluoroquinolone resistant disease, delamanid is essential. If a fifth drug is needed, either ethionamide or PAS can be considered based on resistance pattern (i.e. ethionamide should not be given to persons with known or suspected *inhA* mutations) and tolerance.
- Regimen design in children aged under 3 years can present some challenges and these recommendations are based mainly on clinical experience. Pharmacokinetic and safety data for many of the second-line drugs are limited in this population. Children in this age group

with no evidence of fluoroquinolone resistance should be treated with Lzd-Lfx-Cfz-Cs (although there are limited data on the pharmacokinetics and safety of these drugs in this population, especially clofazimine and cycloserine). If a fifth drug is needed, clinicians will need to choose between delamanid, ethionamide and PAS, and there are no data to guide drug selection in this situation. Some providers will prefer to give delamanid since it has been assessed in pharmacokinetic and safety studies, and has a stronger body of evidence supporting its efficacy in adults. However, in pharmacokinetic studies, the selected doses did not result in adequate blood levels. Some clinical centers prefer to give PAS and have reported excellent outcomes with the use of this medication, although dosing and safety of PAS in children in this age group has also not been well established. Finally, ethionamide could be considered if there is no evidence of an inhA mutation. For children <3 years with fluoroquinolone resistance, linezolid, clofazimine and cycloserine should be given as well as at least one of delamanid, PAS or ethionamide. Others of these drugs can be added to strengthen the regimen. Ethambutol and/or pyrazinamide could be considered if susceptibility to these drugs is confirmed.

Extrapulmonary TB and TB meningitis:

The national recommendations on longer MDR-TB regimens apply also to patients with extrapulmonary disease. Adjustments may be required depending upon the specific location of disease. Treatment of MDR/RR-TB meningitis is best guided by DST of the infecting strain and by the knowledge on the properties of TB medicines to cross the blood-brain barrier. Levofloxacin and moxifloxacin penetrate well the central nervous system (CNS), as do ethionamide/prothionamide, cycloserine/terizidone, linezolid. High-dose isoniazid and pyrazinamide can also reach therapeutic levels in the cerebrospinal fluid and may be useful if the strains are susceptible. PAS and ethambutol do not penetrate the CNS well and should not be counted on as effective agents for MDR-TB meningitis. Amikacin and streptomycin only penetrate the CNS in the presence of meningeal inflammation. There are little data on the CNS penetration of clofazimine, bedaquiline or delamanid.

Table 5.9 Treatment of extrapulmonary MDR/RR-TB.

Drugs	**Recommendations**
Bdq	Very limited experience with Bdq in TB meningitis or TB osteomyelitis. One patient with meningitis had undetectable levels of Bdq in CSF. Drug is protein bound and likely has low penetration into the CSF.
Dlm	Very limited experience with Dlm in TB meningitis or TB osteomyelitis. Drug is protein bound and likely has low penetration into the CSF.
Lzd	Excellent bone and soft-tissue penetration; commonly used for osteomyelitis due to gram-positive bacteria.
Cfz	Cfz has been used extensively to treat leprosy lesions in soft tissue, though it is unclear if this means that bone and soft tissue penetration is adequate.
Ipm/Cln Mpm	Both Ipm/Cln and Mpm reach measurable concentrations in CSF, but Mpm is thought to be less neurotoxic (seizures). Both drugs have been used to treat osteomyelitis caused by other bacteria.

Pregnancy:

Knowledge about the safety of bedaquiline and delamanid in pregnancy and during breastfeeding is still sparse. However, new evidence from an observational study in South Africa included information on 58 mothers who received bedaquiline during pregnancy. The results of this study indicated that fetal exposure to bedaquiline in utero was associated with low birth weight (<2500 gm), with no other significant differences in infant outcomes, pregnancy outcomes or maternal treatment outcomes, including weight gain in the infants until 1 year of age. It is recommended that, in pregnancy, a longer regimen be individualized to include components with an established safety profile. The outcomes of treatment and pregnancy, and postpartum surveillance for congenital anomalies, should be documented to help inform future recommendations for MDR-TB treatment during pregnancy.

Amikacin, streptomycin, prothionamide and ethionamide are usually contraindicated during pregnancy.

In MDR-TB patients who are pregnant, the main objective is to design a regimen that is effective and likely to cure the mother. The highest risk to both mother and fetus is from inadequately treated MDR-TB. While drugs with identified teratogenic risks should not be primary choices, the potential teratogenic impact of these drugs should be considered in perspective of the risks to the other/baby/family/community of not treating the mother with an appropriate regimen.

- Amikacin, streptomycin, prothionamide and ethionamide are usually contraindicated during pregnancy. Knowledge about the safety of bedaquiline and delamanid in pregnancy and while breastfeeding is sparse.
- Pregnancy is not a contraindication for treatment of drug-resistant TB. Both DRTB and its treatment carry risks to the fetus and the mother. Treatment of DRTB in pregnancy requires analyzing the risks and benefits to fetus and mother. While there are known SLDs with fetal toxicities, the effect of most second line anti TB drugs on the human fetus is not yet fully understood.
- All female patients of childbearing age should be tested for pregnancy upon initial assessment. Last Normal Menstrual Period (LNMP) should be asked routinely during each follow up.

A. Initial assessment:

In general, the following steps should be taken in the initial evaluation of MDR-TB patients who are female and in the reproductive age group.

- Initial pregnancy testing for all women of child-bearing age,
- If pregnancy test is negative, contraceptives are strongly recommended during MDR-TB treatment
- Pregnant patients should be carefully assessed, taking into consideration;
    - Gestational age, and
    - Severity of the disease- drug-resistant TB.

B. What is the best time to start treatment in patients with DR TB who are pregnant:

The general principle is that the risks and benefits of treatment should be carefully considered, and all options should be discussed with the mother. Majority of teratogenic effects occur when the drugs are taken in the first trimester. Usually pregnant ladies are started on treatment as soon as they are diagnosed if the disease is severe.

However, if the disease is not severe and the patient is stable, you may delay treatment in the first trimester. Initiate MDR-TB therapy during second or third trimester to achieve smear conversion prior to delivery of the baby

Decision to postpone the start of treatment is based primarily on the clinical judgment resulting from the analysis of life-threatening signs/symptoms and severity/aggressiveness of the disease.

General principles regarding treatment of pregnant patients with DR-TB:

- When therapy is started, three or four oral drugs with demonstrated efficacy against the infecting strain should be used. Injectable agents (Amk, S) shouldn't be initiated during pregnancy,
- Pyridoxine should be given for all MDR cases with Pregnancy,
- If pregnancy occurs while on treatment, refer patient to the treatment initiating center for subsequent treatment decision,
- When the condition of the mother is so poor that a pregnancy would carry a significant risk to her life, a medical abortion may be indicated.

C. Are there drugs that need to be avoided during pregnancy:

1. Aminoglycosides:

Aminoglycosides are potentially toxic to the developing fetal ear and should not be used in the regimens of pregnant patients.

2. Ethionamide and Prothionamide:

Ethionamide should be avoided in pregnant patients because teratogenic effects have been observed in animal studies. Ethionamide can increase the risk of nausea and vomiting associated with pregnancy.

The following table summarizes the limited evidence about the safety of medicines used for MDR/RR-TB in pregnant and lactating women. Little is known about the safety of other MDR-TB drugs as well, but drugs like injectables and ethionamide are generally avoided during pregnancy.

Table 5.9: Treatment of pregnant or lactating women with SLDs

Drugs	**US FDA safety class**	**Summary**
Bdq	B	Animal studies have not revealed any evidence of harm to the fetus or any effects on fertility in females; some males treated with high doses failed to produce offspring. There are no controlled data in human pregnancy. Pharmacokinetic data in rats treated with doses 1-2 times the human clinical dose have shown 6- to 12-fold higher bedaquiline concentrations in milk than the maximum concentrations observed in maternal plasma.
Dlm	Not yet assigned an FDA safety class.	In rabbits reproductive studies, embryo-fetal toxicity was observed at maternally toxic dosages. Avoid in pregnancy; however the benefits in patients with no other options may outweigh the risks. Pharmacokinetic data in animals have shown excretion of delamanid /metabolites into breast milk. In lactating rats, the C_{max} for delamanid in breast milk was 4-fold higher than that of the blood.
Lzd	C	Animal studies have failed to reveal evidence of teratogenicity, but embryofetal toxicity was observed at maternotoxic doses. Placental transfer of this drug and/or its metabolites was observed in rats. There are no controlled data in human pregnancy.
Cfz	C	There are no studies of clofazimine use in pregnant women. Few cases of clofazimine use during pregnancy have been reported in the literature. Embryofetal toxicity studies were conducted in rats, rabbits and mice. In mice, clofazimine-induced embryotoxicity and fetotoxicity was evident.
Ipm/Cln	C	Developmental toxicity studies with imipenem and cilastatin sodium (alone or in combination) administered to monkeys, rabbits, rats, and mice revealed no evidence of teratogenicity. However, an imipenem-cilastatin dose of 40 mg/kg given to pregnant monkeys by bolus intravenous injection caused significant maternal toxicity including death and embryofetal loss. It is not known whether imipenem-cilastatin sodium is excreted in human milk.

Breast Feeding-

- In general, a woman who is breastfeeding and has drug-resistant TB should receive a full course of DR-TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to her Baby.
- Sputum conversion should be achieved as soon as possible to prevent transmission of infection to the baby.
- Any effects on infants of such exposure during the full course of DR-TB treatment have not been established. Thus, the mother can opt to either continue with breast feeding or substitute formula feeding if feasible.

- The mother and infant should not be completely separated. But if the mother is smear positive, the time she spends with the infant should be limited and in a well-ventilated area with proper infection prevention precautions.

Contraception

DR-TB treatment is not a contraindication to the use of oral contraceptives. In fact Contraception is strongly recommended for all non-pregnant women receiving therapy for drug-resistant TB because of frequent and severe ADRs to the mother, teratogenicity of treatment to the fetus and to the new born.

Preferred options for contraception:

- Injectables/Implants (preferable for patients who have vomiting)
- IUCDs
- Barrier methods like Diaphragm/Condom
- OCPs

All patients are encouraged to use condoms to protect against sexually transmitted disease including HIV. Patients who vomit directly after taking an oral contraceptive can be at risk of decreased absorption of the drug and decreased efficacy. These patients should be advised to take their contraceptives apart from times when they may experience vomiting caused by the anti- tuberculosis treatment.

Patients who vomit at any time directly after, or within the first two hours after, taking the contraceptive tablet, should use a barrier method of contraception until a full month of the contraceptive tablets can be tolerated. Other methods of contraception such as injectables and IUCDs should be used if patients continue to experience frequent vomiting.

DR TB management in HIV co-infection

Diagnosis of DR-TB in HIV-positive Patients: The diagnosis of tuberculosis (including MDR-TB and XDR-TB) in HIV-positive people is challenging f o r a number of reasons. To begin with, there are many pulmonary and systemic infections that mimic Tuberculosis. In addition, the presentation is more likely to be extra-pulmonary, disseminated, atypical, or sputum smear-negative than in HIV negative TB patients, especially as immune-suppression advances. This can result in misdiagnosis or delays in diagnosis, and in turn, higher morbidity and mortality. HIV infected individuals are considered as high- risk groups for DRTB as they have higher mortality and drug toxicities. Therefore HIV positive individuals suspected of

having DR-TB should be urgently e v a lu a t e d by DST preferably by the rapid molecular diagnostic tests for early diagnosis and treatment.

Concomitant Treatment of DR-TB and HIV

The treatment of DR-TB in patients with HIV is very similar to that in patients without HIV and is described in the treatment of MDR TB section, with the following peculiarities:

- ART plays a crucial role, as mortality in MDR-TB/HIV without the use of ART is extremely high.
- Adverse effects are more common in patients with HIV. The multiple medicines involved in DR-TB management with recognized high toxicity risks, often combined with ART and other drugs for OIs, results in a high incidence of adverse effects. Some toxicities are common to both anti-tuberculosis treatment and ART, which may result in either added or synergistic rates of adverse events.
- The overall treatment is a big challenge because of high pill burden, ADRs, other concomitant OIs and multiple psychosocial factors. Hence, treatment monitoring needs to be more intensive for ensuring adherence, monitoring response to therapy and ADRs.
- Immune reconstitution inflammatory syndrome (IRIS) may complicate therapy.
- In addition to the second line anti-TB treatment, comprehensive TB/HIV care should be given to co-infected individuals including CPT, ART and management of OIs.
- If there is delay in performing rapid DST, consider empirical therapy, after discussion with the panel team, with second-line anti-tuberculosis drugs in seriously ill HIV positive individuals when MDR-TB is highly likely for instance, in patients with failure of retreatment, or symptomatic patients having close contact history with confirmed DR-TB
- It is advisable to arrange treatment follow-up for co-infected individuals by a multi-disciplinary team.

There are two scenarios in DR TB/HIV co-management:

1) **Initiating ART treatment in patients with DR-TB:**

Antiretroviral therapy in HIV-infected patients with TB improves survival for both drug-resistant and susceptible disease. However, the likelihood of adverse effects could compromise the treatment of either HIV or DR -TB if both treatments are started simultaneously. On the other hand, undue delay in the start of ART could result in significant risk of HIV-related death among patients with advanced disease.

The WHO strongly recommends provision of ART for all patients with HIV and DR-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. In HIV infected patients with profound immunosuppression (CD4< 50uL), earlier initiation of ART within 02 weeks of initiating anti-TB is recommended. Therefore HCWs should provide ART to co- infected MDR-TB patients as soon as they tolerate the second line anti-TB drug treatment.

When DR-TB occurs in patients already receiving ART:

- Consider ART regimen modification or intensify follow up if drug-drug interaction or overlapping toxicity is highly likely.
- Bedaquiline is metabolized by CYP3A4, therefore ART drugs like Efavirenz and Protease inhibitors are better avoided or used with extreme caution if there are no other options. Nevirapine based regimen is the better option followed by atazanavir among the PIs.
- The ART of choice in patients taking Delamanid is non-PI based if that option exists. But if PIs should be used, then frequent ECG monitoring for QT prolongation should be implemented.
- Assess patient to check whether the presentation of active DR-TB in a patient on ART constitutes ART failure. If ART failure has been diagnosed, it is not recommended to begin a new second-line ART regimen at the same time as initiation of a DR-TB regimen. Instead, continue the present ART regimen and switch to the second-line ART regimen two to eight weeks after the start of DR-TB treatment.

Important drug-drug interactions in the treatment of HIV and DR-TB

Currently, little is known about drug-drug interactions between second-line anti-tuberculosis agents and antiretroviral drugs. There are several known interactions between drugs used to treat HIV and TB, they are summarized below:

- **Rifamycin derivatives:** While rifamycin derivatives are not routinely used in DR- TB treatment, they are used in the treatment of rifampicin-sensitive poly- and mono- resistant TB. Guidance on use of rifamycin derivative-based regimens and ART (including with PI- based regimens) is available in WHO and national guidelines.

- **Ethionamide/prothionamide**: Based on limited existing information of the metabolisim of the thiamides (ethionamide and prothionamide), this drug class may have interactions with antiretroviral drugs. Ethionamide/prothionamide is thought to be metabolized by the CYP450 system, though it is not known which of the CYP enzymes are responsible. Whether doses of ethionamide/prothionamide and/or certain antiretroviral drugs should be modified during the concomitant treatment of DR-TB and HIV is completely unknown.

Potential drug toxicity in the treatment of HIV and DR- TB

In general, HIV patients have a higher rate of ADRs to both TB and non-TB medications, and the risk of ADR increases with the degree of immunosuppression. Identifying the source of adverse effects in patients receiving concomitant therapy for DR-TB and HIV is difficult. Many of the medications used to treat DR-TB and HIV have overlapping, or in some cases additive toxicities. Often it may not be possible to link side-effects to a single drug, as the risk of resistance for ART therapy precludes the typical medical challenge of stopping all medications and starting them one by one.

It should be noted that relatively very little is known about the rates of adverse effects in the concomitant treatment of DR-TB and HIV. When possible, avoid the use of agents with shared side-effect profiles. Often, however, the benefit of using drugs that have overlapping toxicities outweighs the risk. Therefore, if two drugs with overlapping toxicities are determined to be essential in a patient's regimen, these guidelines recommend increased monitoring of adverse effects rather than disallowing a certain combination.

Monitoring of DR-TB and HIV therapy in co-infected patients:

HIV treatment must be taken daily without exception to prevent the evolution of drug - resistance. DOT is particularly important in the setting of second -line anti-tuberculosis therapy, since it can result in a large pill-burden and numerous side-effects that make taking ARVs more difficult.

The complexity of antiretroviral regime ns and second-line TB treatment, each with its own toxicity profiles and some of which may be potentiated by concomitant therapy, demands rigorous clinical monitoring.

Given that the regimens together are particularly difficult to take the following could be particularly challenging:

- The stigma associated with both diseases can result in serious discrimination,

- 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.

Immune reconstitution inflammatory syndrome:

Immune reconstitution inflammatory syndrome (IRIS) has emerged as an important complication of ART. This syndrome can present as a paradoxical worsening of the patient's clinical status, often due a previously subclinical or unrecognized opportunistic infection. These reactions may present as fever, enlarging lymph nodes, worsening pulmonary infiltrates, respiratory distress, or exacerbation of inflammatory changes at other sites. It commonly presents within three months (but as early as 02 weeks or as late as 02years) of the initiation of ART and is more common with a low CD4 cell count (<50 cells/mm3). IRIS is relatively common in mild to moderate forms in patients with TB started on ART (seen in up to one third of patients in some studies); however, it is relatively rare in its severe forms.

It is important to note that IRIS is a diagnosis of exclusion. Patients with advanced AIDS may show clinical deterioration for a number of other reasons. New opportunistic infections or previously subclinical infections may be unmasked following immune reconstitution and cause clinical worsening. IRIS can also be confused with TB treatment failure, and co-infected patients may be demonstrating progression of TB disease due to drug-resistance. CD4 count and Viral load should be determined to differentiate IRIS from ART treatment failure when it occurs after 6 months.

The management of IRIS is complex and depends on the clinical status of the patient, the site and extent of involvement. Various treatment modalities have been employed, including NSAIDs in mild disease and corticosteroids in moderate-severe disease. Management of IRIS does not necessitate interruption of ART but rather prompt supportive care and standard treatment of the OI.

Diabetes Mellitus and DR-TB:

Diabetic patients with MDR-TB are at risk for poor outcomes. The presence of diabetes mellitus may potentiate the adverse effects of anti-tuberculosis drugs, like renal dysfunction and Peripheral neuropathy. Diabetic patients are 3-5 times more likely to develop TB. TB (both sensitive and resistant) is more difficult to diagnose in patients with diabetes due to its atypical chest radiographic presentation and more frequent extra pulmonary disease.

Management of diabetic patients with DR-TB may be more difficult due to:

- Overlapping symptoms of toxicity of SLDs and complications of DM (e.g. neuropathy, renal failure)
- Existing diabetes complications may make administration of certain SLD difficult or impossible (e.g. Neuropathy, nephropathy)
- Increased pill burden due to use of oral hypoglycemic agents and drugs for complications of diabetes along with SLD.
- Possible drug -drug interactions.
- Glycemic control may become an issue; i.e. Ethionamide may make blood sugar control difficult.

In General the following management principles should be applied:

- Oral hypoglycaemic agents are not contraindicated during the treatment of drug-resistant TB but patient may require frequent monitoring of blood sugar and dose adjustment. If it is difficult to control the blood sugar level, shifting to insulin can be considered.
- Creatinine and potassium levels should be monitored more frequently, often weekly for the first month and then at least monthly thereafter.
- DOT of diabetes medications may help improve outcome of tuberculosis.

Renal insufficiency:

Patients with MDR-TB may have renal insufficiency at the time of MDR-TB diagnosis or they may develop it later while on treatment secondary to use of injectables. Base line BUN and creatinine should be done routinely for every patient to be started on SLDs.

The lab tests should also be subsequently monitored monthly for those with normal baseline RFT and more frequently for those with abnormal test and with diabetes mellitus.

Patients with the following conditions have higher risk of developing renal insufficiency and hence require close follow-up:

- Diabetes Mellitus
- Hypertension
- History of prolonged usage of amino glycosides
- Elderly
- Prolonged duration of TB illness

Great care should be taken in managing MDR-TB patients with renal insufficiency. The dose and/or the interval between dosing should be adjusted based on the GFR. Consultation should be made with the treatment center when making dose adjustment and if there is any evidence of deterioration of renal function while on treatment such patients should be referred to the TIC for specialist care. Please also refer the dose adjustment table in the guideline.
(See annex 4 for dosing of Medication in pts with renal insufficiency).

Liver disorder and toxicity:

The liver is one of the commonest organs which can be affected by anti TB drugs. Both first line and second line anti TB drugs can cause liver toxicity. On the other hand patients with MDR-TB who need second line anti TB drugs may have an underling liver disease. In both cases meticulous clinical and laboratory monitoring should be done to follow up the progress. Patients developing liver toxicity should be managed with supportive care and treatment modification as appropriate.

Management considerations in patients with underlying liver disease who need treatment with second line anti TB drugs:

- In general, patients with chronic liver disease should not receive pyrazinamide.
- All other drugs can be used, but close monitoring of liver enzymes is advised.
- If significant aggravation of hepatitis occurs, the drugs responsible may have to be stopped or substituted.
- It is possible to defer anti-tuberculosis treatment until the acute hepatitis has been resolved for those patients with acute hepatitis unrelated to the anti TB drugs.
- 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 including FQs, injectables, cycloserine.

Table 5.10 Recommendations for HIV Infected and other patients with co-morbidities

Situation	**Recommendations**
HIV	Antiretroviral therapy (ART) should be given to all HIV co-infected MDR/RR-TB patient without delay. ART can be started as soon as MDR-TB treatment is tolerated—usually within a few days. The risk of immune reconstitution syndrome can be mitigated by designing an appropriate MDR-TB regimen. Bedaquiline has important interactions with ART that will affect the choice of ART
Chronic renal insufficiency	Bedaquiline and delamanid are not renally excreted and no dose adjustment is required in mild/moderate renal insufficiency. There is no data on the use of either of these drugs in patients with severe renal impairment. No dose adjustment of linezolid is required in patients with renal impairment; however, the two primary metabolites of linezolid accumulate in patients with renal impairment and the clinical significance of this is unknown. No dose adjustment of clofazimine is required in patients with renal impairment.
Hepatitis C	MDR-TB can be correlated with hepatitis C infection in many countries. Active hepatitis C is a risk factor for MDR-TB treatment failure. Direct-acting antivirals (DAA) are well-tolerated when given with MDR-TB treatment.

Seizure disorder:

Patients with MDR-TB who require treatment may have concomitant seizure disorders. In the treatment preparation evaluation of patient's history of current or past seizures should be included. If there is history of seizures further evaluation is needed.

- Is the patient on treatment for the seizure?
- When did the last attack of seizure occur?
- What was the underlying cause for the seizure (If it is known)
- If the cause is unknown, we may need to evaluate to know the cause.

Management considerations for patients with DR-TB and seizure disorder:

- If the seizure is 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. Cases where cycloserine is a crucial component of the treatment regimen, it can be given and the anticonvulsant medication needs to be adjusted to control the seizure disorder. The risks and benefits of using cycloserine should be discussed with the patient and the decision to use cycloserine should be made together with the patient.
- High dose INH also carries great risk in patients with active seizure and should be avoided.
- In mono- and poly-resistant cases, the use of Isoniazid and Rifampicin may interfere with many of the anti-seizure medications. Rifampicin causes fast metabolization of other drugs in the body. Thus, the serum level of the other drugs may decrease when taken together with Rifampicin.

Psychiatric disorders and DR TB:

Evaluation for psychiatric disorders is very important at the initiation of MDR TB treatment and during follow up. Some of the reasons are:

- Baseline psychiatric disorders are very common among patients with MDR-TB due to the chronicity of the illness and the socioeconomic stressors associated with the disease.
- Psychiatric disorders can be important barriers to adherence
- SLDs like Cycloserine, commonly cause psychiatric disturbance like depression and psychosis.

Psychiatric evaluation during DR-TB treatment

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

The initial evaluation should document:

- Any existing psychiatric condition and
- Establishes a baseline for comparison if new psychiatric symptoms develop while the patient is on treatment

Subsequently the patient should be evaluated for newly developing or worsening of existing psychiatric disorders and the problems should get a timely treatment.

Management options for psychiatric disorders in MDR-TB treatment

The management options are:

- Medical (drug) treatment.
- Individual counseling or group therapy. 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 in the treatment of MDR-TB in psychiatric patients. But, it might be better to use one of the repurposed drugs in the place of cycloserine. Adverse effects from cycloserine may be more prevalent in psychiatric patients, but the benefits of using this drug may outweigh the potentially higher risk of adverse effects. So the following precautions should always be applied:

- 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 referral system for psychiatric emergencies.

Health care workers should be watchful for signs of Psychiatric emergencies that include:

- Psychosis,
- Suicidal ideation
- Any situation involving the patient's being a danger to him or herself or others. These manifestations are usually danger signs and such patients should immediately be referred to the Treatment Initiating Center after stabilization. Psychiatric problems may affect the adherence of patients to SLDs. In patients with acute psychiatric problems whose TB is not severe, initiation of SLDs may be delayed until the patient is stabilized.

Substance dependence and abuse:

Substance abuse and dependence cause challanges in MDR-TB treatment such as:

- Poor adherence,
- Increased risk of transmission to the community
- Higher occurrence of psychiatric disorders and other health problems.
- More frequent drug adverse effect of cycloserine

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. However, if the treatment is repeatedly interrupted because of the patient's addiction, therapy should be suspended until successful addiction treatment or measures to ensure adherence have been established. Good DOT give the patient an opportunity to have frequent contact with and support from health-care providers, which often allows complete treatment even in patients with substance dependence.

Note: 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. Therefore, it is better to avoid in such cases and use other drugs instead. However, if cycloserine is considered important to the regimen, it should be used and the patient closely observed for adverse effects.

Cautions and warnings for medicines used in longer MDR/RR-TB Regimens

Most second line TB drugs, including Bdq, Dlm, Lzd, and Cfz have contraindications for use, although most are relative. If the clinician judges that the potential benefits outweigh the potential risk, treatment may proceed with caution. The national/regional Clinical Review Committee is always available for case-by-case advice.

Table 5.11 Contraindications for medicines used in longer MDR/RR-TB Regimen

Drug	Relative contraindications	Remarks/Precautions
All drugs	Known hypersensitivity to the drug	A history of anaphylaxis or severe drug reaction like Stevens-Johnson syndrome is an absolute contraindication.
Bdq, Dlm	Baseline ECG demonstrating a QTcF > 500 ms (repeated); or History of syncopal episodes, ventricular arrhythmias or severe coronary artery disease	Absolute contra indication for use
	Baseline ECG demonstrating a QTcF > 450/470 in male/ female ms (repeated)	Use with caution if QTcF > 450/470 ms in male/female patients. Weekly ECG monitoring and serum electrolyte screening should be performed if Bdq or Dlm is being used in the presence of cautionary clinical conditions. Dlm may prolong the QT interval less than Bdq.
Bdq	Severe hepatic failure	Caution in patients with severe hepatic impairment.
Bdq, Dlm, Lzd	Severe renal failure	Caution in patients with severe renal impairment.

Drug-Drug interactions

Table 5.11 Possible drug-drug interactions with SLDs

	Drugs	Examples/notes
Avoid use with Bdq	Strong/moderate inducers of cytochrome P450 may decrease blood levels of Bdq	Efavirenz Rifamycins: Rifampicin, Rifapentine, Rifabutin Phenytoin Carbamazepine Phenobarbital
	Strong/moderate inhibitors of cytochrome P450 may increase blood levels of Bdq	Ritonavir-boosted PIs Oral azole antifungals (can be used up to two weeks): ○ Itraconazole ○ Fluconazole† Macrolide antibiotics other than azithromycin‡: ○ Clarithromycin ○ Erythromycin
Avoid use with Dlm	First-line standard anti-TB therapy (isoniazid, rifampicin, ethambutol, pyrazinamide)	First line anti-TB therapy with fixed dose combination of HREZ appears to decrease levels of Dlm in early studies. The mechanism is not clear.

† All four oral azoles inhibit CYP3A4; itraconazole and posaconazole are more potent inhibitors than fluconazole or voriconazole.

‡ Azithromycin does not inhibit CYP isoenzymes but does prolong the QT interval so may want to be avoided for this reason.

Table 5.12 possible drug-drug interactions between antiretrovirals and medicines used for RR/MDR-TB Treatment

	Drugs	Instructions
ARVs to avoid with Bdq	Efavirenz (EFV) (Using EFV with Bdq will result in low levels of Bdq)	Substitute nevirapine (NVP) or integrase inhibitor instead of EFV. Allow a 5 day washout of EFV if possible (substitute NVP on day 1 and then start MDR regimen 5 days later). If patient is critically ill with MDR-TB, no washout period is necessary. When switching back to EFV after ending treatment with Bdq, this can be done immediately after Bdq is stopped.
	Ritonavir containing protease inhibitors (PIs) (Using ritonavir with Bdq will result in high serum levels of Bdq)	If possible, use an ARV regimen with no PI. One possible solution is to substitute the PI with integrase inhibitors (INSTIs), e.g. dolutegravir (DTG) or raltegravir (RAL). If a ritonavir-containing PI must be used, check ECG every two weeks.
ARVs to avoid with Dlm	None	Dlm has very little drug-drug interactions with ARVs and no extra drug monitoring or regimen adjustment is needed.

Overlapping toxicities

Every effort should be made to avoid the use of drugs with overlapping toxicities. However, there may be circumstances where no other option is available and the potential benefits outweigh the risks. For example, a patient with a high risk of suicide that must have linezolid in the regimen (no other anti-TB drug options) could require a serotoninergic medication.

Psychiatric drugs are commonly used in MDR-TB patients for the treatment of cycloserine-induced psychosis or reactive depression. The anti-psychotics in particular are well-known to prolong the QT interval. It is the responsibility of the TB physician to understand the effects and side effects of psychiatric drugs, and to monitor MDR-TB patients taking these drugs carefully, even if the patient is referred to a psychiatrist.

Finally, a number of cardiac drugs are listed in this table. Cardiac drugs are used in MDR-TB patients for a number of incorrect reasons, such as to "prevent" arrhythmia, to treat cardiac symptoms, or to decrease the QT interval. In fact, there is no cardiac drug that can counteract or "protect" from QT prolongation. Cardiac rhythm-controlling and rate-controlling drugs should therefore only be used for clear indications. Sinus tachycardia is often a physiologic response to other pathologies. It should be viewed as a symptom, not as a cardiac disorder. For example, beta-blockers should not be used to treat sinus tachycardia in TB patients.

Table XX Non-TB drugs that have potential overlapping toxicities with the new TB drugs

	Drugs	Examples/notes
Avoid with Bdq, Dlm	Drugs that cause QT prolongation or affect the heart rhythm*	Oral azole antifungals (can be used up to two weeks): Ketoconazole, Itraconazole, Fluconazole Macrolide antibiotics: Azithromycin, Clarithromycin, Erythromycin Antipsychotics (all have some risk), including: Haloperidol, Risperidone Many anti-nausea drugs, for example: Ondansetron, Granisetron, Domperidone, Chlorpromazine Methadone Cardiac drugs that may affect the heart rhythm, for example: Amiodarone, Beta-blockers, Digoxin, Quinidine
Avoid with Lzd	Medicines that increase serotonin levels	Serotonin re-uptake inhibitors (SSRIs): fluoxetine, paroxetine Tricyclic antidepressants: amitriptyline, nortriptyline Serotonin 5-HT1 receptor agonists MAO inhibitors: phenelzine, isocarboxazid Other serotoninergic agents: meperidine, bupropion, or buspirone, quetiapine

* This is not a comprehensive list. Doctors should inform themselves about potentially QT-prolonging drugs that their MDR-TB patients may be taking (see CredibleMeds.org).

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.

Corticosteroids-

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

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.

Other severe forms of EPTB (pericardium, bone, joints) will need individualized regimen and the duration of treatment is determined by clinical and radiological response. Surgical and orthopedic consultations are important to manage any sequelae.

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. Corticosteroids should be used cautiously in pregnancy and PLHIV.

Pyridoxine supplementation-

Patients who receive treatment with DR-TB regimens require pyridoxine (Vitamin B6) supplementation for the period of the whole treatment duration given majority have underlying malnutrition and most receive regimens containing Isoniazid or cycloserine or linezolid to prevent neurological side-effects. For patient receiving the shorter standardized regimen should receive dailyoral pyridoxine 50mg tablet, while patients receiving cycloserine containing regimens receive 50mg of pyridoxine for every 250mg of cycloserine administered.

Surgery for DR TB

- Surgery as an adjunct to chemotherapy for patients with localized disease with sufficient pulmonary reserve can significantly improve outcomes where skilled thoracic surgeons and excellent pre- and postoperative care are available,
- Surgery Can be done for those Eligible candidates after they have been on chemotherapy treatment for a minimum of three months prior to surgery,
- 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,
- Patients should continue Chemotherapy Treatment for a minimum of 24 months past culture Conversion.

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

- Failure to demonstrate clinical or bacteriologic response to chemotherapyafter four 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 osteoarticular TB.

Treatment monitoring outcome assignment in longer MDR/RR-TB Regimens

Recommendation:

- In MDR/RR-TB patients on longer regimens, monthly sputum culture and sputum smear microscopy is recommended to monitor treatment response.

To monitor the treatment response in patients on longer MDR-TB regimens, it is strongly recommended that sputum culture be repeated at monthly intervals, in addition to sputum smear microscopy. The evidence used to explore the added value of culture over sputum smear microscopy alone showed a higher sensitivity of monthly culture in predicting treatment outcomes when compared with monthly smear microscopy.

Monthly culture increased the detection of patients with a true positive bacteriological result when compared with sputum smear microscopy alone; also, it reduced the proportion of patients with a false negative result. Concomitant use of sputum smear microscopy and culture test results helps to identify patients whose bacteriology remains positive or reverts to positive following initial conversion to negative. This combined testing will help clinicians to identify patients whose treatment is likely to fail, and thus to plan alternative options and institute infection control measures in a timely manner. Additional benefits would be expected from reduced transmission and development of resistance, and from appropriate changes to treatment regimens.

Regular microscopy and culture of sputum or other specimens remain important to ensure that treatment failure is detected early. Using smear microscopy or culture to assess conversion of bacteriological status is an important means of assessing response, and most patients are expected to have converted to a sputum negative status within the first few months of starting treatment. Persistence of culture positivity beyond that point, or close to the expected end of the intensive phase when injectable agents are in use, should trigger a review of the regimen and performance of DST. If DST to certain agents is not available, the strains should be stored for further investigations at the supranational TB reference laboratory. If the risk of resistance is high (e.g. after treatment failure in TB cases who are contacts of a drug-resistant TB case), sequencing methods may also provide valuable information.

It is important to use culture to continue to monitor patients at 3, 6 and 12 months after completion of treatment, to ensure sustained cure. In children, smear and culture monitoring

of the response to treatment may be challenging, for the same reasons it is difficult to obtain a bacteriological confirmation of the diagnosis. In children with a bacteriologically confirmed diagnosis, all reasonable efforts should be taken to demonstrate bacteriological conversion. Once cultures have become negative or in children who never had a confirmed diagnosis, repeated respiratory sampling may not be useful if the child is otherwise responding well clinically. Resolution of clinical symptoms and weight gain can be used as indicators of improvement. All children should have regular clinical follow-up, including weight and height monitoring. Drug dosages should be adjusted with weight gain, as needed.

Besides monthly bacteriological monitoring using monthly culture tests for the early detection of treatment failure, findings from clinical examinations (e.g. ECG, urinalysis, blood tests and radiographs) need to be taken into consideration when monitoring patients on longer regimens. The medicines included in the selected regimen determine what monitoring tests are needed; for example, clinical and biochemical assessment for linezolid; clinical assessments for peripheral neuropathy and psychiatric disturbances; electrocardiography and monitoring of electrolytes, particularly when the regimen contains multiple QT interval prolonging agents (e.g. bedaquiline, delamanid, moxifloxacin and clofazimine). Any adverse events during treatment should be managed immediately to relieve suffering, minimize the risk of treatment interruptions, and prevent morbidity and mortality. Schedules for clinical, biochemical and microbiological testing are indicated in Table 5.12 below. Treatment monitoring should be carried out in the context of mainly ambulatory care, using a decentralized model of care.

Treatment monitoring and follow-up

Patients should be seen by a doctor or experienced Health officer after discharge from the DR-TB Centre, at monthly TIC Visits 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.

The monitoring should follow standard clinical assessment:

a) Clinical monitoring:

- 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) 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 5.12. : Schedule for Clinical monitoring in DR TB Treatment

	Baseline Visit	**W 2**	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**While on injectable***	**Until end of treatment**	**End of treatment**	**Post-treatment month 6**
Clinical evaluation												
Vital signs	X		X	X	X	X	X	X	Monthly			
Brief Peripheral neuropathy screen (BPNS)	X		X	X	X	X	X	X	Monthly		X	X
Audiometry (patients on SLI)	X		X	X	X	X	X	X	Monthly		X	
Visual acuity and color vision screen	X		X	X	X	X	X	X	Monthly		X	X
Outcome consultation											X	X
Assessment/follow-up of AEs	X	X	X	X	X	X	X	X	At each scheduled /unscheduled visit		X	X
Weight	X	X	X	X	X	X	X	X	Monthly		X	
Bacteriological testing												
Smear	X		X	X	X	X	X	X	Monthly		X	X
Culture	X		X	X	X	X	X	X	Monthly		X	X
Xpert MTB/RIF	X											
Hain GenoType MTBDRsl	X			If smear- or culture-positive								
Culture-based FL DST	X			If smear- or culture-positive								
Culture-based SL DST	X			If smear- or culture-positive								
Laboratory/Clinical/Radiology testing												
ECG	X	X	X	X	X	X	X	X			X	X
Full Blood Count	X	X	X	X	X	X	X	X	Monthly		X	
Urea, creatinine	X		X	X	X	X	X	X	Monthly		X	
Serum electrolytes	X		X	X	X	X	X	X	Monthly		X	
Liver function tests	X		X	X	X	X	X	X	Monthly		X	
TSH	X				X				every 3 months			
Hepatitis Bs Antigen	X											
Hepatitis C Antibody	X											
HbA1c or FBS	X											
Pregnancy test	X											
HIV serostatus	X											
CD4 (repeated every 6 months if HIV+)	X											
HIV VL (repeated every 6 months if HIV+)	X											
Chest X-Ray	X							X			X	

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 back to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. The purpose of defined treatment failed, reversion is considered only when it occurs in the continuation phase.

General Notes on Monitoring

- 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.
- Objective laboratory evidence of improvement often lags behind clinical improvement.
- 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.
- 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,
- If patients are adherent to an effective regimen, culture will convert to negative by three months of treatment.
- Patients with fewer effective drugs in their treatment regimens (e.g., XDR- TB) will convert more slowly.
- The recurrence of TB symptoms after sputum conversion, for example, may be the first sign of failure.
- Persistently positive cultures beyond the month 4 are a sign of likely treatment failure. Non-Tuberculous Mycobacteria (NTM) could also be possible reasons.
- For patients who remain smear- and culture-positive beyond four months during treatment, second line DST should be done.
- Reversion of cultures back to positive in continuation phase after converting negative defines treatment failure.

Post-Treatment Monitoring

Post treatment monitoring is important to:

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

Once patient has completed the RR/MDR-TB Regimen (shorter or longer regimen), post treatment assessment must be performed at month **3**, month **6** & month **12** after completion of the recommended regimen.

Recording of post treatment follow up result (treatment card, register) should be done.

The post treatment completion 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.

Post-treatment final outcome of treatment:

All patients defined as treatment cure, complete, treatment outcome other or transfer out will be assessed for:

Relapse-free: a DR TB patient who met the criteria of cured or completed treatment based on the nationally recommended DR-TB treatment protocol, and who is declared free of active TB disease at the end 12 month after treatment completion.

Relapse: a DR TB patient who meets the criteria of cured or completed using nationally recommended DR-TB treatment, and is subsequently diagnosed with at least one sample of bacteriologically positive MDR TB by culture and DST at any time during the 12 month post treatment follow up period.

Loss to follow up during post treatment follow up: a DR TB patient with an outcome at the

end of treatment of treatment cure, complete, who is loss to follow up during the 12 month post treatment period (as assessed at the end of 12 months).

Note that if patients miss the 6 month post treatment follow up appointment but are assessed at the 12 month follow up review they are still able to be assessed for an end of follow up period final outcome.

Death during post treatment follow up: An MDR TB patient with an outcome at the end of treatment of treatment cure, complete, who dies of any cause during the 12 months post treatment follow up period.

MANAGEMENT OF DR TB TREATMENT INTERRUPTIONS

All efforts should be made to ensure that DR 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 two days. 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 treatment supporter 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.

Management of treatment interruptions

Patients in IP(intensive phase)/ CP(continuation phase) 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.

1. **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. (for both STR and Individualized Regimen)

2. **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.(for both Shorter & longer Regimen)

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 registration group 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.
6. For patients on All-Oral Bdq containing Shorter regimen, and who fulfil the criteria of lost to follow up and return (has taken the treatment for > 1 month and discontinued for > 2month) should stop their regimen regardless of duration of discontinuation is < 6 month , should have SLD DST sent and put on Individualised longer Regimen based on DST pattern after consultation with Regional/ National CRC.

A) Re initiating 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 with an individualized regimen; • Send sputum for culture and DST and adjust regimen according to the results.
3 months to end of intensive phase	Negative	• Consult clinical review committee for further recommendations
	Positive	• Consider designing a new individualised regimen using latest SL-DST with consultation of CRC
Continuation Phase	N/A	• If patient has no evidence of clinical deterioration during the interruption, Send sputum for culture and DST; o If negative- monitor the patient quarterly if develop active disease. o If positive- do SLD DST and review with report and

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
- And put the patient on individualized regimen based on the DST result.

APPROACH TO MDR-TB TREATMENT FAILURE:

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.

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.

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 drug 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.

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 in consultation with Regional/National CRC.

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.

Treatment of Rifampicin susceptible and isoniazid resistant TB (Hr-TB)

- In patients with confirmed rifampicin-susceptible, isoniazid resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months.
- In patients with confirmed rifampicin-susceptible, isoniazid resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen.

The recommended Hr-TB regimen in Ethiopia is therefore

Hr-TB Regimen: 6(H)REZ-Lfx

All medicines in this regimen are to be used daily for 6 months. When fixed-dose combination formulations are used, isoniazid is included but is not obligatory for the regimen. If levofloxacin cannot be used because there is fluoroquinolone resistance or intolerance or other contraindications to the use of fluoroquinolone, then 6(H)REZ may be prescribed daily for 6 months.

Eligibility Criteria for Hr-TB Regimen

The Hr-TB regimen is recommended once isoniazid resistance has been confirmed and rifampicin resistance excluded.

Rifampicin resistance needs to be excluded using rapid molecular tests (e.g. Xpert MTB/RIF) before levofloxacin is used; this is to avoid the inadvertent treatment of MDR/RR-TB with an inadequate regimen. Ideally, DST for fluoroquinolones and pyrazinamide is also performed.

It is not advisable to give a regimen for Hr-TB unless isoniazid resistance is confirmed or highly suspected (e.g. confirmed TB patient who is the close contact of a documented Hr-TB case). This will avert the unnecessary use of levofloxacin and prolonged pyrazinamide exposure in TB patients who may be cured with 2HREZ/4HR.

Once the Hr-TB regimen has been started, if the results of initial DST reveal isoniazid susceptibility, the regimen may be modified so that the patient effectively completes a course of first-line TB treatment.

The recommendations apply to both adults and children, including people living with HIV (PLHIV). Thus, HIV testing and treatment of PLHIV with antiretroviral therapy (ART) is important, and the aim is to start ART within 8 weeks of TB treatment initiation (regardless of CD4 count), or within the first 2 weeks in patients with profound immunosuppression (e.g. CD4 counts <50 cells/mm3

). The regimen is also likely to be effective in patients with extrapulmonary Hr-TB; however, consultation with appropriate specialists is advised.

Hr-TB treatment needs to be started if either of the following circumstances apply:

- Hr-TB is confirmed and rifampicin resistance ruled out before TB treatment is started – in such cases, the 6(H)REZ-Lfx regimen is started immediately. If the diagnosis is strongly presumed (e.g. close contacts of a confirmed Hr-TB source case) but results of DST are still pending, the regimen may be introduced. Should DST results taken at

the start eventually show susceptibility to isoniazid, then levofloxacin is stopped and the patient continues treatment in order to complete a 2HREZ/4HR regimen; **or**

- Hr-TB is discovered after the start of treatment with the 2HREZ/4HR regimen (this includes patients who had undiagnosed isoniazid resistance at the start or who developed isoniazid resistance while on first-line treatment) – in such cases, rapid molecular testing for rifampicin resistance must be done (or repeated). Once rifampicin resistance has been excluded, a full 6-month course of (H)REZ-Lfx is given. The duration is driven by the need to give levofloxacin for 6 months, which usually implies that the companion first-line medicines are taken for longer than this. A report of resistance during treatment presents the clinician with a challenge, because the results may no longer reflect the drug susceptibility of the current bacterial population, given that an inadequate regimen – at times a functional monotherapy – may have favoured the acquisition of additional resistance in the interval. The unexpected discovery of resistance to one agent should prompt the clinician to repeat DST for other agents in the regimen.

Table 5.13: Decision table for initiation of Hr-TB Regimen in Ethiopia

TB Treatment Status	Lab Confirmation Status	Recommended actions	Remark
Newly Detected	Confirmed Hr-TB	• Initiate treatment with Hr-TB Regimen • Do SL-LPA (if not done already) to rule out FQ-Resistance	If FQ Resistance is detected, consult the regional/national CRC for regimen design.
	Suspected Hr-TB (e.g. TB patient who is the Contact of confirmed Hr-TB)	• Do Xpert MTB/RIF Test (if not done already) • Send sputum sample for DST (FL-LPA and SL-LPA) • Initiate Hr-TB Regimen while awaiting the DST results	Adjust the regimen once DST results becomes available based on DST results
Previously Treated or Hr-TB discovered in a patient on DS-TB Treatment	Confirmed Hr-TB	• Update DST (including Xpert/MTB RIF test, FL-LPA, SL-LPA) • Initiate the full Hr-TB Regimen (6 months of (H)REZ-Lfx	The companion medicines for Lfx (R,E,Z) to be taken for more than six months in such cases
	Suspected Hr-TB (e.g. TB patient who is the Contact of confirmed Hr-TB)	• Do Xpert MTB/RIF Test (if not done already) • Send sputum sample for DST (FL-LPA and SL-LPA) • Initiate Hr-TB Regimen while awaiting the DST results	Adjust the regimen once DST results becomes available based on DST results

Composition and duration of the Hr-TB regimen

The duration of Hr-TB treatment is driven by the need to complete 6 months of a fluoroquinolone containing regimen. This implies that, when Hr-TB is diagnosed after the start of a first-line regimen, the companion medicines (HREZ) would end up being given for more than 6 months.

In patients with cavitary disease and with persistent positivity on sputum smear and culture, prolongation of (H)REZ-Lfx beyond 6 months could be considered on a case-by-case basis. Prolongation of treatment increases the risk of toxicity, particularly from pyrazinamide and ethambutol, which are usually only given for 2 months in the first-line TB regimen. The evidence reviewed for the WHO guidance on Hr-TB precluded a recommendation to limit the pyrazinamide duration to less than 4 months when a fluoroquinolone is given.

Levofloxacin is the preferred fluoroquinolone for Hr-TB regimens, for two reasons. First, exposure to moxifloxacin decreases markedly when it is combined with rifampicin. This effect has not been reported in the case of levofloxacin, possibly because this interaction has attracted less study. Second, levofloxacin appears to cause less QT interval prolongation than moxifloxacin.

Levofloxacin is included in Hr-TB regimens except in the following instances:

- when rifampicin resistance cannot be tested for,
- when there is documented resistance or known intolerance to fluoroquinolones, and
- when there is pre-existing prolongation of the QT interval and pregnancy.

If a fluoroquinolone cannot be used, a patient with Hr-TB can still be treated with 6(H)REZ; streptomycin is not required in such cases.

For patient convenience and ease of administration, the HREZ fixed-dose combination (FDC) may be used to treat Hr-TB (since no REZ FDC is currently available). The dosage of other first-line agents in the Hr-TB regimen is the same as in the standardized first-line 2HREZ/4HR regimen.

The inclusion of isoniazid in the regimen has not been shown to lead to substantial benefit or harm to patients; however, isoniazid may attenuate the hepatotoxicity of pyrazinamide.

High-dose isoniazid (10–15 mg/kg per day) may still be effective when used in combination regimens in the presence of isolated inhA mutations linked to low minimum inhibitory concentration (MIC), even in “fast acetylators” (i.e. those who metabolize isoniazid rapidly). In the presence of both inhA and katG mutations, addition of isoniazid (even at a high dose) is unlikely to add value to the regimen.

Patients with Hr-TB may have a higher risk of acquiring additional resistance and MDR-TB, which may manifest in the course of the same treatment episode or in a subsequent relapse. The effect of additional resistance to ethambutol and pyrazinamide on the treatment of Hr-TB is unclear.

Considerations for implementation of HR-TB Regimen

The regimens recommended for treatment of Hr-TB do not have an intensive and a continuation phase – this simplifies the delivery and monitoring of treatment. Treatment is given daily, and intermittent treatment should be avoided. Relevant measures to support adherence, such as directly observed treatment (DOT), social support and the use of digital technologies should be considered to ensure favourable treatment outcomes.

Use of FDCs simplifies treatment and lowers costs, and the use of dispersible formulations of HRZ, ethambutol and levofloxacin is preferred in children.

There is currently no diagnostic platform approved for the detection of Hr-TB that matches the rapidity and convenience of Xpert MTB/RIF for rifampicin resistance, although a new Xpert cartridge that can detect isoniazid resistance is in the pipeline. First-line LPA can detect isoniazid resistance; it requires infrastructure that is typically available in a TB reference laboratory. Typical processing time for an LPA specimen is about 2–3 days, owing to batching. DST based on liquid culture (or MGIT) could also detect Hr-TB at the level of a reference laboratory, but this means an obligatory processing delay of at least 10 days. Testing on solid media is also an option, but it takes several months to obtain results; hence, this approach is of limited use for baseline testing and monitoring of treatment response.

Current epidemiological data indicate that more than three quarters of the global burden of Hr-TB occurs among previously untreated ("new") TB cases. Previous TB treatment is thus not a strong indicator of risk of Hr-TB – the correlation with previous TB treatment is weaker than it is with MDR-TB. Reserving isoniazid DST to such patients is therefore unlikely to yield many Hr-TB cases.

There are various concerns about empirical Hr-TB treatment of previously treated TB cases, without prior drug susceptibility testing.

- First, such treatment will lead to unnecessary overtreatment with fluoroquinolones and prolongation of pyrazinamide use in many patients. Most re-treatment cases will not have Hr-TB and can be cured with a 2HRZE/4HR regimen.
- Second, unless rifampicin resistance is excluded at the baseline, patients with MDR/RR-TB would be exposed to an inadequate regimen, with the risk of acquiring additional resistance, including fluoroquinolones.
- Third, this policy would deflect the focus of the programme from testing new (previously untreated) TB patients, who usually harbour the main burden of Hr-TB.
- Finally, this approach would risk creating once again a "re-treatment regimen", similar to the situation that prevailed in many settings until recently with the indiscriminate use of the streptomycin-containing 8-month "Category 2" regimen in all previously treated TB patients.

In a situation where access to DST is good, a logical diagnostic algorithm would start with Xpert MTB/ RIF as the initial test for all patients evaluated for TB. Cases in whom TB is confirmed and rifampicin resistance is not detected would be further tested with LPA. Liquid culture may replace LPA, but the additional delay in getting results is a disadvantage.

Treatment of patients with Hr-TB shall be initiated at DR-TB TICs in Ethiopia with subsequent follow up at any TB clinic closer to patient's home. If initiation of treatment can not be done at TIC level for one or another reason, treatment can be safely initiated at the DS-TB Clinic nearby patient's home, with supply of Lfx to be requested from catchment TIC.

Treatment monitoring of Hr-TB

The clinical monitoring of patients on Hr-TB treatment follows similar principles to those that apply to other first-line TB regimens.

Bacteriological monitoring of sputum generally follows the same schedule as drug-susceptible TB, with direct microscopy at months 2, 5 and 6. It is desirable, however, to perform a culture together with smear microscopy (or at least in the last month of treatment) to check for any

emergent resistance, especially to rifampicin. Non-response to treatment should be investigated with DST.

Liver and kidney function and other blood tests may be necessary, based on clinical manifestations and medications in use. Electrocardiography (ECG) for patients on 6(H)REZ-Lfx is not usually required unless there are other risks for QT interval prolongation.

The first-line TB agents may cause adverse drug reactions, which are mostly mild, not serious and self-limiting, or manageable with basic measures. TB Focal persons at health facilities are likely to be more familiar with the use of these medicines than with levofloxacin, which has a fairly good safety profile in both adults and children when used at the dose recommended, even when taken for longer than 6 months (as in MDR-TB regimens).

Dosage adjustment is recommended if creatinine clearance is below 50 mL/min, in consultation with a specialist or CRC. Adverse drug reactions should be reported to the pharmacovigilance systems as per the national requirement. In patients on regimens for Hr-TB, aDSM is not mandatory.

Treatment of Hr-TB with Lfx containing treatment should be initiated at the nearby TIC as ambulatory care and DOT should be practiced at the nearby catchment TFC with similar clinical and bacteriologic monitoring as susceptible TB and monthly drug supply from the TIC.

Hr-TB cases given fluoroquinolones or other second-line agents in addition to 6(H)REZ shall be registered in the second-line TB register to monitor how many patients are being given regimens containing second-line medicines. It is important that cases without RR-TB are not enumerated with the MDR/RR-TB cohort for treatment outcome monitoring purposes.

It will be helpful to monitor efforts to improve testing coverage, detection, enrolment and outcomes for Hr-TB separately from other TB or MDR/RR-TB cases. The indicators for MDR/RR-TB may be adapted for this purpose; outcome definitions are the same as for non-MDR/RR-TB. Reporting can be aligned to the same frequency recommended for standard monitoring of other TB cohorts.

Combining data for patients with different resistance patterns into a single cohort may complicate comparison of performance between centres and determination of trends over time, given that these patients may have different risks for treatment failure. However, treatment of TB patients who do not have rifampicin resistance with regimens discussed in this section should lead to a successful outcome in most patients, and maximizing the likelihood of success should be the end objective of TB programmes. The use of electronic case-based databases facilitates the grouping of patients by comparable resistance patterns or treatment episode to undertake more advanced analyses, allowing the adjustment for at least some covariates.

6. MANAGEMENT OF ADVERSE DRUG REACTIONS

Learning Objectives:

By the end of the session, participants will be able to:

- Identify common adverse drug reactions (ADR)
- Screen, detect and manage common ADR to second line drugs

Key Definitions

Side Effect: Any unintended effect of a pharmaceutical product occurring at doses normally used in humans which is related to the pharmacological properties of the medicine. Such effect may be either positive or negative. Such effects may be well-known and even expected and may require little or no change in patient management.

Adverse Drug Reaction (ADR): Any response to a drug which is noxious and unintended, and which occurs at doses normally used in human for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.‖ In other words, an ADR is harm directly caused by the medicine at normal doses, during normal use.

Adverse Drug Events (ADE): Any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product that occurs while the patient is taking the medicine but is not, or not necessarily, attributable to it. AE includes also adverse drug reaction (ADR), Medication Error (ME), or Product Quality Defect (PQD).

Monitoring for ADR

Drugs have other additional effects than their initial intended effect. Harmful effects of drugs are called adverse drug reactions (ADR). The second line anti-TB drugs have more ADR than the first line drugs. Systematic monitoring for ADR, early detection and management is crucial to prevent permanent morbidities, improve adherence and avoid TB treatment failure. Patients with co- morbidities require more frequent ADR monitoring.

Systematic ADR monitoring includes:

1) Active Symptomatic screening and regular physical examination at every visit,
2) Regular laboratory and other diagnostic test evaluations. (see table in monitoring section…).

The health care provider should anticipate ADR early and provide the appropriate management. Most of the ADR occur in the early period of treatment initiation and diminish with the progress of the treatment.

Since MDR regimens contain several drugs, it is very difficult to incriminate one of the drugs as a cause. ADRs can be due to:

- One or multiple drugs
- Drug–drug interactions
- Overlapping and additive toxicities
- The presence of underlying co-morbid conditions (eg. Renal failure, liver disease)

Management of ADR

The management of the ADR is equally important as the treatment of TB itself. Proper management starts from the pretreatment 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 interaction.
- Regular monitoring of treatment for early detection of signs of Adverse effect/toxicity.

Once ADR occurs, the management requires comprehensive evaluation and multidisciplinary approach.

ADRs may be classified according to their severity;

While some ADRs are mild and self-limiting, some are severe and persistent requiring discontinuation of the offending agent.

Table 6.1. Classification of ADRs and Management

Degree of ADRs	**Management at Primary level**	**Management at hospital level**
Mild	• The condition should be explained to the patient and reassured. • The necessary supportive measures and ancillary drugs can be given. • No need for patient referral to higher level, unless persistent.	• Patient counseling and reassurance. • Supportive treatment with ancillary drugs is recommended • Management does not require treatment interruption or change in drug dose/frequency of administration.
Moderate	• Resuscitate the patient and • Refer immediately to TIC for proper management • Referral arrangement shall be made to hospital for decision on further management	• Stabilize the patient • Investigate for the immediate and underlying cause of the problem • Management may require temporary discontinuation or dose adjustment to lower therapeutic level of the causative agent(s) till recovery. • After recovery of patients' condition, the offending agent may be substituted with alternative drug or it could be re-administered.
Severe (life-threatening Or very disabling to the patient)	• The common conditions include severe hepatitis, nephrotoxicity, acute psychosis, suicidal ideation or a generalized hypersensitivity reaction • Immediate management requires resuscitation of the patient, discontinuation of the offending drug or temporary discontinuation of the whole treatment • Patient referral should be arranged to hospital immediately.	• In-patient management is required • Stabilization of the patient's general condition should be given priority while investigation for the immediate and underlying cause of the problem • Management may require permanent discontinuation with regimen modification • Consult senior expert in the subsequent Patient's management.

Health care provider at treatment follow up centers should be able to identify ADR and start the initial management measures such as explanation of the situation for the patient, prescribing the necessary ancillary medications and supportive psychosocial care. In case of severe ADRs it is recommended to hold on the suspected offending agent and refer without delay to the treatment initiation center for better evaluation and management.

Ancillary medication and adjunctive therapy:

Ancillary medications are very important for the management of ADR and should always be made available at treatment centers.

Pyridoxine should always be prescribed to patients taking medications with neurotoxic ADRs like H, Cs, & Lzd for prophylaxis and therapeutic purpose. The dose of pyridoxine is in a proportion of 50 mg to every 250mg of Cs and 300 mg of H prescribed daily. It may be increased to 200mg in patients who develop neuropsychiatric side effects. A single dose of pyridoxine 50 mg is enough for prophylaxis of other medicines unless there is additional indication for the increment of the dose.

Indications for adjuvant steroid therapy is similar to that of drug sensitive TB.

Specific ADR management:

Common adverse events are summarized as follows in table below and details on symptomatic management of ADR specific to Anti-TB treatment are presented on Annex 3.

AEI	Severity grading	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Peripheral neuropathy	Paresthesia (Burning, Tingling, etc.)	Mild discomfort; no treatment required; and/or BPNS subjective sensory neuropathy score 1- 3 on any side.	Moderate discomfort; non-narcotic analgesia required; and/or BPNS subjective sensory neuropathy score 4-6 on any side.	Severe discomfort; or narcotic analgesia required with symptomatic improvement; and/or BPNS subjective sens	Incapacitating; or not responsive to narcotic analgesia
	Action	Stop Cs, high dose H, and Lzd. If symptoms improve, consider restarting these drugs. Consider restarting Lzd at a lower dose (300mg daily or 600 mg thrice weekly). If Cs or high dose H are not essential to the regimen, consider suspending these drugs.	Stop Cs, high dose H, and Lzd. If symptoms improve, and if the drugs are essential to the regimen, consider restarting Cs or high-dose H. Do notreintroduce Lzd. Provide symptomatic relief as described in Annex 8.	Same as Grade 2.	Same as Grade 2.
Myelosuppression	Hgb	10.5 - 9.5 g/dL	9.4 - 8.0 g/dL	7.9 - 6.5 g/dL	< 6.5 g/dL
	Platelets count	99,999 - 75,000 /mm³	74,999 - 50,000 /mm³	49,999 - 20,000 /mm³	< 20,000 /mm³
	WBC count	<LLN - 3,0	<3,000 -2,000/mm	<2,000 -1,000/mm3	< 1,000/mm3
	Neutrophil count	1500 -1000/mm3	999 - 750/mm3	749 - 500/mm3	<500/mm3
	Action	Monitor carefully, and consider reduction of dose of Lzd (300mg daily or 600 mg thrice weekly).	Monitor carefully, and consider reduction of dose of Lzd (300mg daily or 600 mg thrice weekly); in case of Grade 2 neutropenia, stop Lzd immediately. In case of Grade 2 anemia, consider EPO. Restart at reduced dose once toxicity has decreased to Grade 1.	Stop Lzd immediately. In case of Grade 3 anemia, consider EPO. Restart at reduced dose once toxicity has decreased to Grade 1	Stop Lzd immediately. Consider hemotransfusion or EPO. Restart at reduced dose once toxicity has decreased to Grade 1.

Prolonged QT Interval	Electrocardiogram QT Corrected Interval Prolonged	QTcF 450 – 480 Ms	QTcF 481 – 500 Ms	QTcF >= 501 ms Without signs/ symptoms of serious arrhythmia	QTcF >= 501 or >60 ms change from baseline and one of the following: Torsade pointes or PVT or signs of serious arrhythmia
	Action	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade 1. Replete electrolytes as necessary.	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade 1. Replete electrolytes as necessary.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.	Stop the suspected Causative drug(s). Hospitalize and replete Electrolytes as necessary.
Optic nerve disorder		Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye (20/40 [6/12] or better)	Limiting vision in the affected eye (worse than 20/40 [6/12] but better than 20/200 [6/60])	Blindness (20/200 [6/60] or worse) in the affected eye
	Action	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart.
Hepatitis	ALT (SGPT)	>ULN – 3.0 x UL	>3.0 – 5.0x ULN	>5.0 – 20.0 x ULN	>20.0 x UL
	AST (SGOT)	>ULN – 3.0xULN	>3.0 – 5.0 x UL	>5.0 – 20.0 x ULN	>20.0 x UL
	Action	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Continue TB Rx regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Stop all rugs, including anti-TB drugs; measure LFTs weekly. Treatment may be re-introduced after toxicity is resolved.	Stop all drugs, including anti-TB drugs; measure LFTs weekly. Reintroduce treatment after toxicity is resolved.

Hearing impaired	Hearing Impaired	Adults Enrolled on a Monitoring Program (on a 1, 2, 4, 3, 6 and 8 kHz audiogram): threshold shift of 15 -25 dB averaged at 2 contiguous test frequencies in at least one ear or subjective change in the absence of a Grade 1 Threshold shift. Pediatric (on a 1, 2, 4, 3, 6 and 8 kHz audiogram): threshold shift >20 dB at 8 kHz in at least one ear.	Adult enrolled in monitoring program (on a 1, 2,3, 4, 6 and 8 kHz audiogram): threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear. Adult not enrolled in monitoring program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL. Pediatric (on a 1,2, 3, 4, 6 and 8 kHz audiogram): threshold shift >20 dB at 4 kHz and above in at least one ear.	Adult enrolled in monitoring program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated. Adult Not enrolled in monitoring program: Hearing loss with hearing Aid or intervention indicated; limiting self-care ADL. Pediatric (on a 1, 2, 3, 4, 6 & 8kHz audiogram): hearing loss sufficient to Indicate therapeutic intervention, including hearing aids): Threshold shift >20 dB at 3 kHz and above in at least one ear; additional speech-language related services indicated.	Adults: profound bilateral hearing loss (Threshold >80 dB HL at 2 kHz and above); nonsurvivable hearing Pediatric: audiologic indication for cochlear implant and additional Speech-language related services indicated.
	Action	Consider regimen shifting to injectable free LTR	Consider regimen shifting to injectable free regimens	Consider regimen shifting to injectable free regimens	Consider regimen shifting to injectable free regimens
Acute kidney injury	Acute Kidney Injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequence; dialysis indicated
	Action	Consider regimen shifting to injectable free regimens	Consider regimen shifting to injectable free regimens	Consider regimen shifting to injectable free regimens	Consider regimen shifting to injectable free regimens

Hypokalemia	Hypokalemia	Serum Potassium 3.4 - 3.0 mmol/L	Serum Potassium 2.9 - 2.5 mmol/L	Serum Potassium 2.4 - 2.0 mmol/L or intensive replacement therapy or hospitalization required	Serum Potassium < 2.0 mmol/L or abnormal potassium *with* paresis, ileus or life- threatening arrhythmia
	Action	Consider regimen shifting to injectable free regimens if on injectables	Consider regimen shifting to injectable free regimens if on injectables	Consider regimen shifting to injectable free regimens if on injectables	Consider regimen shifting to injectable free regimens if on injectables
Hypomagnesemia	Hypomagnesemi	0.70-0.60 mmol/L	0.59-0.45 mmol/L	0.44-0.30 mmol/L	<0.30 mmol/L
	Action	Start oral magnesium replacement therapy.	Start aggressive oral magnesium replacement therapy.	Start intravenous magnesium replacement therapy in addition to oral. Replace other electrolytes as necessary.	Start intravenous magnesium replacement therapy in addition to oral. Replace other electrolytes as necessary.
Hypothyroidism		Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; Thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL hospitalization Indicated	Life-threatening consequence; urgent intervention indicated
	Action	Continue anti-TB drugs.	Continue anti-TB drugs. Start thyroxine.	Continue anti-TB drugs. Start thyroxine.	Stop all anti-TB drugs. Start thyroxine.
	*NCI Common Terminology Criteria for Adverse Event, v.4.03 14-Jun-2010. Adapted from EndTB Consortium. *endTB Clinical and Programmatic Guide for Patient Management with New TB Drugs*. Version 4.0; January 2018.				

Pharmacovigilance or drug safety monitoring for TB drugs:

Pharmacovigilance (PV) is the science and activities relating to thedetection, assessment, understanding and prevention of adverse drug reactions or any other drug-related problems.

All patients, irrespective of the treatment regimen, are monitored and assessed clinically for AEs (including lab abnormalities) at all visits during treatment. Systematic symptomatic screening and referral for potential AEs is a mandatory part of scheduled and unscheduled visits. In addition, the evolution and outcome of the previously recorded AEs should be systematically assessed.

Laboratory screening for hematologic and biochemical abnormalities and ECG for monitoring of the QT length are conducted at specific scheduled visits during treatment and whenever is indicated. Safety data collection starts at time of first MDR TB treatment administration. Each AE is followed-up until resolution or stabilization.

Approaches to Pharmacovigilance

1. Spontaneous reporting:

Spontaneous (or voluntary) reporting (also called passive pharmacovigilance) is the most common form of PV whereby no active measures are taken to look for adverse effects other than the encouragement of health professionals and others to report safety concerns. Reporting is entirely dependent on the initiative and motivation of the potential reporters. It can be designed to be a targeted Spontaneous reporting (TSR) if it is intended to capture ADEs in a well-defined group of patients on treatment.

2. Active Pharmacovigilance:

In active Pharmacovigilance, active measures are taken to detect adverse events & is achieved by the active monitoring at start, during and at times after treatment.

The events may be detected by screening patient records, direct questioning of the patients and through laboratory testing at predefined intervals.

An Active Pharmacovigilance can be implemented in two ways:

I. Cohort Event Monitoring (CEM): is a prospective, observational, cohort study of adverse events associated with one or more medicines. It is usually recommended to enroll 10,000 in the cohort for analysis.

II. Active Drug Safety Monitoring and Management (aDSM): refers to the active and systematic, clinical and laboratory assessment of patients on treatment to detect, manage and report suspected or confirmed drug toxicities. The use of novel regimens such as regimens containing BDQ/DLM and shorter standardized DRTB treatment in the treatment of DR-TB are main reasons for the national TB program to introduce active DSM(aDSM) as part of the treatment services.

aDSM is a pre-requisite for a successful introduction and continued use of novel RR/MDR-TB treatment regimens, either longer or shorter treatment regimens.

Safety data collection for drugs used in DR-TB Treatment

The rationale for aDSM is largely supported by the increasing worldwide use of combinations of new and repurposed medications in MDR-TB treatment regimens. The toxicity of certain agents may increase with the duration of use (such as nerve damage with linezolid) and may limit their continued use in a patient, and at times, result in complete cessation of treatment.

All PMDT sites treating eligible patients with regimen containing bedaquiline or delamanid; novel shorter standardized MDR-TB regimens or for XDR-TB required to collect a safety data on medicines. In addition to SAEs, TICs should collect and report a safety data on the following elements:

- **Serious Adverse Events (SAEs):** defined as any untoward medical occurrence that, at any dose:
  - Results in death,
  - Requires hospitalization or prolongation of hospitalization,
  - Results in persistent or significant disability/incapacity,
  - Is life-threatening; life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe,
  - Results in/Is a congenital anomaly or a birth defect,
  - Is otherwise medically significant; Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above.

- **AEs of special interest** is an AE documented to have occurred during clinical trials and for which the monitoring programme is specifically sensitized to report regardless of its seriousness, severity or causal relationship to the TB treatment & pertaining to the following medical conditions:
  - Peripheral neuropathy (paraesthesia)
  - Psychiatric disorders and central nervous system toxicity
  - Optic nerve disorder (optic neuritis) or retinopathy
  - Ototoxicity
  - Myelosuppression
  - Prolonged QT interval
  - Hepatitis
  - Hypothyroidism
  - Hypokalemia
  - Acute kidney injury (acute renal failure)
- **Pregnancy** must be avoided during DR-TB treatment and effective contraception is recommended. If despite all precautions, a patient is found to be pregnant, the pregnant patient should be referred to TIC for urgent decision if patients are on follow up at TFC and to ensure the patient receives standard of DR-TB treatment for pregnant women. All pregnancies (including pregnancies of partners of male patients) should be followed-up until an outcome is known. Infants born from exposed pregnancies should be followed-up until they reach 12 months of age.
- **Medication errors** are unintended mistakes in the prescribing, dispensing and administration of a medicine that could cause harm to a patient (e.g. wrong drug prescribed, overdose) must be managed on a case by case basis. Hospitalization should be considered as appropriate. The clinician is responsible for appropriately managing AEs, drug-exposed pregnancies, and potential medication errors in accordance with the local standards of care and for referring the patient to the appropriate specialist if needed. He/she should additionally assess the benefit of the continuation of the current TB treatment in the light of the whole clinical picture: weighing treatment continuation benefits vs. the risks (including AEs, pregnancy exposure, abnormal lab results, etc.).

Recording, medical assessment and notification of adverse events:

A) Immediate reporting (within 24 hours of awareness) of Serious Adverse Events (as defined in section 6.5.6), drug-exposed pregnancies and medication errors (with or without associated AEs/SAEs) to the FMHACA, NTP, CRC, as recorded as follows:

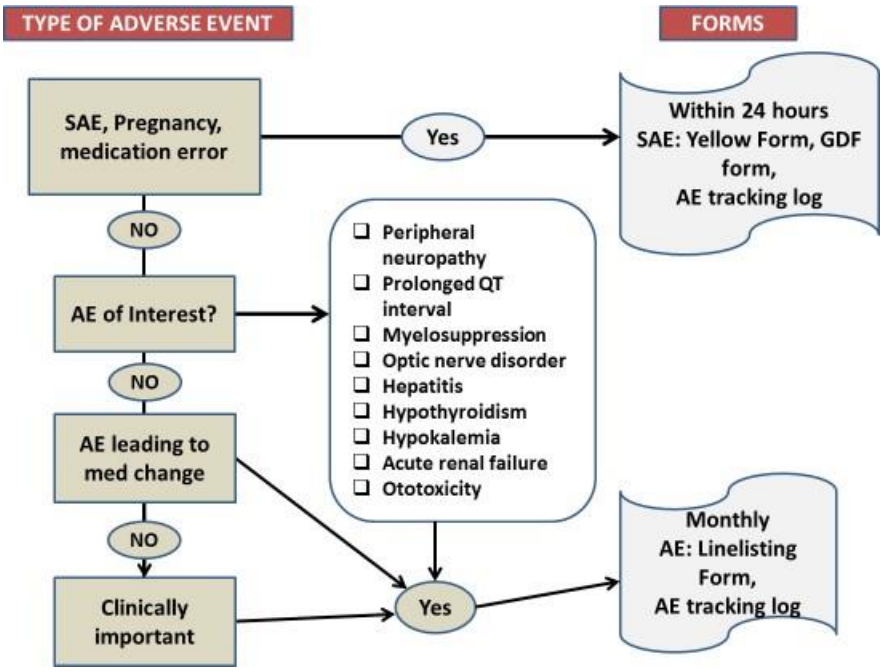
Health professionals may use one or more of the following mechanisms for immediate transmission of report ADEs to FMHACA and national TB program using:

1) Pre-paid Yellow form
2) Telephone 0115524122,0115523205, 8482 (free toll)
3) www.fmhaca.gov.et online reporting (PVDMS.net)
4) efmhacapharmacovigilance@gmail.com

B) Routine recording of all other AEs (non-serious) such as AEs of special interest, AEs leading to treatment change, and AEs otherwise judged to be clinically significant by the treating physician using the AE Form.

All AEs of the novel regimens (longer or shorter regimen) should be reported on monthly bases using monthly AE line listing form

Fig 6.1 : Reporting mechanism and Timeline of AE/SAE/AEIs:



Required medical assessment of documented SAEs/AEs:

Two types of medical assessment are expected from the clinician at time of data collection. Upon recording, all SAEs and AEs should be graded for severity according to the provided Severity Grading Scale (grades 1- 4). For those AEs not described in the Severity Grading Scale, the general definition of clinical severity should apply.

Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Life threatening
Transient or mild discomfort (<48 hours); no medical intervention/therapy required.	Mild to moderate limitation in activity* Some assistance may be needed; no or minimal medical intervention/therapy required.	Marked limitation in activity*, some assistance usually required; medical intervention/therapy required, hospitalizations	Extreme limitation in activity*, significant assistance required; significant medical intervention/therapy required, hospitalization hospice care probable

**The term 'activity' covers basic self-care functions such as bathing, dressing, toileting, transfer/movement, continence and feeding; but also, usual social and functional activities or adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.*

Besides, causality assessment also needs to be conducted to find out the relationship between the suspected drug and AE using commonly used internationally accepted scales.

Table 6.2. . WHO-UMC Causality Categories:

Causality term	**Assessment criteria***
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake Cannot be explained by disease or other drugs Response to withdrawal plausible (pharmacologically, pathologically) Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) Re-challenge satisfactory, if necessary.

Probable/ Likely	Event or laboratory test abnormality, with reasonable time relationship to drug intake Unlikely to be attributed to disease or other drugs Response to withdrawal clinically reasonable Re-challenge not required.
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake Could also be explained by disease or other drugs Information on drug withdrawal may be lacking or unclear.
Unlikely	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) Disease or other drugs provide plausible explanations.
Conditional/ **Unclassified**	Event or laboratory test abnormality More data for proper assessment needed, or Additional data under examination.
Unassessable/ Unclassifiable	Report suggesting an adverse reaction Cannot be judged because information is insufficient or contradictory Data cannot be supplemented or verified.

7 INFECTION CONTROL IN THE CONTEXT OF DRUG RESISTANT-TB

LEARNING OBJECTIVES: -

By the end of this unit, participants will be able to:

- Understand the rationale for TB IC Describe risk of TB transmission
- Explain the packages of TB IC measures
- Prioritize & implement basic TB IC activities at health facility level
- Address TB IC measures in congregate and household settings

INTRODCUTION

TB infection control (TB IC) is a combination of measures aimed at minimizing the risk of TB transmission within populations. The foundational work in infection control is early and rapid diagnosis, and effective treatment of TB patients. TB IC requires and complements the implementation of core interventions in TB control, HIV control and strengthening of health systems.

TB infection control is growing in importance because of the association of TB with HIV and the emergence of DR-TB. The situation is worsened by the increasing number of patients without corresponding infrastructure expansion and healthcare worker enrolment, leading to overcrowding of patients, delayed diagnosis and delayed or ineffective treatment resulting in increased TB transmission.

Healthcare workers are at increased risk of TB infection compared to the general population. Non-medical staffs in healthcare settings are also at risk, as undiagnosed pulmonary TB patients with cough present the risk of TB transmission to close contacts and healthcare workers. Enclosed waiting rooms and corridors where patients wait to receive medical care are also areas of particular risk on most occasions.

Incidence of TB among people living or working in congregate settings (e.g. correctional facilities or nursing homes) and among household contacts of TB patients also exceeds that of the general population. For this reason this document provides guidance on preventing TB transmission in health facilities, congregate settings and household settings.

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 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.

SET OF TB IC 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. Managerial control measures

Managerial control measures provide the managerial framework for the implementation of TB infection control in health-care facilities.

Managerial Measures for facility-level TB infection control include:

a. Identify and strengthen local coordinating bodies for TB infection control and develop a facility IC implementation plan (including human resources, and policies and procedures to ensure proper implementation of the administrative, environmental and personal Protective controls measure listed below).
b. Rethink the use of available spaces and consider renovation of existing facilities or construction of new ones to optimize implementation of controls.
c. Conduct on-site surveillance of TB disease among health workers and assess the facility.
d. Address advocacy, communication and social mobilization (ACSM) for health workers, patients and visitors.
e. Monitor and evaluate the set of TB infection control measures.
f. Participate in research efforts.

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.

An administrative control also includes a package of interventions for Health care workers on TB and HIV prevention.

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.
- Early TB diagnosis should be facilitated and treatment should be started fast
- 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.

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 nfected from contagious TB patients
- Presumptive TB cases from TB patients or other patients

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.
- 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:

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.

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-

- Particulate Respirators (also known as high-filtration masks) provide a bacterial filtration efficiency of greater than 95 percent if challenged with 0.3-0.05 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.

- M. tuberculosis is trapped in the filter of a mask, which will not be released with or other physical movements of the mask. It eventually dies once outside
- 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 suspected and confirmed DR-TB patients.

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, preferably with rapid diagnostic testing, molecular (GeneXpert) and other tests, as necessary.
- 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 known to be HIV positive should not work in MDR-TB wards, medical wards, out-patient TB/MDR-TB clinics.

MONITORING, EVALUATION & SURVEILLANCE OF TB AMONG HCWS:

Establishing surveillance of active TB rates among HCWs in the health facility provides a useful information about the status of TB IC intervention in a given health facility, It is considered as one of the TB IC indicators.

Surveillance should include information about the main risk factors such as:

- Work location (e.g. outpatient clinic, medical ward etc.); Occupation (nurse, health officer, physician, cleaning person etc);
- History of recent exposure to TB patients at work or outside the workplace; History of treatment for TB; History of HIV testing and results

INFECTION CONTROL FOR CONGREGATE SETTINGS:

The recommendation for congregate settings are less specific than those from health facilities, because congregate settings are so diverse. They include a mix of settings that range from correctional facilities and military barracks, to homeless shelters, refugee camps, dormitories and nursing homes. Each facility differs in the type of population it contains and the duration of stay for dwellers; in turn, this affects the dynamics of TB transmission.

The incidence of TB infection and TB disease among individuals in congregate settings exceeds the incidence among the general population. The association of HIV and the emergence of MDR-TB and XDR-TB increase the need to give urgent and appropriate attention to implementation of TB infection control in congregate settings and to prioritize measures that aims at prompt identification upon entry/periodically and upon exit, separation and effective treatment of those diagnosed with TB.

REDUCING TRANSMISSION OF TB IN HOUSEHOLDS

Various actions are needed to reduce transmission of TB in households because household members of persons with infectious TB are at high risk of becoming infected with TB and consequently developing the disease.

Studies show that the major risks for infection are through close contact (exposure) to the infectious case before diagnosis. This applies for both susceptible and drug-resistant TB. Early case detection remains one of the most important interventions for reducing the risk of TB transmission in the household. TB contact investigation and basic infection control behavior-change campaigns should be part of any community sensitization and education. The infection control messages need to promote the importance of early identification of cases, cough etiquette and adherence to treatment.

Behavior-change campaigns for family members of infectious TB patients and health service providers should aim at minimizing stigma.

To reduce exposure in households:

- Houses should be adequately ventilated, particularly rooms where people with infectious TB spend considerable time (natural ventilation may be sufficient to provide adequate ventilation);
- Anyone who coughs should be educated on cough etiquette and respiratory hygiene so as to behave accordingly at all times; while infectious TB patients should spend as much time as possible outdoors;
- Sleep in an adequately ventilated room;
- Minimize contact with children (< 5yrs) and immunosuppressed individuals
- Spend as little time as possible in congregate or crowded settings such as churches, markets and public transport.

Exercise 2.1

1. Which of the following can be used/advised for cough hygiene

a) Cloth or paper mask (surgical mask)

b) Tissue paper

c) Covering mouth and nose with patient's forearm

d) All of the above

e) None

2. Matching: Match interventions in column one with appropriate actions or practices from column two.

Column A:	Column B
I. Managerial Measures to decrease TB transmission _____	1. Open window
II. Administrative measures to reduce risk of TB transmission_____	2. Open door
III. Mechanical ventilation	3. Advocacy, Communication & social mobilization about TB Infection control
IV. Natural ventilation	4. Window fans
	5. Move people suspected of having TB to front of line

	6. Speed up diagnosis of TB 7. Training Health care providers on TB infection control 8. Build Waiting room outside without walls 9. Provide tissue paper for coughing patients 10. Renovating rooms

3. Mark each statement as _True_ or _False_ and explain why:

   a. Coughing patients should be sent to the toilet to produce sputum samples
   b. A face mask (surgical type) worn by a coughing patient with TB can help Prevent TB transmission.
   c. A face mask (surgical type) worn by a health worker is a good way to protect him/her from TB infection and disease.
   d. Coughing patients should be sent outdoor/open and ventilated space to produce sputum sample.
   e. The risk of TB transmission is only in adult medical and TB clinics

8. DR – TB PROGRAM DESIGN, COORDINATION AND MANAGEMENT IN ETHIOPIA

Learning Objectives:

By the end of the session, Participants' will be able to:

- Describe the MDRTB program Design Identify treatment delivery strategies
- Discuss MDRTB program coordination

MDR-TB PROGRAM DESIGN AND MODEL OF CARE

The National Tuberculosis Control program has shifted from the hospitalized model of care for DR-TB case management to Clinic–based Ambulatory model since 2013 for rapid decentralization of PMDT services in the local context and creates better convenience for patient follow-up.

Clinic-based Ambulatory Model of care: is designed to deliver the treatment course on outpatient basis so long as the clinical panel team decides that the patient is fit to ambulate. 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, at referral centers, with the decision of the panel team.

DR-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
- Re-evaluate and conduct baseline investigations, baseline clinical assessment

- Prepare patients for new drugs initiation
- Manage patients with the recommened regimen
- Responsible for identification, reporting and management of SAEs and AEs of clinical significance
- Responsible for recording and reporting on programmatic indicators.(detection, enrollment, interim results, final outcomes, efficacy and safety indicators)
- Conduct treatment monitoring and follow up of all patients
- Arrange patient discharge and outpatient follow up.
- Provide clinical mentoring support to TFCs
- Provide patient support packages

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

PATIENT SELECTION CRITERIA FOR ENROLLMENT TO DR – TB TREATMENT

All registered MDR-TB patients at TIC must be evaluated by the MDR-TB Panel team to decide on Patients'enrollment to treatment program either as inpatient or outpatien

a) Patients candidate for outpatient/Ambulatory treatment initiation:

- Patients who are regular resident within the catchment area from the treatment initiating and follow up centers
- Stable clinical condition decided by the clinicians and clinical panel team
- Patients with controlled comorbid medical conditions
- Stable HIV/AIDS patients (stage I & II with CD4 count >350cells/ul) &/or on ART Patient written informed consent to be treated outpatient basis.

Satisfactory follow up plan:

- TFC available in the nearby to patient's residence,
- Established link with the woreda/subcity TBL officers,
- Established link with the responsible HEWs,
- Availability of reliable treatment supporters (family supporter and/or HEW).

b) MDR-TB treatment shall be initiated as inpatient for patients with any of the following conditions:

- Patients with acute illness requiring medical admission,
- Pediatric age (Age<12yrs), or geriatrics (age >60years)
- Pregnant women,

- Patients with no satisfactory treatment follow up plan (Ex: Homeless, those from congregate settings such as prisoners and orphans, and those living outside the catchment areas of MDR-TB treatment centers),
- Patient with Uncontrolled co-morbid conditions,
- Poorly controlled/ complicated:
  - Diabetes
  - Liver failure
  - Renal insufficiency
  - Psychiatric illness
  - Cardiac problems
  - Substance dependency disorder
  - Advanced immunosuppression (stage III & IV &/or CD4 <350cells/ul) and not yet on ART XDR suspect

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.

The Clinical Review Committee (CRC) is a team of technical experts composed of program managers, experienced DR-TB clinicians from referral hospitals, microbiologist, pharmacist and senior physicians etc.

The CRC (national and regional) is responsible for:

- Providing expert advice on potential eligibility and contraindications of taking new TB drugs for each individual patient.
- Providing scientifically sound and evidence-based advice to support physicians in managing the diagnosis and treatment of MDR/XDR-TB cases and ensuring the best possible treatment results for each patient by reviewing individual clinical data, by strictly monitoring and supervising the implementation of programmatic and clinical introduction of new TB drugs.

Clinical panel team:

Every Treatment initiating center needs to establish a MDR-TB 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:

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
- Decision on MDR-TB treatment regimen for patients ,in particular for empirically 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
- Ensure the implementation of minimum TB IC package at TIC and TFC To assist TFCs, together with the program, to practice standard of care.

Team composition:

- Clinicians from MDR-TB center
- Nurses, pharmacist, laboratory technologist
- Chief Clinical officer and executive officer of TIC Social workers at TIC
- Local health office (regional, zonal &/or woreda) TBL officers
- Representative from TFC whenever possible
- Technical advisors from partners

COMMUNICATION, REFERRAL NETWORKING AND SUPPORT MECHANISM

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.

The referral network involves referral and cross-referral in PMDT services involves four levels:

- MDRTB suspects: will be identified and sent to diagnostic labs by all DOT clinics
- MDRTB confirmed: will be referred/linked to TIC by the DOT clinic
- MDRTB patients on treatment: will be linked to TFC by the TIC
- complicated and difficult cases: will be refer back to TIC.

All referral and communications amongst these levels should be using standard referral forms for ease of communication and referral.

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 wereda offices and representatives of contributing partners.

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.

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.

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 after discharge

LABORATORY SERVICE ARRANGEMENT:

Sample of MDRTB suspects at DOTS centers is transported by courier system to diagnostic regional culture and DST centers to establish the diagnosis. Confirmed MDRTB cases are promptly linked to MDRTB treatment initiating centers for definitive treatment.

Laboratory networking, sample transportation and linkage:

Laboratory networking: the RHB and Regional laboratory should develop SOP for lab networking system and sample transportation based on the regional contexts and situations.

The development of SOP includes identification and networking of referring DOT clinics, sample collection center and diagnostic lab.

Sample collection and transportation: samples will be transport first from the referring DOT clinics to the sample collection center where the sample will be transported to the diagnostic lab. The results will be returned trough the courier back to the referring DOT clinics.

Linkage of confirmed MDRTB cases: the referring DOT clinic must link those patients with confirmed MDRTB result to the designated treatment initiating center.

Pharmaceuticals supply management system for DR-TB treatment

In order to achieve sustainable program implementation, it is very important to ensure that every health unit involved in the prevention, diagnosis and treatment of DR-TB has an adequate and uninterrupted supply of drugs, laboratory reagents, medical supplies and equipment.

Distribution to treatment initiating centers:

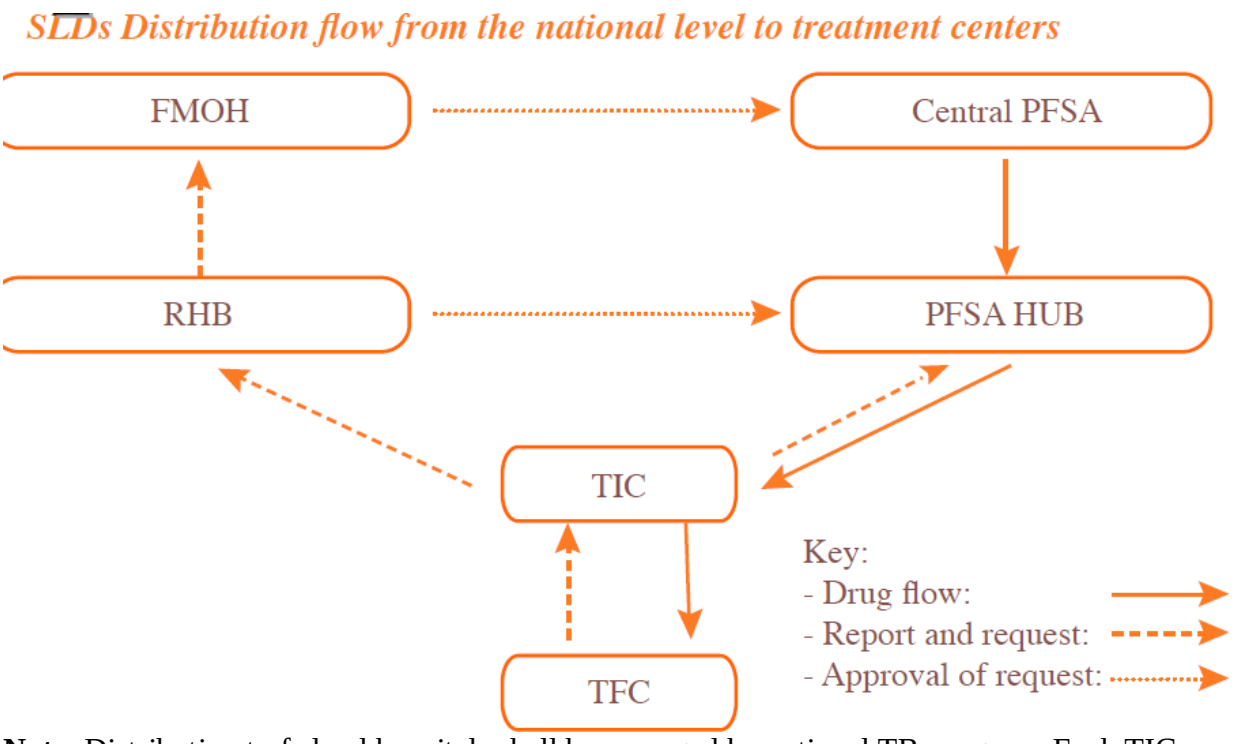
Current distribution system

The current distribution system in place is described as follows;

- FMOH –NTP shall prepare a six-month distribution plan based on the patient enrollment and stock status data, and issue a letter to the central EPSA based on the report received from each RHBs. The central EPSA will issue the quantity to respective EPSA hubs every six- months.
- EPSA hubs will deliver SLDs to respective TICs every two months based on their request or TICs will collect the drugs by themselves to avoid any delay.
- TICs make SLDs request using the standard SLDs request and report template (the excel sheet). TICs report should be filled until the 5th day of the reporting period and send it along with RRF request to respective EPSA hubs for the resupply. This is done to align it with IPLS schedule. The resupply from EPSA hub to TIC should be done until the 10thth day of the reporting period.
- TICs will deliver SLDs to TFCs everyone to three months depending on the proximity of the centers, the patients load at TFC and suitability of logistic arrangement by TIC. Note that the frequency of supply to each and every TFC should be decided and reviewed as needed by the panel team.

To get the resupply, TFCs must fill Internal Facility Reporting and Resupply Form (IFRR) and send/submit the request to the TIC based on agreed schedule. Based on the stock on hand at TFC level, TICs will refill the quantity required for the requested period.

Figure 8.1: Flow of commodities and information



Note: Distribution to federal hospitals shall be managed by national TB program. Each TIC should re-supply health centers serving as catchment TFCs_on pre-determined interval decided by clinical panel team.

Ordering and reporting system:

In order to timely deliver and refill of the products either electronically or manual reports can be employed. Therefore, each TIC can fill excel based format and send it to RHBs through email or the hard copy every two months and as the same time RRF to respective hubs for the resupply.

The RHBs upon the receiving of excel based request from TIC, they will give feedback through email/telephone to the TIC on the appropriateness of the requests for the number of new and existing MDR TB patients. However, this doesn_t mean that EPSA hubs will wait for approval. Rather for the next refill period, each TIC will be responsible to correct the report based on the feedbacks coming from RHBs.

Emergency ordering:

If the facility enrolled higher number of patients and/or if there is significant regimen change than planned during the reporting period, the facility should place emergency order after thorough evaluation of their stock for potential stock out.

The report format to place an emergency order will be the same as with the routine reporting RRF and excel based format. After placing a request the refill process should be completed in not more than 5 days.

The New Distribution System Design:

A new distribution system is designed to alleviate the above-mentioned challenges and ensure uninterrupted and continuous supply of SLDs. The new system implementation will be started along with the introduction of full oral regimen. SLDs distribution is fully integrated to IPLS and will be done according to IPLS principles.

Rationale for the new design:

The rationale for designing a new distribution system to SLDs is attributed to the following

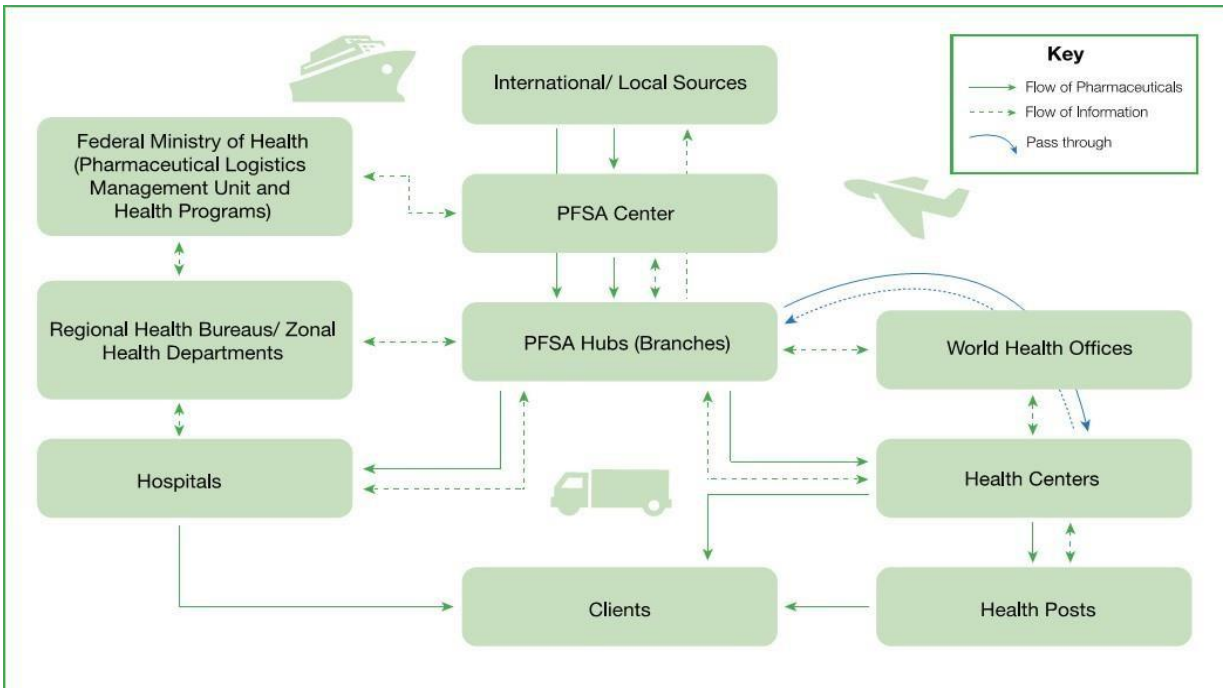
Points:

- To improve the role and active engagement of EPSA hubs in the distribution of SLDs
- To monitor the distribution system for improvement in quality, timeliness and relevant patient and stock status data for decision making
- To improve the relationship between EPSA hubs and TICs for resupply decision
- To strengthen use of logistics and patient data for monitoring and supervision purpose at all level.

Issuing second line drugs

- EPSA central will deliver SLDs to respective EPSA hubs every two months as per EPSA hubs request.
- EPSA hubs will deliver SLDs to respective TICs every two months based on their request.
- The resupply request shall be done using the existing reporting and resupply format. The format is inclusive of patient target enrolment, existing patient enrolment data and logistics data.
- TIC report should be filled until the 5th day of the reporting period and send it to EPSA hubs along with RRF and one copy to RHBs for monitoring purpose.
- TICs will deliver SLDs to TFCs every one - two months based on their mentoring and supervision schedule to TFCs.
- Delivery of SLDs shall be integrated with routine IPLS schedule whenever possible. But delay shall be avoided waiting regular IPLS refill period.

Figure 8.2.: Flow of SLDs thorough the new distribution mechanism (IPLS)



Ordering and reporting system:

- In order to timely deliver and refill the products either electronical or manual reports can be employed. Therefore, each TIC can fill excel based format and send it to EPSA hubs and one copy for RHBs and emergency order when the stock level is below desired level.
- One copy of the requesting format will be sent to RHBs for monitoring purpose.
- RHBs shall aggregate the report in both soft and hard copy and share it to FMOH for monitoring purpose.
- EPSA hubs aggregated all future six months enrolments plans and request products need to EPSA central
- EPSA hubs report stock status report every two months to EPSA central along with the patient data and aggregated request of TICs
- EPSA centre will send feedback report every two months to EPSA hubs

Supplies and stock management at TFC level:

SLDs and related commodities to TFCs are re-supplied from the respective catchment TIC based on predetermined interval in similar fashion with re-supply to health posts from health centers in IPLS.

Frequency of re-supply from TIC to TFCs could range from one to three months _interval depending of the proximity of the centers, the patients load at TFC and suitability of logistic arrangement by TIC.

Note that the frequency of supply to each and every TFC should be decided and reviewed as needed by the panel team.

The TIC pharmacy department must review the item in the request in accordance with current number of active patients on treatment at the TFC considering the loss/adjustments. TIC Pharmacy personnel at TIC is advised to use the Excel spreadsheet prepared by the national program to quantify the amount of SLDs required to be requested for the upcoming period.

ANNEXES:

ANNEX 1. MEDICATION FACT SHEET FOR COMMON ANTI – TB DRUGS USED FOR DR – TB TREATMENT

Fluoroquinolones:

The fluoroquinolones have potent in vitro and in vivo activity against M. tuberculosis and the los s of a fluoroquinolone from a DR-TB treatment regimen is associated with poor treatment outcomes. WHO recommends that all patients with MDR-TB receive a later generation fluoroquinolone (and specifically avoid the use of ciprofloxacin). Use of the fluoroquinolones was associated with cure and this association was strongest with later generation fluoroquinolones.

Mfx or high-dose Lfx (750-1000 mg) should be used in the treatment of all cases of MDR- and XDR- TB except in the setting of documented in vitro resistance to high concentrations of M fx. Recent studies suggest no clinical advantage between Mfx or Lfx for MDR-TB.

Resistance to the fluoroquinolones is conferred by mutations in gyrase A and B. Cross resistance among the fluoroquinolones is common but not universal.

Potential side effect profiles may influence choice of fluoroquinolones. Some general considerations include:

- Lfx has less effect on the QT interval compared with Mfx; therefore, Lfx may be warranted in some cases where this is a concern such as in cases receiving Cfz and Bdq. Lfx requires d o s e - adjustment with renal impairment (if creatinine clearance <50 mL/min), but is presumed to be safe to use with liver disease.
- Mfx does not require dose adjustment in renal failure, but is infrequently associated with hepatotoxicity and thus should be used with caution in cases of liver impairment

Bedaquiline:

Bedaquiline (Bdq) is a drug for the treatment of DR-TB that was approved by the U.S. FDA in 2012, the EMA in 2013 and the Medicines Control Council (MCC) in 2014. The WHO recommended Bdq for the treatment of MDR-TB in 2013, providing that it is used under optimal conditions, including careful selection of patients.

However; with further evidence on the safety and efficacy of BDQ WHO 2019 consolidated DR TB guideline considered BDQ as a core drug for the management of DR TB & incorporated under group A of the new drug re-grouping.

The drug has a novel mechanism of action and works by inhibiting the mycobacterial ATP synthase.

The drug is in a completely novel class, but data show that it has cross-resistance with clofazimine thought to be due a shared efflux pump mechanism.

In terms of safety, the drug is relatively well-tolerated, although when compared with placebo, higher rates of liver function test abnormalities were seen. Bdq has also been associated with moderate QTc prolongation, although no clinical cardiac events were associated with its use.

The drug comes in tablets of 100mg which have a shelf life of 2 years. There is a loading dose phase in which the drug must be given at a dose of 400mg daily for 14 days. After this, the drug is given at a dose of 200mg three times a week for an additional 22 weeks, although some providers have used this drug for a longer duration in patients with limited treatment options.

The half-life of bedaquiline is 5.5 months. When used with EFV, the concentration of Bdq is reduced, and thus it is recommended that alternative ART agents be used—including NVP and lopinavir/ritonavir.

Linezolid:

Linezolid (Lzd) is an oxazolidinone antibiotic that was initially approved to treat resistant gram - positive infections, but has been used off-label for the treatment of DR-TB. Multiple observational cohorts have shown that Lzd can be effectively used to treat patients with highly - resistant forms of TB, and the drug is being proposed as a key component in multiple clinical trials.

Lzd is an active drug and should be considered for all MDR- and XDR-TB regimens.

The drug has multiple adverse events, especially when given at doses exceeding 600mg per day. These include bone marrow suppression, optic neuritis and peripheral neuropathy. Adverse events seem to be related to the cumulative trough dose, and there are clinical trials trying to establish the optimal dose of Lzd, including every-other-day dosing strategies.

In order to avoid hematologic toxicity, Lnz should be given once daily at 600 mg per day. Patients should be monitored closely for development of neurologic or hematologic toxicity, and the dose reduced to 300 mg per day in selected patients who develop toxicity.

Lzd should not be used with antidepressants of most classes, as this can precipitate serotonin syndrome.

Group B: (Cfz, Cs):

Clofazimine:

Clofazimine (Cfz) is a drug which has been used for the treatment of leprosy for decades and has been used in the treatment of patients with MDR-TB in a variety of program settings. Cfz is a fat-soluble riminophenazine dye. The drug has a mechanism of action that is not completely understood, and it has been shown to have cross-resistance with Bdq.

Safety and efficacy data in DR-TB comes from observational data and from a recent non-blinded randomized study. In randomized trial of patients with MDR-TB in China those who received Cfz had a higher rate of culture conversion and the treatment success rate.

The drug has two main classes of side effects: skin and gastrointestinal.

- Cfz causes skin pigmentation changes that range from an orange co lor to a dark black/purple color. These skin changes are reversible over time.
- Cfz can also cause symptoms of abdominal pain, as the drug accumulates in the wall of the GI tract.
- Cfz has been associated with QT prolongation.

Cfz comes in caplets of 100mg, and the usual dose is 100-200mg per day. It is used for the entire duration of the treatment course. The drug has a shelf life of 5 years. It has a half -life of 70 days. It appears to be safe to give with all forms of ART. It has been used in pregnant and breastfeeding women, children, and the elderly.

Delamanid:

Delamanid (Dlm) is a new drug that was approved for the treatment of DR-TB by the EMA in 2013 and by the Pharmaceutical and Medical Device Agency of Japan in 2014.

The drug was recommended for the treatment of DR-TB by the WHO in 2014 providing that it is used under optimal conditions, including careful selection of patients, close patient monitoring, use in a multi- drug regimen that follows WHO principles.

Currently WHO 2019 DR TB consolidated guideline incorporates Dlm in group C of SLDs.

Dlm is a nitroimidazole agent that works by inhibiting mycobacterial cell wall synthesis.

In terms of safety, the drug is well tolerated, and the main side effect reported was moderate QTc prolongation without clinical cardiac events. Of note, the drug is metabolized by albumin, and increased rates of adverse events were seen in patients with low albumin.

Dlm is given at a dose of 100mg twice daily for 24 weeks. Of note, some providers have used this drug for a longer duration in patients with limited treatment options. The drug comes in tablets of 50mg and has a shelf life of 4 years. The half-life of the drug is 38 hours.

Dlm can be given safely with most forms of ART based on short-term studies. Dlm has been recommended for children above 6 years and is considered safe in this population.

Injectables (Am, S, Km, Cm):

- The aminoglycosides (Km and Amk) and polypeptide (Cm) are active in vitro against M. tuberculosis and represent a critical component in treatment regimens during the initial phase of therapy. They can be given either intramuscularly (IM) or intravenously (IV).
- Streptomycin (S) is relatively well tolerated, but resistance to this drug is common. Many experts avoid the use of Streptomycin, even if testing shows susceptibility, if the drug has been used before.
- There have been no clinical trials comparing the effectiveness of the different injectables. When choosing an aminoglycoside or polypeptide agent, weigh toxicity profiles, cost, and likelihood of cross-resistance of the different drugs.
- All of the injectable agents have potential for renal toxicity and electrolyte disorders. Ototoxicity and vestibular toxicity are more common with Am than Km.
- The volume of injection for Amk IM is larger than for the comparable dose of Cm.

- Significant electrolyte disturbances can occur with the aminoglycosides, so close monitoring is required.

Resistance to the aminoglocosides and polypeptides is most commonly conferred through a mutation in the *rrs* gene. Studies have reported variable rates of cross - resistance among these drugs, but in general:

- Am-resistant isolates are resistant to KM and occasionally CM.
- Km-resistant isolates are usually resistant to AK and possibly CM.
- Cm-resistant isolates are variably resistant to KM and AK.
- S-resistant isolates are usually susceptible to other injectables unless the other drugs have been used previously.

Carbapenems (Imp/Cln, MPM):

β-lactam antibiotics undergo rapid hydrolysis by beta lactam enzymes in M. tuberculosis rendering them inactive. However, the combination of amoxicillin plus a β-lactamase inhibitor was shown to be active in vitro against M. tuberculosis and in an early bactericidal study in humans. Although the carbapenem antibiotics are poor substrates for β-lactam enzymes, they have variable in vitro and in vivo activity against M. tuberculosis.

The combination of carbapenems with the β-lactamase inhibitor clavulanate has been shown to improve the MIC of MPM and is bactericidal in murine tuberculosis. Clinical experience with carbapenems f o r the t reatment of MDR/XDR-TB is limited and the duration of treatment is generally restricted to the intensive phase. Based on some studies, it appears that a carbapenem plus clavulanate can be used as an active component of an MDR/XDR-TB regimen.

High-dose INH:

Resistance to INH is most commonly conferred through mutations in katG or inhA. Resistance to katG results in inhibition of catalase activity and the development of high-level resistance (resistance at 1.0 mg/mL on solid media) to INH whereas mutations in inhA or the promoter region result in lower levels of resistance (resistance at 0.2 mg/mL). Theoretically, it may be possible to overcome the resistance in the setting of low-level resistance by increasing the dose of INH. There was a higher frequency of peripheral neuropathy in the high-dose INH arm. High-dose INH should be considered in patients whose isolate has low-level resistance in vitro and evidence of an inhA mutation with no evidence of a kat G mutation.

There is a cross resistance between INH resistance with inhA mutation and Protionamide/Ethionamide.

ANNEX 2: TB ADR SYMPTOMS AND THEIR MANAGEMENT

ADR	Suspected agent	Management	Remarks
Nausea, vomiting	**Eto/Pto, PAS**, H, E, Z, Cfz	1. Assess for dehydration; and rehydrate if indicated. 2. If mild symptoms and no signs of dehydration, ○ Encourage patients to increase fluid intake (water, juice, tea) ○ Encourage patient to continue treatment – Start antiemetic therapy Metoclopramide 10 mg taken 30 minutes before anti-TB drugs (maximum dose is 15 mg twice daily). (Caution when taking QT prolonging Drugs) – Promethazine 25 mg taken 30 minutes before anti-TB drugs or before meals, up to three times daily. – If vomiting is severe and non- responsive to above measures, chlorpromazine 12.5 mg IV may be given. 3. If there is dehydration or persistence of symptoms, • Initiate rehydration accordingly • Refer patient to treatment initiating center if nausea and vomiting persist despite adjustments to the dosing schedule.	1. Nausea and vomiting is very common in early weeks of therapy and usually abate with time and adjunctive therapy. 2. Electrolytes should be monitored and replaced if vomiting is severe. 3. Reversible upon discontinuation of suspected agent. 4. Clofazimine can cause severe abdominal pain and acute abdomen. This is rare, but if occurs, clofazimine should be suspended.

Gastritis	**PAS, Eto/Pto**	1. Give antiTB drugs with small food, avoid caffeine, cigarettes and assess for signs of severity 2. If mild symptoms give H2-blockers, proton-pump inhibitors. 3. Decrease the Dose of the offending drug if symptoms aren't controlled by PPI. You can split the Dose in to 2/3rd morning and 1/3rd Evening 4. If severe (severe persistent dyspepsia, hematemesis/coffee ground vomitus, blsck tsrry stool, initiate rehydaration and refer	1. Severe gastritis, as manifested by haematemesis, melaena or haematechezia, is rare. 2. Dosing of antacids should be carefully timed so as to not interfere with the absorption of antituberculosis drugs (take 2 hours before or 3 hours after antituberculosis medications). 3. Reversible upon discontinuation of suspected agent(s). 4. 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.
Hearing loss	**Km, Am, Cm**	1. Confirm that this is not due to ear wax or other conductive problems. 2. Check whether patient has history of hearing loss previously 3. Document hearing loss objectively (preferably using audiometry) and compare with baseline audiometry if available. 4. If ototoxicity is confirmed consider shifting regimen. regimen is not compromised. 5. Refer, if it is new event or worsening of complaint.	1. Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of MDR-TB therapy. 2. Hearing loss is generally not reversible. 4. While the benefit of hearing aids is minimal to moderate in auditory toxicity, consider a trial use to determine if a patient with hearing loss can benefit from their use.

Electrolyte disturbance (Low K and Mg) Manifesting as fatigue, muscle cramp, muscle spasm	**Cm**, Km, Am,	1. Check potassium (if available). 2. If potassium is low also check magnesium (and calcium if hypocalcaemia is suspected). 3. Initiate potassium supplement if K+> 3.0meq/L) and monitor Potassium weekly (600mg KCL PO BID-QID) 4. Correct if there are contributing causes of hypokalemia (Vomiting, diarrhea)	1. If severe hypokalaemia is present, consider hospitalization. 2. Amiloride 5–10 mg QD or Spironolactone 25 mg QD may decrease potassium and magnesium wasting and is useful in refractory cases. 3. Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhoea.
		5. Refer if K+<3.0meq/L to TIC for inpatient management. 6. Inpatient management at TIC: a) If serum K is in moderate to severe range(< 3.0 meq/L use 40 – 80 mEq IV KCL in 250 ml of NS to run over 8 hours and to be repeated to a maximum of three times in 24 hours. or b) In patients with severe Hypokalemia and IV replacement serum electrolyte should be checked 1 hour after iv infusion and every 6 hours thereafter. 7. In cases of refractory hypokalemia, consider replacing Mg and Calcium.	

Peripheral neuropathy	**Cs, H, Lnz, Km, Am, Cm, Eto/Pto**	1. Increase pyridoxine to maximum daily dose (200 mg per day). 2. Initiate therapy with tricyclic antidepressants such as amitriptyline. Non-steroidal anti- inflammatory drugs or acetaminophen may help alleviate symptoms. 3. If no improvement refer	1. Patients with co-morbid disease (e.g. diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here. 2. Neuropathy may be irreversible; however, some patients may experience improvement when offending agents are suspended
Seizure	**Cs, H, FQs**	1. Suspend suspected agent pending resolution of seizures. 2. Initiate anticonvulsant therapy (e.g. Phenytoin, Valproic Acid). 3. Increase pyridoxine to maximum daily dose (200 mg per day). 4. Refer after controlling seizure	1. Anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agent discontinued. 2. History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient‘s seizures are well
			controlled and/or the patient is receiving anticonvulsant therapy. 3. Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy

Psychosis	**Cs, H, FQs, Eto/Pto**	1. Stop suspected agent (usually cycloserine) immediately 2. In patients with new onset of Psychosis. Check Serum creatinine and Electrolytes to rule out decrease in renal function which will lead to high levels of cycloserine. 3. Initiate antipsychotic therapy. - Haloperidol 0.5 – 5.0 mg twice daily - Risperidone 0.5 – 5 mg twice daily - Chlorpromazine 75- 300 mg po/d in divided doses. 4. Once Psychosis is resolved put patients on individualized regimen which doesn‘t include Cycloserine.	1. Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy. 2. Previous history of psychiatric disease is not a contra-indication to the use of agents listed here but may increase the likelihood of psychotic symptoms developing during treatment. 3. Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent.
Jaundice/Hepatitis	**Z, H, R, Eto/Pto, PAS, E, FQs, Bdq**	1. Drug Induced Hepatitis is diagnosed with Liver enzymes elevated 5 times the ULN without symptoms of hepatitis or 3 times Elevated ULN with Symptoms of hepatitis. 2. Stop all therapy pending resolution of hepatitis. 3. Reintroduce Anti Tb drugs starting from list hepatotoxic once it resolves. Pyrazinamide is considered the most hepatotoxic drug and can be taken out of the regimen if it‘s not essential to regimen.	1. History of previous hepatitis should be carefully analyzed to determine most likely causative agent(s); these should be avoided in future regimens. 2. In such patients HBV, HCV should be screened. 2. Generally reversible upon discontinuation of suspected agent

		4. Refer to the TIC, if patient if found in TFC, after stopping Anti TB drugs.	
Nephrotoxicity (body swelling, decreasing urine, new onset or worsening hypertension)	**Km, Am, Cm**	1. Monitor Serum Electrolyte and Creatinine on monthly bases. If there is increment in serum creatinine from base line(Normal range) or has doubled Acute kidney injury should be entertained. 2. In such cases discontinue the injectable agents and refer to TIC. 3. If at TIC discontinue injectable agents and communicate with Regional/ National CRC to shift patient to individualized Regimen(Delamanid based preferable). 4. Monitor Serum electrolyte for disturbance as it may coexist with raised serum creatinine elevation. 5. Calculate GFR and determine degree/ severity of kidney Injury. 6. Do not reintroduce injectable or decrease frequency since there are alternate novel drugs.	1. in patients who are taking SLD and with laboratory evidence of Renal failure should be assessed for other comorbid conditions like DM, HIV, other nephrotoxic drugs… 2.History of diabetes nephropathy, HIV Nephropathy or renal disease is not an absolute contraindication to the use of the agents listed here, none the less there are novel drugs available which can substitute this drugs (Bdq, Dlm) hence shouldn‘t be the drug of choice as patients with these co-morbidities may be at increased risk for developing renal failure. 3. Renal impairment may be permanent 4. One might consider substituting ARV drugs in patients with TB/ HIV co infection, since TDF and injectable have both renal Toxicities.

Depression	**Cs, FQs, H, Eto/Pto**	1. Improve socioeconomic conditions. 2. Group or individual counseling. 3. Initiate antidepressant therapy. 4. Refer if severe depression	1. Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression. 2. Depressive symptoms may fluctuate during therapy and may improve as illness is treated. 3. History of previous depression is not a contraindication to the use of the agents listed but may increase the likelihood of developing depression during treatment.
Hypothyroidism (swelling,	**PAS, Eto/Pto**	1. Check serum TSH if available to confirm the diagnosis, Refer to TIC	- Completely reversible with discontinuation of the drug
slowing, fatigue, day time sleepiness)		2. In patients with hypothyroidism, most adults will require 100 to 150 mcg of levothyroxine daily. o Young healthy adults can be started on 75 to 100 mcg daily, while older patients start with 50 mcg daily. o Patients with significant cardiovascular disease start at 25 mcg daily.	- it will be more frequent in patients receiving regimen having combination of PAS and Eto/Pto.

		Children clear thyroxine faster than adults, so daily replacement doses may be higher. o Children (4-15 years): 4 mcg/kg/ day (max 200 mcg). o Infants (1-3 years): 10-15 mcg/kg/day (max 200 mcg). 3. Monitor TSH everyo n e to 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. 4. Levothyroxine replacement may need be prolonged for months after completion of DR-TB treatment.	
Blurring of vision	**E, Eto, LZD**	1. Stop Inflicting drugs and refer patents.	

Arthralgia	**Z, FQ**	• Initiate therapy with non-steroidal anti-inflammatory drugs. ○ Ibuprofen 400 mg Po PRN ○ Diclofenac 100mg Po PRN ○ Indomethacin Supp. 100 mg PR/d • Consider decreasing the dose of inflicting drug if not compromising the regimen; Frequently Pyrazinamide till symptoms resolve. Refer, after discontinuing inflicting drug if severe or no improvement.	
QT prolongation	**Bdq, Dlm, Mox, Clf, Lfx**	Refer above table on severity grading for management.	

Annex 3: Adjustment of Anti-TB medications in patients with renal insufficiency

Drug	Change in frequency of administration	Recommended dose and frequency for patients with creatinine clearance <30
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-	No change	4 g/dose, *twice daily*
Streptomycin	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.

Annex 4: Potassium and Magnesium replacement therapy:

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).

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).

ANNEX 5 : SPECIMEN COLLECTION AND REFERRAL SOP

PURPOSE

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	 Signature	Effective Date:	
Approved by: TB Lab Head	 signature	Revised Date: Laboratory area	

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 8oC 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:

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

Annex 6: Yellow form for ADR Reporting

Food Medicine and Health Care Administration and Control Authority of Ethiopia (FMHACA)
Adverse Drug Event reporting form

Patient Name (abbreviation)	Card No	Age, Date of birth	Sex	Weight	Height

Ethnic group	Substance of abuse

Information on suspected drug/vaccine **S=suspected drug** **C=concomitantly used drugs**

Drug name(write all information including brand name batch no and manufacturer	S/C	Dose/dosage form, route, frequency	Date drug taking was started (D/M/Y)	Date drug reaction started (D/M/Y)	Date drug taking was stopped (D/M/Y)	Indication (Reason for drug use)

Adverse drug event description(include all available laboratory test results)

Reaction necessitated:	Reaction subsided after D/C of suspected drug?
Discontinuation of drug/s ☐ YES ☐ No	☐ YES ☐ No ☐ Information not available
Hospitalization prolonged ☐ YES ☐ No	Reaction reappeared after restart of suspected drug? ☐ YES ☐ No ☐ Information not available

Treatment of reaction:

Outcome: ☐ Died due to the adverse event ☐ Died, drug may be contributory ☐ Not yet recovered
☐ Recovered without sequelae ☐ Recovered with squelae ☐ Unknown

Squelae:

Relevant medical conditions such as allergies, renal disease, liver disease, other chronic diseases, pregnancy etc

Reported by: Name	Profession:	Email address:	Telephone

Name of health institution: Date