Guidelines for Clinical and Programmatic Management of TB, TB/HIV, DR-TB and Leprosy in Ethiopia

7th edition

August 2021

Addis Ababa, Ethiopia

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MINISTRY OF HEALTH - ETHIOPIA
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FOREWORD

Tuberculosis (TB) is a major global public health problem. About a quarter of the world's population is infected with Mycobacterium Tuberculosis and thus at risk of developing TB disease. TB is among the top 10 causes of death globally. According to 2020 WHO Global TB Report, an estimated 10.0 million people fell ill with TB, 1.2 million TB deaths among HIV-negative people and an additional 208,000 deaths among PLHIV in 2019. Drug-resistant TB continues to be a global public health threat with 3.4% of new TB cases and 18% of previously treated cases having multidrug resistant TB or rifampicin-resistant TB (MDR/RR-TB).

According to 2020 Global TB Report, Ethiopia is among the 30 High TB and TB/HIV burden countries, with annual estimated TB incidence of 140/100,000 populations and death rate of 19 per 100,000 populations. Among the notified TB cases 1.1% of new TB cases and 7.5% among previously treated TB cases were also estimated to have MDR-TB in 2019.

Cognizant of the burden of TB in Ethiopia, the Ministry of Health has given priority to the prevention and control of TB and implementing high-impact interventions. As a result of our past investments and successful implementation of the strategies, substantial gains were made in reducing the disease burden. The TB incidence has declined from 268 per 100,000 populations in 2010 to 140 per 100,000 populations in 2019. The TB mortality rate has also declined from 33 per 100,000 populations in 2014 to 19 per 100,000 populations in 2019. This year, Ethiopia has been removed from the MDR-TB high burden countries list. However, TB and leprosy is still among high public health problems in Ethiopia. We are still missing about 29% of TB cases each year. If undiagnosed and not treated, those individuals can die or become chronically ill and continue to transmit TB, allowing for the TB epidemic to continue. HIV co-infection impedes the TB control efforts contributing to around 5% of annually notified TB cases in Ethiopia.

Ethiopia has expressed commitments to end TB epidemic by 2035 by endorsing the END TB strategy and new global targets set in the political declaration at the first UN high-level meeting on TB, in September 2018. The country has revised its National TBL Strategic Plan in line with the global targets. The National End TB strategy aims to end the TB epidemic by reducing TB related deaths by 95% and incident TB cases by 90% between 2015 and 2035; and to ensure that no family is burdened with catastrophic expenses due to TB. The strategy calls for use of robust TB case finding strategies and use of rapid diagnostic technologies to address the gaps in treatment coverage for both Drug Susceptible TB and RR/MDR-TB. The National TBL Control program is committed to improve access to equitable TBL services to all vulnerable population groups where TBL burden concentrates. The program also recognizes the need for intensified research and innovations to sharply bend the TB epidemic curve to meet the ambitious targets for 2035.

The current COVID-19 pandemic is posing a substantial challenge to our progress. It has affected our programming and services delivery. Continued investment to build resilient health systems, integrated and adaptive programming based on the lessons learned so far are needed to mitigate the continued pressure.

This 7th edition of the national guidelines on clinical and programmatic management of TB, TB/HIV, DR-TB and Leprosy is an expression of the highest government commitment to end TB and eliminate leprosy through the introduction of latest global policies, strategies and best practices in the prevention and care of TB and leprosy.

Ministry of Health would like to call all actors in the fight against TB and Leprosy by joining the National TBL Control Program in implementing these guidelines to ensure the delivery of high-quality patient-centered TB, TB/HIV, DR-TB and Leprosy Care in Ethiopia and help meeting the target of End-TB strategy.

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State Minister, FDRE Ministry of Health

ACKNOWLEDGEMENT

The development of this 7th edition of the national guidelines was result of the immense contributions of several experts on TB, DR-TB, TB/HIV, and Leprosy from the national TBL Control Program and its local and international partners.

The following individuals served as members of the Guidelines Review Group (GRG), coordinated by Dr Andargachew Kumsa (FMOH/USAID) under the overall guidance of Taye Letta (NTP Coordinator). The Ministry of Health gratefully acknowledges their great contributions:

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The Ministry of Health owes special appreciation for the following senior experts for reviewing various sections of the guidelines:

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The Ministry of Health extends its special gratitude for following individuals who served as the external reviewers group: *Dr Mohammed Yassin (Senior Disease Advisor-TB, The Global Fund to fight HIV/AIDS, TB and Malaria), Dr Nebiat Gebresillassie (WHO, Geneva), Dr Sabine VERKUIJL (WHO, Geneva), Dr. Mansa Mbenga (KNCV, The Hague)*.

Finally, the Federal Ministry of Health of Ethiopia would like to thank all its partners for their technical and financial support in the revision of this guidelines.

Hiwot Solomon

Director, Diseases Prevention and Control Directorate, FDRE Ministry of Health

ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
ART	Anti-Retroviral Treatment
COPD	Chronic Obstructive Pulmonary Disorders
CSOs	Civil Society Organizations
CPT	Cotrimoxazole Preventive Treatment
DOT	Directly Observed Treatment
DOTS	Directly Observed Treatment, Short-Course
DST	Drug Susceptibility Test
EPHI	Ethiopian Public Health Institute
EPTB	Extra-Pulmonary Tuberculosis
EQA	External Quality Assurance
FMOH	Federal Ministry of Health
HAART	Highly Active Anti-Retroviral Treatment
HCT	HIV Counseling and Testing
HEP	Health Extension Program
HEW	Health Extension Worker
HIV	Human Immunodeficiency Virus
HMIS	Health Management Information System
IGRA	Interferon gamma release Assay
IPT	Isoniazid Preventive Therapy
IPLS	Integrated pharmaceutical Logistic system
IRIS	Immune Reconstitution Inflammatory Syndrome
MB	Multi-Bacillary leprosy
MDR-TB	Multi-Drug Resistant TB
MDT	Multi-Drug Therapy
OI	Opportunistic Infection
PB	Pauci-Bacillary leprosy
PLHIV	People Living With HIV/AIDS
POD	Prevention of Disability in Leprosy
PPM	Public-Private/Public-Public Mix
QA	Quality Assurance
RHB	Regional Health Bureau
RRL	Regional Reference Laboratory
SCC	Short Course Chemotherapy
SLD	Second line anti-TB drugs
SOPs	Standard Operating Procedures
TB	Tuberculosis
TPT	TB Preventive Therapy
TST	Tuberculin skin test
XDR-TB	Extensively Drug Resistant Tuberculosis

1. SUMMARY OF THE KEY UPDATES AND RECOMMENDATIONS

This 7th edition of national guidelines on clinical and programmatic management of TB, DR-TB and Leprosy presents the most updated guidance on management of Tuberculosis and Leprosy in Ethiopia in accordance with the latest global recommendations.

Series of landmark global policy changes in TB, TB/HIV, DR-TB and leprosy prevention and care have occurred recently necessitating the need for revision of national guidelines. Notably, new global recommendations for the use of rapid diagnostics for TB and RR-TB, use of Chest X-Ray as TB screening tool, new TB Preventive Therapy (TPT) regimens, RR/MDR-TB Treatment regimen changes including the recommendations for the use of an all-oral Bdq-containing RR/MDR-TB Shorter Regimen, BPaL Regimen for XDR-TB (a novel Fully oral STR under OR conditions) and others are remarkable. These and other updates are reflected in this 7th edition.

The programmatic areas explain aspects of TBL program and service organization, coordination and management, definition of terms and registration and guidance on TBL recording and reporting system. It also highlights on the TBL commodity supply system in the country. Strategies to engage all relevant stakeholders and empowering the community ownership is included with aim of equitable access to quality TB services.

The clinical sections, on the other hand, present the latest recommendations on TB and Leprosy case finding strategies approaches for patient evaluation and use of appropriate diagnostics in the national TB diagnostic algorithms. It as well presents details of treatment of patients with TB, DR-TB and leprosy as well as monitoring of response during treatment. Key recommendations in this document are summarized as follows.

Summary of the key updates and recommendations are indicated below.

Key Updates and recommendations

The following key changes and updates are reflected in this 7th edition of the guidelines.

1. The latest global and national epidemiological situation, updates in the definitions of XDR-TB and Pre-XDR-TB and new treatment outcome definitions are included.
2. Changes to the TB case finding and diagnostic algorithms:
    a. Molecular WHO-Approved rapid diagnostics (mWRDs) are recommended as an initial test for TB diagnosis and detection of rifampicin resistance instead of smear microscopy or culture.
    b. All patients with signs and symptoms suggestive of TB or with CXR abnormalities suggestive of TB shall be evaluated bacteriologically using the mWRDs such as Xpert MTB/RIF test (Or Xpert Ultra) as an initial test instead of smear microscopy.
    c. The use of CXR as a screening tool for TB in addition to the symptom based TB screening algorithm among high-TB risk populations is recommended.
    d. Universal access to DST among all bacteriologically confirmed PTB cases at least for rifampicin and further SL-DST at least for Flouroquinolones among all RR/MDR-TB patients is recommended.
    e. Besides the Xpert MTB/RIF Assay, additional WRDs are recommended for use in Ethiopia including the use of Xpert MTB/RIF Ultra Assays, Truenat MTB, MTB Plus and MTB/RIF –Dx assay, Line Probe Assays (FL-LPA, SL-LPA), Loop-mediated isothermal amplification (TB-LAMP); and Lateral flow lipoarabinomannan assay (LF-LAM) test.
    f. The use of the following biological specimens is recommended for mWRDs in patients being evaluated for TB: Sputum, Nasogastric Aspirate, Nasopharingeal Aspirate, Stool, Lymphnode aspirate, Cerebrospinal fluid, Synovial fluid, Plueral and pericardial fluid, Urine, and Blood (in advanced HIV infection).
3. Changes to the DS-TB treatment:
    a. Treatment of DS-TB patients remain unchanged.

b. The follow up algorithm for all bacteriologically confirmed PTB cases is updated. FL-LPA is now recommended for all patients who remain sputum smear positive after completion of the 2nd month of treatment with FLDs or later to detect Hr-TB cases besides evaluation for occurrence of RR-TB. FL-LPA and Xpert tests are also indicated as a baseline test for all previously treated patients and for new TB patients who are contacts of confirmed Hr-TB.

4. SL-DST Recommendations:
    a. SL-DST using SL-LPA is recommended for all RR/MDR-TB patients and Hr-TB patients as a baseline prior to treatment initiation with either the RR/MDR-TB Regimen or Hr-TB regimen.
    b. Further SLD DST using phenotypic DST is also recommended among RR/MDR-TB patients for medicines in the regimen and for which genotypic methods are not available.
5. Changes in TB Preventive Therapy (TPT):
    a. TPT is recommended for the following priority populations in Ethiopia:
        i. Adolescents and adults living with HIV who are unlikely to have active TB based on symptom and/or chest radiography screening.
        ii. Children 12 months or older who are living with HIV and are considered unlikely to have active TB on an appropriate clinical and/or chest x-ray evaluation.
        iii. Infants younger than 12 months who are living with HIV and who have been exposed to an index PTB case and are unlikely to have active TB on an appropriate clinical and/or radiologic evaluation.
        iv. HIV negative children and adolescents (≤ 15 years of age) who are household contacts of a bacteriologically confirmed pulmonary TB case after active TB is rulled out based on appropriate clinical and/or radiologic evaluation.
        v. Patients initiating anti-TNF therapy, receiving dialysis, preparing for organ or hematologic transplant and patients with silicosis after excluding active TB disease.
    b. The recommended TPT regimens in Ethiopia are 3HR, 3HP and 6H.
6. Key changes on the treatment of DR-TB patients:
    a. An all-oral, bedaquiline containing shorter RR/MDR-TB regimen of 9-12 months is recommended for all RR/MDR-TB patients in whom resistance to flouroquinolones is rulled out and all the eligibility criteria are met.
    b. RR/MDR-TB who are not eligible for treatment with all-oral Bedaquiline containing shorter regimen will be treated with a longer RR/MDR-TB regimen of 18 - 20 months duration (either an all-oral longer RR/MDR-TB Regimen or an individualized longer regimen).
    c. Medicines used in longer RR/MDR-TB regimens are now regrouped in to three groups (Group A, Group B and Group C) based on their effectiveness and safety.
    d. 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 duration.
    e. In patients on longer RR/MDR-TB regimens, a total treatment duration of 18-20 months or 15-17 months after culture conversion is recommended.
    f. In patients with rifampicin susceptible and Isoniazid resistant TB (Hr-TB), a 6-month treatment regimen composed of 6(H)REZ-Lfx is recommended.
    g. Active drug safety monitoring and management (aDSM) is recommended for all patients on RR/MDR-TB regimens.
7. The following updates were made on leprosy management and prevention:
    a. A 3-drug regimen of rifampicin, dapsone and clofazimine for all leprosy patients, with a duration of treatment of 6 months for PB leprosy and 12 months for MB leprosy is recommended.
    b. For rifampicin-resistant leprosy, treatment with at least two second-line drugs (clarithromycin, minocycline or a quinolone) plus clofazimine daily for 6 months, followed by clofazimine plus one of these drugs for an additional 18 months is recommended.
    c. Single dose rifampicin (SDR) is recommended as preventive treatment for adult and child (2 years of age and above) contacts of leprosy patients, after excluding leprosy and TB disease and in the absence of other contraindications.
8. To mitigate the impact of COVID-19 on TB, an integrated TB/COVID-19 Screening, testing and management algorithms have been recommended to be implemented at health facility and community settings in Ethiopia.

2. EPIDEMIOLOGIC BURDEN AND NATIONAL STRATEGY TO END TB

2.1 Burden and Epidemiology of TB

Tuberculosis remains the top infectious killer in the world claiming close to 4000 lives a day. Millions of people continue to fall ill with TB- a preventable and curable disease each year. It affects individuals of all ages and both sexes. About a quarter of the world's population is infected with M. tuberculosis, the causative agent of TB. TB tends to disproportionately concentrate among certain population groups that have either higher risk of exposure to infectious cases or increased risk of progression to active TB, if infected. TB usually affects economically and culturally disadvantaged segment of a population where access to health services is often limited.

In 2019, an estimated 10 million people have fallen ill from TB, and it has claimed the lives of 1.2 million people and additional 208,000 deaths among PLHIV (WHO, 2020). Emergence of drug-resistant tuberculosis (DR-TB) pauses major challenge to end the TB epidemic. In 2019, an estimated 3.3% of new and 17.7% of previously treated TB cases have Rifampicin Resistance/Multi-Drug Resistant TB (RR-/MDR-TB). Worldwide, DR-TB is a threat to global health security and is the leading cause of death from antimicrobial resistance (AMR).

Ethiopia is among the 30 high TB and TB/HIV burden countries globally with an estimated TB incidence rate of 140/100,000 populations (157,000 persons annually); and 21,000 (19/100,000 population) TB deaths in 2018 (WHO, 2019). The TB Incidence has declined with annual average of 8-9%, from 421 per 100,000 in 2000 to 140 per 100,000 population in 2019. Ethiopia has also experienced a decline in TB mortality in the last decades though in slower rate compared to incidence decline.

Among the estimated incident TB cases, total of 108,196 persons with all forms of TB were notified to the national programme in 2020 making the TB treatment coverage to be 71%. Males account for 56% of the notified cases, a proportion which remained constant over several years. The TB case notification has been in steady decline since 2016.

Among the notified TB cases in 2020, 41% were bacteriologically confirmed, 27% clinically diagnosed and the remaining 31% were extrapulmonary TB cases. These proportions remained stable over the years with modest increases in bacteriologically confirmed cases following the rollout of the GeneXpert MTB/RIF assay system in the diagnostic network.

About 9.9% of the notified TB cases in 2020 were children less than 14 years of age. There is a steady decline in proportion of children below 14 years among notified TB cases since 2015.

About 13% of the nationally notified TB cases were contributed through community based TB care interventions and about 17% through the PPM-TB activities.

There is huge sub-national variation in TB burden in Ethiopia as documented in the national Population based TB prevalence survey in 2011 and several sub-national studies.

2. 2 Burden of Drug Resistant TB

Drug resistant TB continues to pose a major threat in the national respose to TB in Ethiopia. The magnitude and extent of drug resistance in TB is being monitored in Ethiopia through periodic drug resistance surveys (DRS). The third national DRS was completed in 2019. The prevalence of RR-TB is 1.1% among new and 7.5% among previously treated TB cases, respectively according to the preliminary report of the 2019 national TB Drug Resistance Surveys (DRS). MDR prevalence was

1.03% among new and 6.52% among previously treated TB patients. Any INH resistance (6.16%) had highest detected prevalence of all first line drug resistance. XDR TB was not detected in this survey. Pre-XDR TB was detected in one case (2.7%) of MDR/RR TB patients. Capreomycin resistances were detected in 5(13.5 %) of MDR/RR TB and 21 (3.5%) non-MDR TB patients. Clofazimine/bedaquiline resistance was detected in 0.5% of non-MDR TB patient the study participants who had WGS result.

The RR/MDR-TB treatment coverage in Ethiopia stands at 41.7% (584/1400) in 2020. The RR/MDR-TB Treatment success rate was 75.1% in 2020 indicating one of the highest among high-burden countries. The DR-TB/HIV Co-infection rate remains high. In 2018, close to 22% of nationally notified persons with DR-TB are also living with HIV, which is 4 times higher than the HIV co-infection among those with drug-susceptible (DS-TB). Among nationally notified persons with RR/MDR-TB, 98% have bacteriologically confirmed pulmonary and/or Extra Pulmonary TB (EPTB), while 58% have history of past TB treatment. Children younger than 15 years of age constitute around one percent of the nationally notified RR/MDRTB cases.

2.3 Burden of TB/HIV

The national responses to the TB and HIV epidemics begun in 2004 and have succeeded in saving lives of hundreds of thousands of affected citizens. Despite this, TB remains to be the leading causes of death of people with HIV, accounting for around 40% of AIDS-related deaths. Both diseases together form a lethal combination, each speeding the other's progress.

The TB/HIV Co-infection rate has declined over several years in Ethiopia ranging from 17% in 2011 to 6% in 2020. There is regional variations in the TB/HIV co-infection rates, with high rates in Gambella and major urban areas. The HIV associated TB mortality rates has also declined from 5.7% in 2014 to 2.8% in 2020. This is attributed largely to the increased ART coverage and universal ART (test and treat) policy of the country.

To address the dual TB/HIV burden, the country continues to focus on joint programming of TB and HIV/AIDS control programs through the implementation of core set of TB/HIV collaborative activities. Please refer to the TB/HIV collaborative activites section of the guidelines for details.

2.4 National Strategy to End TB

Ethiopia has adopted the post-2015 TB strategy called the End TB Strategy which aims to end the TB epidemic by 2035 by reducing TB incidence by 90% and mortality by 95% from the 2015 baselines, and percent of affected households facing catastrophic costs due to TB to zero. Further, the country has also committed to attain the targets set for the political declaration of the United Nations General Assembly High-Level Meeting on TB (TB-UNHLM), in 2018, which reaffirms the global commitment to end the TB epidemic by 2030.

The END TB strategy encompasses a package of interventions and ten components organized under three pillars underpinning four core principles that necessitate government stewardship, a strong coalition with communities and civil society organization, a human rights-based, ethical and equitable approach to implementation, and adaptation of the strategy at the country level.

The national TBL Control Program has prepared a new 5-years national Strategic plan (NSP) to end TB and eliminate leprosy following an iterative consultative process and informed by a comprehensive end-term external review of the previous TBL NSP. The TBL NSP 2021-2025/6 goals, targets and strategic objectives were provided in the following figure.

Fig 1: TBL NSP 2021-2025/6 at a glance

Vision, Objectives and Targets of the NSP	Strategic Objectives of the NSP

Vision	The vision of the health sector is to see healthy, productive and prosperous society in Ethiopia.
Mission	The mission of the health sector is to promote health and wellbeing through providing and regulating comprehensive package of equitable quality health services in Ethiopia.
TBL-NSP aim	The aim of the TBL-NSP is to contribute to the vision of the health sector by ending the TB epidemic and leprosy as public health problems in Ethiopia.
TBL-NSP Strategic Objectives	▪Address gaps across the patient pathway. ▪Prevent infection and active disease. ▪Provide people-centred equitable quality TBL services. ▪Enhance bold policies and strengthen supportive systems. ▪Generate and use TBL strategic information and research outputs.
TBL-NSP Impact.	**By 2025/26:** ▪ Reduce TB incidence from 151 to 91 per 100,000 population. ▪ Reduce TB deaths from 22 to 7 per 100,000 population. ▪ Reduce families facing catastrophic costs due to TB to ≤ 25%. ▪ Reduce leprosy prevalence from 0.3 to 0.1 per 10,000 population. ▪ Reduce the proportion of people with leprosy diagnosed with grade-2 disability from 14% to less than 5%.
TBL-NSP Outcomes	**By 2025/26:** ▪ Maintain treatment success rate (TSR) of notified DS-TB cases ≥90%. ▪ Achieve ≥ 90% TSR among children < 15 years of age. ▪ Increase DR-TB TSR from 72% to 80%. ▪ Achieve ≥ 90% TSR among TB/HIV co-infected persons.
TBL-NSP Output and Coverage	**By 2025/26:** ▪ Increase DS-TB treatment coverage from 69% to 95%. ▪ Increase DR-TB treatment coverage from 46% to 90%. ▪ Diagnose and treat 587,643 persons with all forms of TB. ▪ Diagnose and treat 82,270 children with TB. ▪ Diagnose and treat 505,373 adults with all forms of TB. ▪ Diagnose and treat 5,430 persons with RR/MDR-TB. ▪ Provide TPT to 353, 313 household contacts of PTB. ▪ ≥ 95% of newly notified all forms of TB know their HIV status. ▪All TB/HIV co-infected persons start ART while on TB treatment. ▪ 60% of PPM sites will be engaged in TB service provision. ▪ Increase community contribution to nationally notified persons with TB from 15% to 25%. ▪ Universal SL-DST among persons with RR/MDR-TB, around time of diagnosis. ▪ Diagnose and treat 10,000 persons with leprosy. ▪ Provide leprosy preventive therapy to 9000 people.

Please refer to the TBL NSP 2021 -2025/6 for details on prioritized strategies and targets for TBL Control in Ethiopia.

2. 5 Tuberculosis and other comorbidities and risks

Several health and socio-economic conditions influence TB epidemiology and treatment outcomes. The national program needs collaborative activities to synergize core interventions for prevention and management of both TB and comorbid condition. Table 1, below, summarizes the risk factors and estimated number of people with TB attributed to these factors in Ethiopia.

Table 1: Estimated number of TB cases attributed to common TB risk factors in Ethiopia[1]

Risk factor	Estimated number of TB cases [95% CI]
Undernutrition	49,000 (34,000-66,000)
Harmful use of alcohol	8,300 (29-38,000)
HIV	9600(4,400-17,000)
Diabetes	3,600 (530-9,700)
Smoking	2,600 (190-8,200)

[1]*Source: Global TB Report 2020, WHO.*

3. BASIC CONCEPTS AND CLINICAL PRESENTATION OF TB

3.1 Etiology of Tuberculosis

Tuberculosis (TB) is an airborne disease caused by the bacterium Mycobacterium tuberculosis complex (MTBC), rod-shaped "acid-fast" bacillus. M. tuberculosis complex is comprised of M. tuberculosis (MTB) and other closely related mycobacterial species (M. bovis, M. africanum, M. microti, M. caprae, and M. canetti) that are known to cause TB disease in humans, though majority of TB cases are caused by M. tuberculosis organisms, also called tubercle bacilli.

3.2 Transmission and Pathogenesis:

Transmission: M. tuberculosis is carried in airborne particles, called **droplet nuclei**, of 1– 5 microns in diameter. Infectious droplet nuclei are generated when persons who have pulmonary or laryngeal TB disease cough, sneeze, shout, or sing. Depending on the environment, these tiny particles can remain suspended in the air for several hours. M. tuberculosis is transmitted through the air, and transmission occurs when a person inhales droplet nuclei containing M. tuberculosis, and traverse the respiratory tract, and reach the alveoli of the lungs.

The probability of transmission depends on the dynamics of four major factors: the susceptibility of the host; degree of infectiousness of the person with TB disease; environmental factors and level of exposure (proximity, frequency and duration). The risk of infection of a susceptible individual is therefore higher with **close**, **prolonged**, **indoor exposure** to a person with infectious pulmonary TB.

TB affects individuals of all ages and both sexes. However, the TB is found to be concentrated among certain high-risk groups due to either higher risk of progression if infected or living in settings where there is increased risk of transmission among vulnerable population groups.

Population groups with conditions that compromise the immune system, including PLHIV, Diabetics, young age groups and malnourished, are at higher risk of developing Active TB as they fail to contain the latent TB infection from progressing to active disease.

Besides, congregated settings like prisons, refugee camps, homeless shelters and urban slums are usually overcrowded and poorly ventilated. The inhabitants usually are very poor, neglected and marginalized contributing to higher transmission risk and susceptibility to TB.

Consumption of raw milk containing M.bovis is also a possible way of getting infected by TB, though it is much less frequent.

Pathogenesis: Primary infection with the TB bacilli occurs in persons without previous exposure to the bacilli. Pulmonary infection occurs when TB bacilli, contained in a small infectious aerosol droplet, reaches a terminal airway and succeeds in establishing infection. A localized granulomatous inflammatory process occurs within the lung and this is called the primary (Ghon) focus. From the Ghon focus, bacilli drain via lymphatics to the regional lymph nodes. The Ghon focus with associated tuberculous lymphangitis and involvement of the regional lymph nodes is called the primary (Ghon) complex. The development of the primary complex is asymptomatic. From the regional lymph nodes bacilli enter the systemic circulation directly or via the lymphatic duct. This occult haematogenous spread occurs during the incubation period, before adequate immune responses contain the disease. After dissemination, bacilli may survive in target organs for prolonged periods. The future course of

the disease at each of these sites depends on the dynamic balance between host immunity and the pathogen.

Natural history: In the great majority (90-95%) of persons infected with M. Tuberculosis, the immune system either kills the bacilli or perhaps more often, keeps them suppressed (silent focus) resulting in a latent TB infection (LTBI). In immunocompetent individuals, only 5-10% of infected persons develop active disease in their lifetime. Individuals with latent TB infection do not have symptoms as there is no tissue destruction by the bacilli and are not infectious.

Active TB disease may arise from progression of the primary lesion after infection, or from endogenous reactivation of latent foci, which remained dormant since the initial infection, or from exogenous re-infection. The progression from LTBI to TB disease may occur at any time, from soon to many years later. Post primary TB usually affects the lungs though any body part can be affected after haematogenous and/or lymphatic spread of the bacilli. Persons who have Active TB are usually infectious and may spread the bacteria to other people.

3.2 Clinical Presentation of Tuberculosis

The clinical presentation of Tuberculosis is most commonly the result of involvement of the lungs (more than 80% of cases); however, organ specific presentations may be seen upon involvement of extra-pulmonary organs, most commonly lymph nodes, pleura, spine, joints, genito-urinary tract, nervous system or abdomen.

Pulmonary Tuberculosis (PTB): A persistent and progressive cough, often accompanied by non-specific systemic symptoms such as fever, night sweats or loss of weight, is the commonest presentation of pulmonary tuberculosis.

Symptoms of Pulmonary tuberculosis:

- Persistent cough for two or more weeks, (cough of any duration for HIV positives)
- Fever for more than 2 weeks
- Night sweats
- Unexplained weight loss

However, cough might not be the predominant presentation for certain population group, particularly in people living with HIV, young children, and severely malnourished. Hence, high index of suspicion is required to diagnose TB among these groups. A history of contact with infectious TB case, and presence of documented recent weight loss may indicate the presence of TB in such patients to warrant investigation.

Some patients may present with chest pains (due to pleurisy, muscle strain), breathlessness (due to extensive lung disease or concomitant pleural effusion), localised wheeze due to local Tuberculous bronchitis, or because of external pressure on the bronchus by an enlarged lymph node.

Extra-pulmonary TB (EPTB): patients may present with non-specific symptoms such as unintentional weight loss, night sweats and fever for more than 2 weeks. Other symptoms depend on the site or organ affected.

The most common types of extra-pulmonary tuberculosis are:

EPTB Type	Clinical Features
Tuberculous lymphadenitis	• Caused by lymphatic spread of the organism, is one of the commonest forms of EPTB. • Involvement of the lymph nodes is common in children and in person with advanced stages of HIV infection. • Cervical Lymph nodes is the commonest sites of involvement, though axillary and intra-abdominal lymph nodes may also be affected. • **Clinical presentations:** slowly developing painless swelling on the sides of the neck is the commonest complaint. Initially cervical lymph nodes are firm and discrete, and may later be matted together and become fluctuant. The overlying skin may breakdown with the formation of abscesses and chronic discharging sinuses, which heal with scarring. In HIV infected patients, lymphadenopathies can be acute and resemble acute pyogenic lymphadenitis.
Tuberculous pleural effusion	• TB is the commonest cause of a unilateral pleural effusion. It is also the commonest form of HIV-related extra-pulmonary disease. • **Clinical features**: most often present as non-productive cough of acute onset, chest pain, shortness of breath and high temperature. • Findings on clinical examination may include: tracheal and mediastinal shift away from the side of the effusion, decreased chest movement with stony dullness on percussion on the side of the effusion.
TB of bones	• TB can affect any bone but most commonly affects the vertebral column. • It is seen both in children and adults and can be severe, with neurological sequelae. • Involvement of the intervertebral disc occurs by spread of a lesion from the vertebral body. In many cases more than one intervertebral disc is involved. It is characterized by loss of bone density and slow bone erosion, with the disc space being maintained for a long time (differentiating it from pyogenic infections). • Involvement of the thoracic vertebrae causes localized back pain, deformity of the spine, and in extreme cases an angulated kyphosis (gibbus). Spread may occur into the soft paravertebral tissue to form a so-called “cold abscess”.
TB of CNS	• CNS TB is accompanied by high mortality and sequale. • TB meningitis and intracranial tuberculoma are the two most common forms. TB Meningitis is mainly a disease of childhood and young adults in developing countries. It usually evolves over 2 to 6 weeks. • Clinical manifestation include focal neurological deficits, features of raised intracranial tension, signs of meningeal irritation, focal or generalized seizures and cranial nerve palsies, the sixth nerve involvement being the most common. • Intracranial tuberculoma can be asymptomatic or produce headache, seizure or some type of neurological impairment. On brain imaging, solitary tuberculoma (size: few mm to 3-4 cm) are more frequent than multiple lesions.
Miliary TB	• Miliary TB is a severe manifestation of tuberculosis. • It entails a hematogenous spread of the disease. • Risk factors include extremes of ages (very young and elderly), malnourished, altered cell-mediated immunity such as HIV, chronic kidney disease, and solid organ transplant recipients. • The most frequently affected organs are liver, spleen, lung, lymph nodes, meninges, bone marrow and the adrenal glands. • The clinical presentation ranges from severe acute forms involving septic shock, multiple organ dysfunction syndrome and acute respiratory distress syndrome (ARDS) to a more frequent sub-acute presentation with insidious symptoms such as trivial physical examination. Chest imaging shows micronodular infiltrates (miliary pattern) in two-thirds of patients that assist in the diagnosis of military TB.

4. DIAGNOSIS OF TUBERCULOSIS AND TB CASE FINDING

4.1 TB Diagnostic Methods

The diagnosis of TB may be reached using bacteriologic confirmatory techniques including microscopic examination, rapid molecular diagnostic tests such as Xpert MTB/RIF assays and culture. Moreover, additional supportive investigations (imaging techniques, histopathology or biochemical analysis of body parts/fluids) may be used to assist clinicians to diagnose TB in cases where the bacilli are not detected by bacteriologic techniques.

4.1.1 Conventional TB Diagnostic Methods

A. Smear Microscopy: is used to identify acid fast bacilli (AFB) on microscopic examination of stained sputum smears. It is a direct identification of mycobacterial TB bacilli to make a diagnosis and monitor treatment responses.

Two staining methods can be used to identify acid-fast bacilli: **Ziel-Neelsen staining (ZN) or fluorescent auramine staining (LED FM)**.

Although Sputum-smear microscopy has a relatively low sensitivity (25-75% compared to culture) and unable to distinguish drug-susceptible strains from drug-resistant strains, it has been used as front line test. Light emitting diode (LED) microscopy has been used to save time required to perform a test and improve the sensitivity by 10% over ZN technique.

- The World Health Organization (WHO) recommends the use of more sensitive molecular WRDs for the diagnosis of TB as an initial diagnostic test instead of smear microscopy.
- In situations where mWRD test with same day result is not readily available, smear microscopy may be used in the interim for imediate treatment decisions while sending the specimen simultaneously to mWRD site for subsequent confirmation and DST result.
- Two sputum samples (Spot-Spot) are required for AFB Microscopy. One sputum smear positive result confirms TB diagnosis.
- Smear microscopy will remain as the main TB treatment monitoring test.

To ensure provision of quality TB diagnostic services, all AFB microscopy diagnostic centers should regularly participate in TB laboratory quality assurance system as per the national QA protocol. The laboratory should issue AFB results indicating the number/load of bacilli (AFB) seen on each smear examined (see Table 2 below) to inform the clinician on the degree of patient's infectiousness. D*etails on these techniques is presented in TB AFB laboratory manuals*.

Table 2: AFB smear microscopy grading system

ZN Staining		Fluorescent auramine staining		
Number of bacilli seen on smear	**Results reported**	**Number of bacilli seen on smear (200X)**	**Number of bacilli seen on smear (400X)**	**Results reported**
No AFB per 100 oil immersion fields	No AFB Seen	No AFB in one length	No AFB in one length	No AFB observed
1-9 AFB per 100 oil immersion field	Positive Scanty	1-4 AFB in one length	1-2 AFB in one length	*Need confirmation by another reader or prepare another smear.
10-99 AFB per 100 oil immersion field	+	5-49 AFB in one length	3-24 AFB in one length	Scanty
1-10 AFB per 1 oil immersion field	++	3-24 AFB per field	1-6 AFB per field	+
>10 AFB per 1 oil immersion field	+++	25-250 AFB per field	7-60 AFB per field	++
		>250 AFB per field	> 60 AFB per field	+++

B. 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.

C. ***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:

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

Genotypic/ Molecular DST techniques: employs 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.

At present, the national TBL Control Program recommends the following molecular DST techniques for use in Ethiopia:

- Xpert MTB/RIF Assay
- Xpert MTB/RIF Ultra assays,
- Line Probe Assays (GenoType® MTBDRplus and GenoType® MTBDRsl)
- Truenat™ MTB, MTB Plus and MTBRIF Dx tests
- Xpert MTB/XDR Assay as a follow on diagnostic test for detection of additional drug-resistance

Detailed guidance on the use of each of the above molecular tests is indicated under the following section.

4.1.2 WHO-approved nationally recommended rapid tests for diagnosis of TB and DR-TB

Rapid and sensitive molecular tests have become available to replace or complement existing conventional tests for detecting MTBC and drug resistance recently. The National TBL Control Program recommends that these rapid techniques be used as the initial diagnostic test to detect MTBC and RIF resistance, to minimize delays in starting appropriate treatment.

The following rapid molecular diagnostic tests are currently recommended for use in Ethiopia.

1. Xpert® MTB/ RIF and Xpert MTB/RIF Ultra assays
2. Truenat™ MTB, MTB Plus and MTBRIF Dx tests
3. Line-probe assays (LPAs): GenoType® MTBDRplus and GenoType® MTBDRsl)
4. Lateral flow lipoarabinomannan assay (LF-LAM) test to assist in diagnosing TB in selected groups of HIV-infected presumed TB patients.
5. Loop-mediated isothermal amplification (TB-LAMP)

Besides the above rapid diagnostic tests that are recommended as initial test for TB, Xpert MTB/XDR Assay is also recommended as a follow on diagnostic test for detection of additional drug-resistance.

1. Xpert MTB/RIF assay

The Xpert MTB/RIF assay is a cartridge-based automated test that uses polymerase chain reaction (PCR) to identify MTBC and mutations associated with RIF resistance directly from specimens. Xpert MTB/RIF assay detects more TB cases in patients likely to be missed by smear microscopy.

The national TBL Control Program recommends the use of the Xpert MTB/RIF as initial diagnostic test in the following situations:

- In adults with signs and symptoms suggestive of pulmonary TB;
- In children with signs and symptoms of pulmonary TB from sputum, gastric aspirate, nasopharyngeal aspirate, or stool specimens;
- In adults and children with signs and symptoms of TB meningitis, in cerebrospinal fluid (CSF);
- In adults and children with signs and symptoms of EPTB, in lymph node aspirate, lymph node biopsy, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid or urine specimens for the corresponding form of EPTB;
- In adults and children with signs and symptoms of EPTB for rifampicin-resistance detection;
- 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

To use Xpert MTB/RIF assay for tissue biopsy, there is a need for tissue processing before running this test which needs special safety requirement.

2. 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. The 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 as initial diagnostic test 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);
- In children with signs and symptoms of pulmonary TB in sputum or nasopharyngeal aspirates;
- In adults and children with signs and symptoms of TB meningitis, in cerebrospinal fluid (CSF);
- In adults and children with signs and symptoms of EPTB from lymph node aspirate or biopsy;

Notes: *In adults and children with signs and symptoms of EPTB, Xpert Ultra should be used whenever avaialable for rifampicin-resistance detection rather than culture and phenotypic DST.*
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 is not required.*
In children with signs and symptoms of pulmonary TB 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 is recommended if at high-risk.

3. Truenat MTB, MTB Plus and MTB-RIF Dx assays

The Truenat MTB and MTB Plus assays are chip-based real-time micro PCR for the semi-quantitative detection of MTBC directly from sputum specimens. 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 Truenat MTB, MTB Plus and MTB-RIF Dx tests are recommended in areas where access to Xpert/MTB RIF assays is limited.

- In adults and children with signs and symptoms of pulmonary TB as an initial diagnostic test for TB rather than smear microscopy.
- If the initial Truenat MTB or MTB Plus test result is positive, use Truenat MTB-RIF Dx for rifampicin resistance test.

4. LPAs

LPAs are 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 Ethionamide.

- FL-LPAs are recommended for persons with a sputum smear-positive specimen or a cultured isolate of MTBC, 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.

***Note**: 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 patients with confirmed MDR/RR-TB, 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.
- SL-LPA tests are also useful for detecting FQ resistance before starting therapy for both RR/MDR-TB and Hr-TB

5. TB-LAMP assay

The TB-LAMP assay is designed to detect MTBC directly from sputum specimens. This is a manual assay with similar biosafety requirements to sputum smear microscopy. TB-LAMP does not detect resistance to anti-TB drugs.

- TB-LAMP may be used as a replacement test for sputum-smear microscopy for diagnosing pulmonary TB in adults with signs and symptoms consistent with TB.
- TB-LAMP may be used as a follow-on test to smear microscopy in adults with signs and symptoms consistent with pulmonary TB, especially when further testing of sputum smear-negative specimens is necessary
- TB-LAMP does not provide any information on RIF resistance. Hence, the assay should not replace rapid molecular tests that detect both MTBC and RIF resistance.
- TB-LAMP should also not replace the use of rapid molecular tests that have a higher sensitivity for the detection of TB among PLHIV who have signs and symptoms consistent with TB.

6. Urine LF-LAM assay

The urine LF-LAM assay is an immunocapture assay based on the detection of the mycobacterial LAM antigen in urine, and is a potential point-of-care test for certain populations being evaluated for TB. Although the assay lacks sensitivity, it can be used as a fast, bedside, rule-in test for HIV-positive individuals, especially in urgent cases where a rapid TB diagnosis is critical for the patient's survival. The detection of mycobacterial LAM antigen in urine does not provide any information on drug resistance.

The urine LF-LAM test is recommended for use in the following situations:

- **Inpatients**: LF-LAM is recommended to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children with signs and symptoms of TB with advanced HIV disease or who are seriously ill, or with a CD4 cell count of less than 200 cells/mm3, irrespective of signs and symptoms of TB.
- **Outpatients**: LF-LAM is recommended to assist in the diagnosis of active TB in HIV positive adults, adolescents and children who: have signs and symptoms of TB; are seriously ill; or have a CD4 cell count of less than 100 cells/mm3 irrespective of signs and symptoms of TB. It is not recommended to use LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children without TB symptoms and with an unknown CD4 cell count, or with a CD4 cell count greater than 100 cells/mm3.
- For their initial diagnostic test, all patients with signs and symptoms of pulmonary TB who are capable of producing sputum should have at least one sputum specimen submitted for a molecular WRD assay. This also includes children and adolescents living with HIV who are able to provide a sputum sample.
- LF-LAM results (test time < 15 minutes) are likely to be available before molecular WRD test results; hence, treatment decisions should be based on the LF-LAM result while awaiting the results of other diagnostic tests.
- LF-LAM should be used as an add-on to clinical judgement in combination with other tests. It should not be used as a replacement or triage test.

7. Xpert MTB/XDR Assay or low complexity automated NAATs

The Xpert MTB/XDR Assay is low complexity automated NAATs for detection of resistance to

INH and second-line anti-TB drugs. It uses a cartridge designed for the GeneXpert instrument to detect resistance to INH, FQs, Eto and second-line injectable drugs (AMK, kanamycin and capreomycin). However, unlike Xpert MTB/RIF and Xpert MTB/RIF Ultra, which are performed on a GeneXpert instrument that can detect 6 colours, the new test requires a 10-colour GeneXpert instrument.

The Xpert MTB/XDR test is intended for use as a follow-on test in specimens determined to be MTBC-positive; it offers the chance to improve access to rapid DST in intermediate and even peripheral laboratories. The Xpert MTB/XDR test provides results in less than 90 minutes, leading to faster time to results than the current standard of care (i.e. LPAs or culture-based phenotypic DST). This assay requires the same infrastructure and training of technicians as the other Xpert tests.

The Xpert MTB/XDR test (low complexity automated NAATs) is recommended for detection of resistance to INH and second-line anti-TB drugs in the following situations:

- In people with bacteriologically confirmed pulmonary TB, for initial detection of resistance to INH and FQs, rather than culture-based phenotypic DST.
- In people with bacteriologically confirmed pulmonary TB and resistance to RIF, for initial detection of resistance to Eto, rather than DNA sequencing of the *inhA* promoter.
- In people with bacteriologically confirmed pulmonary TB and resistance to RIF, for initial detection of resistance to Amk, rather than culture-based phenotypic DST.

8. Moderate complexity automated nucleic acid amplification tests (NAATs)

The moderate complexity automated NAATs class of tests includes rapid and accurate tests for the detection of pulmonary TB from respiratory samples. Moderate complexity automated NAATs are also able to simultaneously detect resistance to both RIF and INH, and are less complex to perform than phenotypic DST and LPAs. After the sample preparation step, the tests are largely automated. Currently recommended tests in this class are: Abbott RealTime MTB and MTB RIF/INH, BD MAX MDR-TB, Bruker-Hain FluoroType MTBDR, and Roche cobas MTB and MTB-RIF/INH.

Moderate complexity automated NAATs are recommended in people with signs and symptoms of pulmonary TB, moderate complexity automated NAATs may be used on respiratory samples for detection of pulmonary TB, RIF resistance and INH resistance, rather than culture and phenotypic DST.

9. High complexity reverse hybridization NAAT

The “first in class” product for this class is the GenoScholar PZA-TB (Nipro, Osaka, Japan) for the detection of resistance to pyrazinamide. The GenoScholar PZA-TB test is based on the same principle as the FL-LPA and SL-LPA but requires the use of a large number of hybridization probes to cover the full pncA gene (>700 base pairs). It provides faster results than phenotypic DST and is based on molecular detection.

The use of high complexity reverse hybridization NAATs is recommended in the following situations:

- In people with bacteriologically confirmed TB, high complexity reverse hybridization NAATs may be used on M. tuberculosis culture isolates for detection of PZA resistance, rather than culture-based phenotypic DST.
- The recommendation only applies to culture isolates; thus, this test is appropriate for use only where culture facilities are available.

4.2. Additional supportive methods

A. Histo-Pathological Examination

Pathology plays a complementary role in confirming the diagnosis of TB. Multiplication of tubercle bacilli in any site of the human body causes a specific type of inflammation, with formation of characteristic granuloma that can be found on histo-pathological examination. Samples for pathologic examination can be collected using:

- Fine needle aspiration from accessible mass like peripheral enlarged lymph nodes
- Aspiration of effusions from serous membranes; serous fluid analysis however, is much less useful for diagnosis than histology and culture of a serous membrane biopsy specimen.
- Tissue biopsy from any body tissues such as serous membranes, skin, endometrium as well as bronchial, pleural, peritoneal, colonic, gastric or liver tissue.

B. Radiological Examination

Chest radiography, or chest X-ray (CXR), is an important tool for triaging and screening for pulmonary TB, and it is also useful to aid diagnosis when pulmonary TB cannot be confirmed bacteriologically. Ensuring the wider and quality-assured use of CXR for TB detection in combination with laboratory based diagnostic tests, can contribute to earlier TB diagnosis and potentially to closing the TB case-detection gap when used as part of the diagnostic algorithms.

Chest X-ray (CXR) is a rapid imaging technique that allows lung abnormalities to be identified. CXR is used to diagnose conditions of the thoracic cavity, including the airways, ribs, lungs, heart and diaphragm. CXR has high sensitivity for pulmonary TB and thus is a valuable tool to identify TB as a differential diagnosis for patients. However, CXR has poor specificity; although some CXR abnormalities are rather specific for pulmonary TB (for example, cavities), many CXR abnormalities that are consistent with pulmonary TB are seen also in several other lung pathologies and, therefore, are indicative not only of TB but also of other pathologies. Moreover, there is significant intra- and inter-observer variation in the reading of CXRs. Rigorous efforts should always be made to base a TB diagnosis on bacteriological confirmation.

The x-ray findings must be interpreted in the light of the patient's history and clinical findings. CXR can be used as an effective primary screening and triage test for those clinical risk groups seeking care with any complaints. Person with unexplained chest x-ray findings that are suggestive of PTB should be evaluated with bacteriologic techniques to confirm TB. Other indications for the use of chest x-rays include;

- To assist in the diagnosis of suspected complications of TB disease such as pneumothorax, pleural effusion or patients with frequent or severe hemoptysis.
- To help in diagnosing other concomitant lung diseases such as lung cancer, bronchiectasis, lung abscess and pneumoconiosis.
- X-ray of the spines also helps to evaluate patients with suspected involvement of the vertebrae.

The national TBL Control Program recommends the use of CXR under the following situations:

- **Triaging for TB among people with respiratory complaints**: Proper triaging of people seeking healthcare with respiratory complaints is essential for diagnosing TB correctly and early, as well as for the early diagnosis of other conditions. People with pulmonary TB who are seeking care often initially present with non-specific respiratory symptoms that need to be evaluated. CXR can be used as an effective triage test for those seeking care for respiratory complaints. CXR is a sensitive tool for identifying TB, meaning that it identifies most people with a high likelihood of having the disease, while correctly ruling out TB in most persons when the X-ray is read to look for any abnormality consistent with TB. In addition, CXR can help identify other pulmonary conditions, such as lung cancer and occupational lung diseases like silicosis, as well as other intrathoracic diseases that require further diagnostic evaluation. Therefore, CXR is a useful general triage test for pulmonary conditions. A normal CXR helps rule out a number of pulmonary conditions and prompts diagnostic evaluation for conditions consistent with no radiological findings, while an abnormal CXR prompts evaluation for conditions consistent with radiographic changes, including but not limited to bacteriological evaluation for TB. When used as a triage test, CXR should be followed by further diagnostic evaluation to establish a diagnosis. Regardless of the reason for obtaining a CXR, it is important that any CXR abnormality consistent with TB be further evaluated with a bacteriological test.
- **Chest X-ray as a complement to bacteriological TB tests**: Although CXR is a useful adjunct in diagnosing TB, CXR alone cannot establish a diagnosis. Bacteriological confirmation of TB should always be attempted. Making a clinical diagnosis based on medical history (symptoms, TB exposure, risk markers), signs and CXR findings is sometimes reasonable in persons in whom TB cannot be ruled out despite negative bacteriological tests. In combination with clinical assessment, CXR may provide important circumstantial evidence for clinical diagnosis. Repeated CXR examination after a period of time could be considered, as interpretation of image changes could aid in clinical evaluation for TB and other diagnoses. Clinical diagnosis is particularly relevant in certain groups for whom it can be difficult to confirm a TB diagnosis with a bacteriological test. This includes patients for whom bacteriological tests tend to have lower sensitivity, such as people living with HIV or people with other immune-compromising conditions. It also includes patients from whom it is difficult to collect samples for bacteriological confirmation. Moreover, for seriously ill patients (particularly persons with HIV infection), a clinical decision to start treatment often must be made without waiting for test results. In such patients, CXR can be particularly useful as a diagnostic aid given the rapidity with which it delivers results. However, it should be noted that the accuracy of CXR in these groups may be lower than in other groups. If a patient is not critically ill, follow-up bacteriological testing, repeat CXR and reevaluation of TB and differential diagnoses should be considered. Patients in whom a clinical diagnosis of TB has been made should be followed closely to ensure that a non-TB disease has not been misdiagnosed and left untreated. Follow-up should include repeat clinical and radiological assessment. For those who deteriorate or fail to improve, repeat bacteriological testing for TB should be considered and also diagnostic testing for non-TB diseases.

- **Chest X-ray as part of a comprehensive diagnostic pathway in children**: CXR is useful in the diagnostic evaluation of TB as well as other intra-thoracic diseases in children, especially younger children, in whom bacteriological evaluation is commonly negative. It should be part of a comprehensive diagnostic pathway that includes multiple steps, beginning with clinical assessment, the assessment of risk factors and exposure history, and CXR and bacteriological tests, as required. In most cases, children with TB have radiographic changes suggestive of TB. Adolescent patients with TB have radiographic changes similar to those seen in adult patients. A lateral CXR view may be required, especially in younger children and when bacteriological confirmation is challenging. For example, children younger than 4 years are more likely to have primary TB, and a lateral view will be important in identifying mediastinal or hilar lymphadenopathy.
- **Chest X-ray as a sensitive tool for systematic screening of active TB among high-risk groups:** CXR is recommended as a screening tool among high TB risk groups such as household contacts of TB/DR-TB, including children, People who live in urban slums, congregate settings, Prisoners, HCWs, Under-nourished, PLHIV, Diabetics, >65 years, Tobacco smokers or alcoholics, Refugees, returnees, Pastoralist communities, IDPs, Homeless persons.

C) Ultrasonography: is useful in the diagnosis of TB pleural effusion, pericardial TB and peritoneal TB. Ultrasonography of the chest may be helpful in demonstrating fibrin bands, septations, pleural thickening, and multi-loculated pleural effusions.

4.3 Tuberculosis Case finding strategies

Finding the missing TB and DR-TB cases and closing the incidence-to-case notification gaps remain the top priorty in Ethiopia. In 2020 alone, an estimated 29% (48,000 cases) of incident TB cases and 59% (816 RR/MDR-TB cases) were missed in Ethiopia.

Targetted and differentiated TB/DR-TB case finding strategies supported by highly sensitive screening tools and rapid diagnostic tests are required to reach the missed TB/DR-TB cases in Ethiopia with focus on key affected population for TB. The details of the TB case finding strategies and the tools are described in subsequent sections of this guidelines and the TBL National Strategic Plan (NSP) 2021-2025/6.

To ensure early diagnosis and initiation of effective treatment, Health care workers must promptly identify individuals with symptoms and findings consistent with tuberculosis and initiate appropriate clinical evaluations and diagnostic testing. However, early identification and diagnosis of TB requires the use of effective case finding strategies designed considering the health-seeking behavior of the population, index of TB suspicion among health care professionals, TB screening practices in health facilities, the availability and yield of diagnostic tests and the difference in TB burden in the community.

National TB Case finding strategies and approaches:

- Promote care seeking and TB prevention in the community.
- Targeted and differentiated approach to reach high risk groups (see table 3 below for key TB at risk population groups).
- Screening and evaluation of self-presented persons with TB symptoms for TB
- Screening all clients entering a health facility for TB symptoms
- Integrating TB screening at service delivery points like IMNCI, VCT, ANC, EPI, NCD Care clinics, etc.

The national TBL Control Program identifies the following as key and at-risk population for TB for whom systematic TB Screening shall be targeted.

Table 3: Key TB at risk population groups in Ethiopia

Category	Key TB at risk Population groups
People who have increased TB exposure due to where they live or work.	– Household contacts of PTB, including children. – People who live in urban slums. – Prisoners. – Health Care workers. – People residing or working in congregate settings.
People with increased TB risk due to factors that affect immunity.	– Persons with undernutrition. – People living with HIV (PLHIV) – People living with diabetes mellitus. – People who smoke or use alcohol harmfully. – Persons above 65 years of age. – Dialysis patients – Patients receiving chemotherapy for malignancies
People who have limited access to quality services due to combination of reasons	– Adolescents and young men, 15-34 years of age. – Refugees and returnees. – Pastoralist communities. – Internally displaced persons. – Homeless/street persons and families.

4.3.1 Identification of Individuals with Presumptive TB

Identification of individuals with presumptive TB should be routinely practiced both at community and health facility levels:

- **Identification at community level**: Health extension workers at health post implement community based TB care package whereby they screen all individuals presenting to the health post and during regular home visit for Tuberculosis symptoms, and identify close contact of an infectious TB patient during home visit and refer to the catchment health centers for clinical evaluation and investigation for TB.
- **Identification at Health facility level:** health care workers screen their clients for symptoms and findings consistent with tuberculosis and initiate proper clinical evaluation and diagnostic work up using standard algorithms for Tuberculosis. Besides, health facilities should integrate intensified case findings for high risk groups of patient such as HIV infected. TB clinics at health facilities must routinely conduct TB screening services for house hold/close contacts of infectious TB patients registered to receive TB treatment.

4.3.2 Optimizing "patient-initiated pathway" in all health facilities

Optimizing the 'patient-initiated pathway' includes steps that aim to eliminate potential barriers to early case detection. The following main actions should be optimized along the patient-initiated pathway:

- Improve knowledge and awareness of the community to enable them early recognize TB symptoms

- Ensure high awareness and knowledge in communities about health in general and TB and TB services in particular, to enable people recognize TB symptoms and take appropriate action to seek care from appropriate health facilities.
- Ensure client satisfaction to increase service utilization and peoples' health-seeking behavior.
- Minimize barriers to health-care access and enable community to have access to TB services.
- Engage health-care providers both in the formal and informal health sector to engage with and improve presumptive TB identification, referral and diagnosis mechanisms across all public and private providers.
- Intensify identification of TB among clinical risk groups
- Minimize barriers to health-care access for People with limited access to basic Health services including Pastoral communities and urban poor slums

4.3.3 Approaches to systematic screening for active TB

This refers to the systematic identification of people with presumptive active TB in a predetermined and prioritized target group, using sensitive TB screening tools.

A) Systematic active screening for TB for population with increased clinical risk

Strengthening identification of patients with Presumptive TB at health facility setting through an integrated, Intensified Symptom-based and/or CXR–based TB case finding is recommended for all individuals visiting: Chronic HIV/ART clinics, Chronic disease clinics (DM, COPD, cancer, renal problems), Under-five clinics, PMTCT/ANC clinics, Therapeutic Feeding centers for malnutrition, General OPD and Inpatient clinics.

B) Systematic active screening for TB for settings with increased risk of TB exposure

Integrated Symptom-based and/or CXR-based active TB screening is strongly recommended for predetermined and prioritized target groups with increased risk of TB expo- sure and/or disease: these include:

- **Screening on entry:** Symptom-based TB screening upon entry is recommended for prompt triaging of undiagnosed TB and initiate appropriate evaluation before admission and mixing up with potentially susceptible in habitants. Besides, this also helps to identify those who were receiving treatment prior to admission.
- **Exit Screening of prisoners**: it gives an opportunity to detect TB among inhabitants prior to the release to their family and community.
- **Periodic Mass Screening of inhabitants and staffs**: Annual mass screening of inhabitants (or other segment of population) to identify those who develop TB and initiate intervention. However, trade-off between potential yield and cost-efficiency of this intervention should be analyzed before integrating as strategy.
- **Arrange referral before release**: inhabitants of high-risk settings could leave the institution unplanned predisposing those on TB treatment interruption; hence, referral arrangement upon transferring/releasing such inhabitants on treatment to nearby TB clinics to assist finishing their treatment should be given due emphasis by administrators' of such institutions.

C) TB screening strategy for Household and other close contacts

Contact investigation refers to the systematic evaluation of individuals who have been in close contact with potentially infectious TB cases within three months of the commencement of TB treatment. Systematic evaluation of people who have been in contact with potentially infectious cases of TB is recommended as an efficient, targeted approach to intensify TB case finding.

The main purposes of conducting contact screening and management are to identify contacts of all ages with undiagnosed TB disease among the contacts of an index case, do investigation to rule out active TB and to provide preventive therapy for contacts without TB disease that have increased susceptibility to develop Active TB disease following recent infection.

Definitions of terms related to Contact Investigation and Management:

Term	Definition
Index patient (index case)	A person of any age with new or recurrent TB initially identified in a specific household or comparable setting in which others may have been exposed. An index patient is the person on whom a contact investigation is centred but is not necessarily the source.
Contact	Any person who has been exposed to a person with TB disease.
Close contact	A person who does not live in the household but who shared an enclosed space, such as a social gathering place, workplace or facility, with the index patient for extended periods during the day during the 3 months before the current disease episode commenced.
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 patient during the 3 months before the start of current treatment.
Contact investigation	Systematic identification of people with previously undiagnosed TB disease and TB infection among the contacts of an index TB patient in the household and in comparable settings in which transmission occurs. It consists of identification, clinical evaluation and/or testing and provision of appropriate anti-TB therapy (for people with confirmed TB) or TB preventive treatment (for those without TB disease). This term is often used synonymously with "contact tracing"; however, in the context of TB, action beyond identifying contacts is critical.

Priority groups to conduct contact investigation should be given when the index TB cases either:

- has pulmonary TB,
- has presumptive or confirmed drug-resistant TB,
- is a child under 5 years of age or
- Is a PLHIV or
- From high-risk congregated settings such as prison, homeless shelters…

Table 4: Conducting appropriate contact evaluation and management of TB exposed contacts in Ethiopia

Scenario	Condition	Patient management
1. Source case is presumptive/confirmed Drug resistance TB (Contacts who are exposed to a source case with presumptive or confirmed DR-TB)	1.1 If Contacts is clinically well and no active TB at time of evaluation	Educate the client to have quarterly clinical evaluation for at least two years.
	1.2 if the contact is sick and presumptive TB is diagnosed:	Do detailed clinical and laboratory evaluation to diagnose DR-TB and screening for drug resistant TB at least for Rifampicin.
		If decided to treat for TB, do not treat such patient with first line Anti-TB treatment. Refer to MDRTB treatment center if facing difficulty of deciding on next action.
	1.3 if the contact gets sick on follow up evaluation	Conduct full clinical evaluation and work up for DR-TB.
2. The source case has susceptible TB or low-risk for DR-TB.	2.1 if the contact is clinically well and no active TB at time of evaluation	Treat for latent TB infection (TPT) for eligible contacts (Please refer TPT section).
		Educate the client to seek early medical attention if gets sick in 1 to 2 years' time.
	2.2 if the contact is sick and presumptive TB is identified	Do detailed patient evaluation and investigation for TB as per the guidelines.
		If TB is diagnosed, register the patient and treat for TB If TB not diagnosed, provide TPT as per the guidance.

The index patient should be interviewed as soon as possible after diagnosis, preferably within one week, to elicit details about household and other close contacts. Health providers should clearly and sensitively explain the urgency of initiating contact investigations to the index patient, considering the increased risks of progression to TB disease with recent exposure.

The ten key steps in contact investigation*

1. Review available index patient information
2. Assess duration and degree of infectiousness of index TB patient to identify contacts
3. Counsel index patient and enumerate household and close contacts
4. Develop plan for contact investigation in consultation with index patient/guardian
5. Consider other contacts for investigation (such as in the workplace)
6. Conduct home visits or invite contacts to health center for evaluation
7. Conduct clinical assessment and refer for testing as appropriate
8. Provide treatment for TB disease or TPT as per eligibility
9. Review completeness of contact investigation
10. Ensure systematic recording and reporting

**These steps may not always be done in sequential order*
For details of procedures for contact investigation, please refer to the national SOP for CI and TPT.

TB contact Screening strategies and tools:

In order to improve the accuracy of TB screening, additional sensitive tools are required along with the clinical TB screening algorithms. The following screening tools can also be used as appropriate to specific risk groups. These include:

- **Chest x-ray**: A combination of symptom based algorithm and other sensitive tools such as digital Chest x-ray should be used for screening contacts, PLHIV and other at risk populations. CAD may be used as an alternative to human reader interpretation of plain digital CXR for screening and triage for TB.
- **C-reactive protein (CRP):** is an indicator of inflammation that can be measured using point-of-care tests performed on capillary blood collected via finger-prick. CRP can be used in all PLHIV but offers a clinically significant improvement in accuracy over the WHO four-symptom screen among *ambulant people living with HIV who are newly in care and not yet on antiretroviral treatment (ART)*.

D) TB screening strategy for People with limited access to basic Health services

For communities that are known to be underserved either due to their remote geographic location or their mobility or they face cultural or legal barriers may require additional strategies such as community screening through outreach services or mobile health services. These include: Pastoral communities, People living urban slums, remotely located rural communities, individuals from stigmatized and segregated communities such people with disabilities.

5. APPROACH TO DIAGNOSIS OF TUBERCULOSIS

The diagnosis of TB relies on identification of presumptive TB cases (individuals with symptoms and signs suggestive of TB or with CXR abnormalities suggestive of TB), conducting proper evaluation for TB and other conditions followed by investigations with sensitive confirmatory bacteriological tests.

Effective TB case finding strategies indicated earlier under section 4 of this guidelines (and the revised TBL NSP 2021 -2025) along with proper application of the revised national TB diagnostic algorithms based on the nationally recommended bacteriologic tests and other sensitive diagnostic tools is required for early diagnosis of TB.

5.1 Diagnosis of Pulmonary Tuberculosis in Adult and Adolescents

Health care workers are required to promptly identify, triage and investigate patients who report persistent cough of 2 weeks or more (or any duration if HIV positive), fever for more than 2 weeks, drenching night sweats, unexplained weight loss for TB.

Presumptive Tuberculosis case refers to an individual who presents with symptoms or signs consistent with TB or with CXR abnormality suggestive of TB:

- Persistent cough of 2 weeks or more (or any duration if HIV positive)
- Fever for more than 2 weeks
- Night sweats
- Unexplained weight loss

5.1.1 Evaluation of individuals with presumptive TB

Individuals who are identified as presumptive TB case based on TB symptoms screening questions (positive TB screen) should undergo an appropriate clinical evaluation and investigation for TB and other conditions as per national guideline. All presumptive TB patients, including children, who are capable of producing sputum, should be evaluated for TB using the recommended bacteriologic techniques.

Approach to patients with presumptive TB:

- Triaging and Fast-tracking of presumptive TB patients
- Conduct through clinical evaluation of the patient for TB and other conditions
- Assess presence of danger signs warranting urgent investigations and management
- Determine the primary investigation method
- Collect sputum samples or other biological samples as appropriate for bacteriological examination
- Perform lab examination using the appropriate bacteriological tests and supportive investigations (including radiological and histo-pathologic tests if indicated) to reach to proper diagnosis of the patient's condition.

5.1.2 Considerations for Clinical Diagnosis of Pulmonary TB

In patients in whom index of clinical suspicion remains high despite none-revealing results from confirmatory methods, the care provider may continue investigating the patient for TB with the aid of supportive methods including imaging, hematology and histo-pathologic techniques. Treatment for common infections with Antibiotics, other than fluoroquinolones, may be administered while conducting further investigations for TB to benefit the patients for possible concomitant infections. Decision to treat with full course of TB treatment may be decided on the basis of none-bacteriologic evidences from supportive tests and with aid of sound clinical decision by TB expert. This is especially important in patients with profound immunosuppression where there is alteration on clinical presentation and low yield on confirmatory tests.

Standard PTB Case definitions:

Bacteriologically Confirmed PTB Case is defined as:

- A person whose mWRD test result (Xpert MTB/RIF test, Xpert Ultra, Trunat, TB-LAMP, LF-LAM) indicates MTB detected; or
- A person who have at least one positive result on AFB microscopy

Clinically diagnosed PTB Case is defined as:

- A person who have two negative result on AFB microscopy; **and**
- In whom mWRDs test results show no MTB detected; **and**
- Decision to empirically treat with full course of Ant-TB regimen is made with the help of evidences from supporting tests and with aid of sound clinical decision.

5.2 Diagnosis of Extrapulmonary TB (EPTB) in Adult and Adolescents

EPTB contributes to 20-30% of all TB cases. Lymphatic system and pleural membrane involvement constitute around 60% of all EPTB cases. EPTB involvement is more commonly seen in HIV patients with advanced immune-suppression and young children. All attempts should be made to confirm the diagnosis of TB using available techniques.

Approach to Patient with presumptive extra-pulmonary TB:

- Evaluate for concomitant PTB in patient suspected to have EPTB as significant proportions of EPTB patients may have concomitant pulmonary involvement.
- The following specimens could be used for testing with mWRDsrlier: Plueral, pericardial, synovial, CSF, peritoneal and urine for corresponding EPTB site.
- Conduct testing of the specimens from EPTB sites using mWRDs (Xpert MTB/RIF, Ulta, Trunat), smear microscopy, and culture whenever possible
- Conduct biochemical analysis of fluid aspirates (pleural, peritoneal, CSF, Synovial).
- Negative results from EPTB sites may not be definitive evidence to rule out TB
- Offer HIV test as EPTB is commonly seen among HIV positives individuals
- Assess EPTB case for risk of drug resistance and do DST whenever possible
- Arrange early referral for patients with serious form of ETB to higher level (hospital)

See Annex 2 for details on common manifestation and practical approach for investigation of common EPTB cases.

5.3 Diagnosis of TB among PLHIV

TB is one of the main causes of death among PHIV. The mortality rate among HIV-infected TB patients is higher than that of non-infected TB patients, particularly for those with smear-negative PTB and EPTB. The rates of smear-negative PTB and EPTB is higher among PLHIV compared with HIV negative individuals.

Delayed diagnosis, if not missed at all, may be an important cause of excess mortality in PLHIV who have smear-negative pulmonary and EPTB. Hence, optimized use of rapid diagnostic techniques (i.e. Xpert test), and use of supportive evidences from Chest-x-ray, culture and pathologic studies with help of diagnostic algorithms and clinical expert decision are recommended.

The recommended Investigation approaches are:

- HIV care service providers must routinely screen all HIV positives in care for TB at each visit.
- TB screening for people living with HIV should be using a clinical algorithm. Additional TB screening tools such as CXR and CRP are also recommended.
- Adults and adolescents who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases.
- Do thorough clinical evaluation of the patient, including exclusion of other OIs.
- Molecular WRDs (Xpert MTB/RIF test, Xpert Ultra, Trunat), TB-LAMP, and LF-LAM are the preferred initial diagnostic tests among PLHIV.
- In settings where access to mWRDs such as Xpert service on same day is not feasible, do smear microscopy on two samples on spot in the interim, and send specimen for mWRDs.
- Chest X-rays, when available, should be performed early in the course of investigation of TB in seriously sick HIV positives.
- Histo-pathologic studies should be considered from the appropriate specimen.
- In seriously ill HIV positive patients,
    - All available investigations should be done at one go to reduce the time to diagnosis and avoid preventable deaths.
    - LF-LAM test is recommended as a bed-side test to assist TB diagnosis.
    - Primary role of empirical antibiotic therapy is not to rule out TB, but to cover for concomitant bacterial infection in people living with HIV/AIDS with cough or serious illness.
- Sound clinical judgment is needed to put a seriously ill patient with negative Xpert MTB/RIF and/or sputum smear results on full course anti-TB treatment using only suggestive findings on radiography. In such circumstances, the clinical response of the patient has to be monitored and if possible repeat the Xpert tests. Urine LF-LAM test is recommended whenever available under such circumstances.
- For patients with respiratory symptoms in whom TB is less likely and who are treated empirically for bacterial pneumonia or Pneumocystis Pneumonia (PCP), clinical response should not automatically exclude the diagnosis of tuberculosis.
- Acute bacterial pneumonia or PCP may occur in patients with underlying tuberculosis and patients should therefore be re-evaluated for tuberculosis, particularly if respiratory symptoms persist after treatment.

5.4 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 5 for DR-TB risk), and perform confirmatory laboratory-based first and second line drugs susceptibility testing (DST) for core TB drugs using rapid molecular techniques.

5.4.1 Diagnosis of resistance to first line TB drugs

Development of drug resistance is largely a man-made problem resulting from inadequate treatment due to suboptimal adherence, and continued transmission of resistant strains in the community following delayed diagnosis from lack of universal DST(testing all identified TB patients for drug resistance before or at start of TB treatment) and ineffective patients' triaging for risk of Drug resistance. Previous TB treatment is the strongest risk factor to the development of drug resistance. An ongoing person-to-person transmission of drug resistant strains in the household/community and health care or congregate settings is also an important contributor. Inadequate infection control and factors that extend the infectious period such as delayed DR-TB diagnosis and treatment initiation, and delayed bacteriological conversion of sputum due to inappropriate MDR-TB therapy are the main factors for continued person-to-person transmission of the resistant strains.

Under programmatic conditions, prioritization of patients on the basis of their risk of developing/acquiring DR-TB, is applied for systematic screening of presumptive and diagnosed TB cases for possible drug resistant TB. Please refer to the TB/DR-TB diagnostic sections for details.

Table 5: DR-TB Risk and TB patient group/type

DR-TB Risk	TB patient group/type
High risk	• Patients with Treatment after failure of second course of TB treatment • Treatment after failure of treatment regimen for new TB patients • Presumtive TB cases who are contacts of a confirmed DR-TB patient • TB patients who are contacts of a confirmed DR-TB patient
Medium risk	• Relapse TB patients • TB patient whose smear remains positive after two months of TB treatment • Treatment after loss-to-follow up TB patients • TB patients with prolonged living-working history in settings known higher DR-TB prevalence such as congregated settings or health care facility
Low risk	• Newly diagnosed TB patient with no known contact history with DR-TB patient

Individuals with presumptive or confirmed diagnosis of TB should be evaluated for risk of contracting drug resistant forms of TB. Patients diagnosed with active 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 prior to treatment initiation to ensure effectiveness of the treatment regimen. Baseline DST at least for Rifampicin is particularly recommended for all bacteriologically confirmed TB cases as part of the implementation of universal DST policy. All RR/MDR-TB patients should have further DST at least for Flouroquinolones at baseline.

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 months
- Patients with presumed or confirmed TB with contact history with RR/MDR-TB patient
- 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 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.

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 patient.
- 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

5.5 National TB/DR-TB Diagnostic Policies and Algorithms

Effective and efficient TB diagnostic algorithms are key components of a diagnostic cascade designed to ensure that patients with TB are diagnosed accurately and rapidly, and are promptly placed on appropriate therapy.

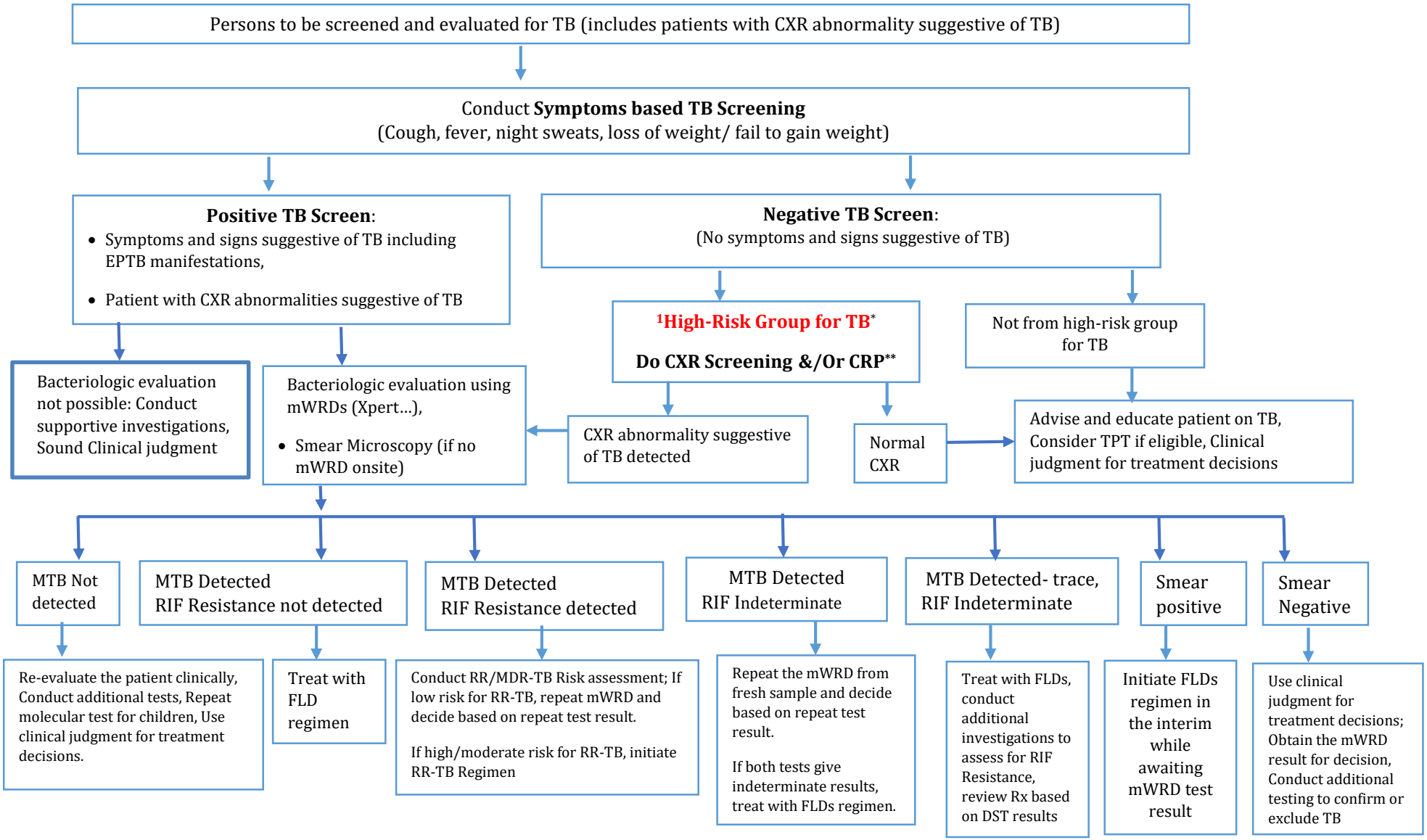
National TB/DR-TB diagnostic algorithms that incorporate the latest WHO recommendations for the diagnosis and treatment of TB and DR-TB are indicated below. The algorithms largely emphasize the use of WHO-recommended rapid diagnostics (WRDs) endorsed for use in Ethiopia.

The national algorithms for TB diagnosis, drug susceptibility testing and patient management express the following policy recommendations:

- All presumptive TB cases should submit sputum or other recommended biological specimens for bacteriologic examination with molecular WRDs (Xpert MTB/RIF assay, Xpert Ultra, TB-LAMP, Trunat) or sputum microscopy. For PLHIV, the use of urine LF-LAM is recommended to aid TB diagnosis besides other mWRDs. Please refer to the LF-LAM algorithms for details.
- If mWRD test (such as Xpert MTB/RIF assay, Ultra, Trunat) service is accessible for same day result, the mWRD (e.g. Xpert MTB/RIF) test is recommended as the initial diagnostic test for all persons with presumptive TB.
- If Xpert service or other recommended mWRDs are not readily available for same day result, sputum microscopy may be used as the primary diagnostic test for TB in the **interim** to avoid diagnostic delay. In the meantime, a specimen should be sent for Xpert testing or other WRDs.
- All individuals diagnosed with bacteriologically confirmed TB should undergo drug resistance screening test at least for Rifampicin at baseline using rapid DST techniques.
- Patients with unexplained abnormal radiological findings on CXR should submit sputum for confirmatory test preferably by mWRDs such as X-pert MTB/RIF test.
- For all patients with confirmed RR/MDRTB, send sputum specimen for SL-DST using LPA before or within one week of treatment initiation with RR/MDR-TB regimen.
- DR-TB Patients with reported resistance on SL-LPA, will require full DST using phenotypic methods while patient is managed on the basis the LPA result.
- In patients in whom the diagnosis of TB remains in doubt despite negative bacteriologic results additional investigations may be performed as needed.
- Individuals with presumptive or confirmed TB should be offered rapid HIV test.

The National Diagnostic Algorithms for Patients with Presumptive TB are given under the following sections (Figures 2).

Figure 2: National TB Diagnostic Algorithm for persons evaluated for TB



*__***High-risk groups for TB***__*: Household contacts of TB/DR-TB, including children, People who live in urban slums, Prisoners, Health workers, People residing or working in congregate settings, Persons with undernutrition, PLHIV, Diabetics, People who smoke or use alcohol harmfully, Persons above 65 years of age, Refugees and returnees, Pastoralist communities, Internally displaced persons, Homeless/street persons and families.*

[1]*For PLHIV, besides bacteriologic evaluation with mWRDs, the use of LF-LAM assay is recommended as a rapid TB diagnostic aid and care providers must refer to the LF-LAM algorithms when evaluating PLHIV for TB.*

Decision pathways in the diagnostic algorithm

1. For all patients being evaluated for TB, with access to CXR, the use of CXR as an initial screening tool in addition to the symptoms screening is recommended. The use of CXR as a screening test for TB is particularly recommended for populations at high-risk for active TB. All patients with CXR abnormality needs to be evaluated bacteriologically. CAD softwares are recommended for the digital CXR results interpretations whenever available.
2. Collect a good-quality specimen and transport it to the testing laboratory. Conduct the molecular WRD. For individuals being evaluated for pulmonary TB, the following specimens may be used: induced or expectorated sputum (preferred), bronchoalveolar lavage, gastric lavage or aspirates, nasopharyngeal aspirates, and stool samples.
3. **If the molecular WRD test result is "MTB not detected**" re-evaluate the patient and conduct additional testing.
    - **a.** Further investigations for TB may include chest X-ray (if not done), additional clinical assessments, additional molecular WRD testing or culture, and, finally, clinical response following treatment with broad spectrum antimicrobial agents (FQs should not be used).
        - In children with signs and symptoms of pulmonary TB and a negative Xpert MTB result on the first initial test, repeat the Xpert MTB test for a total of two tests. The tests may use the same specimen types or different specimen types.
    - **b.** Consider the possibility of clinically defined TB (i.e. TB without bacteriological confirmation). Use clinical judgement for treatment decisions.
4. **If the molecular WRD test result is "MTB detected, RIF resistance not detected"**
    - a. Initiate the patient on an appropriate regimen using first-line TB drugs.
    - b. Request additional DST in the following cases:
        - Molecular or phenotypic DST for INH is indicated particularly if the patient has been treated with INH or is a contact of a known Hr-TB patient;
        - Molecular or phenotypic DST for resistance to RIF may be requested if the patient is considered to be at risk of having RR-TB despite the initial molecular WRD result.
    - c. If additional molecular or phenotypic testing is performed:
        - The molecular and phenotypic testing may be performed in different laboratories.
        - The molecular and phenotypic DST may be performed using the specimen (direct DST) or using bacteria recovered by culture (indirect DST). Direct DST is preferred for molecular testing, whereas indirect DST may be preferred for phenotypic testing.
        - A rapid molecular test is preferred. FL-LPA can identify inhA and katG mutations, which can guide clinicians on the composition of INH-resistant TB regimen.

- Culture-based phenotypic DST for INH and RIF requires 3–8 weeks to produce a result. Phenotypic DST may be useful for evaluating patients with a negative FL-LPA result, particularly in populations with a high risk for INH resistance.

5. If the **molecular WRD test result is "MTB detected, RIF resistance detected**" an MDR-TB risk assessment is needed.
    a. If the patient is at high risk of having MDR-TB, the RIF-resistant test result is definitive. Initiate the patient on a regimen for RR-TB or MDR-TB in accordance with national guidelines. Follow Algorithm SL-DST for additional testing.
    b. If the patient is at low risk of having MDR-TB, repeat the molecular WRD test with a second sample. If FL-LPA is available at the site and the sputum specimen is smear positive, FL-LPA can be used for confirming the RIF-resistant result.
        - If the second test also indicates RIF resistance, initiate an MDR-TB regimen in accordance with national guidelines and follow SLD-DST Algorithm for additional testing.
        - If the molecular WRD result for the second sample is "MTB detected, RIF resistance not detected", initiate treatment with a first-line regimen in accordance with national guidelines. In most situations, false-positive RIF-resistant results due to technical performance of the assay are rare; however, false-positive RIF-resistant results due to laboratory or clerical errors may occur. It is assumed that the repeat test will be performed with more caution, that the result of the second test is correct, and that the result of the first test may have been due to a laboratory or clerical error.
    c. For all patients with RR-TB or MDR-TB, conduct additional investigations to assess resistance to the drugs being used in the treatment regimen. Phenotypic and molecular methods are available to evaluate drug resistance. Rapid molecular methods are preferred. Follow SLD-DST Algorithm for additional testing.
6. If the **molecular WRD gives a result of "MTB detected, RIF indeterminate",** the interpretation and follow-up testing for Xpert Ultra differs from that for other molecular WRD tests (e.g. Xpert MTB/RIF or Truenat MTB-RIF Dx test). With any of the molecular WRD tests, the initial result of "MTB detected" should be considered as bacteriological confirmation of TB. The patient should be initiated on an appropriate regimen using **first-line TB drugs**, unless the patient is at high risk of having MDR-TB (Such patients should be initiated on an MDR-TB regimen).
    a. For most molecular WRD assays, an "MTB detected, RIF resistance indeterminate" result is generally caused by a **paucibacillary** TB load in the sample; in such cases, retesting a fresh specimen at the same testing site is useful. If the result of the second molecular WRD test is "MTB detected, RIF resistance not detected", follow Step 4. If the result is "MTB detected, RIF-resistance detected", follow Step 5. In some cases, testing a second sample, which might also contain very few bacteria, may generate a result of "MTB detected, RIF indeterminate" or "MTB not detected". In these situations, additional investigations such as culture and phenotypic DST may be needed to confirm or exclude resistance to RIF.
    b. "**MTB detected (non-trace), RIF indeterminate**" results obtained with the **Xpert Ultra test** may be due to the presence of **large deletions** or **multiple mutations** in the RIF-resistance-determining region (RRDR) of the bacilli. The Ultra melt curves from "MTB detected (non-trace), RIF indeterminate" samples should be reviewed.

1. Melt curves that suggest the presence of a large deletion or multiple mutations in the RRDR should be interpreted as "RIF resistance detected". In such cases, follow Step 5.
2. If the melt curve is not consistent with the presence of a large deletion or multiple mutations in the RRDR, the result is interpreted as "indeterminate". In such cases, follow Step 6a for additional testing.
3. If the semi-quantitative result is high or medium, FL-LPA or DNA sequencing may be useful.

c. Culture and DST or FL-LPA may be performed for follow-up testing to confirm or exclude RIF resistance.

7. If the **Xpert Ultra test result is "MTB detected trace**", additional evaluations are needed.
   a. Review the clinical evaluation to determine the person's age, HIV-infection status and history of TB treatment, and determine whether the samples are pulmonary or extrapulmonary.
   b. For PLHIV and children who are being evaluated for PTB; for individuals being evaluated for EPTB; and for adult HIV negative PTB, and **without a history of prior TB treatment** within the past 5 years: Consider the MTB detected trace result obtained with the first specimen as bacteriological confirmation of TB and use for clinical decisions. Initiate the patient on an appropriate regimen using **FLDs**, unless the patient is at high risk of having MDR-TB. Initiate such patients on an MDR-TB regimen. Undertake additional investigations (e.g. culture and phenotypic DST) to confirm or exclude resistance to RIF.
   c. For adults being evaluated for PTB, who are not at risk of HIV and **have a history of TB treatment in the past 5 years**: For adults with a history of recent TB treatment or unknown treatment history, consider the possibility of the Xpert Ultra trace result being a **false-positive result** because of the presence of non-viable bacilli. Clinically re-evaluate the patient and conduct additional testing in accordance with national guidelines. Consider the possibility of TB caused by reactivation, relapse or reinfection. In initiating treatment, consider the clinical presentation and context of the patient. Make clinical decisions based on sound clinical judgment. Further investigations for TB may include chest X-ray, additional clinical assessments and clinical response following treatment with broad-spectrum antimicrobial agents.
8. If the **mWRD test does not give a result, or gives a result of error or invalid**, repeat the **mWRD** test at the same testing site with a second specimen. If FL-LPA is available at the site and the second specimen is smear positive, FL-LPA can be used for the repeat testing (although repeat Xpert MTB testing is preferred because it has a lower LOD than the FL-LPA).

Results of Sputum AFB microscopy (When mWRDs not available in the interim):

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). Re-evaluate the patient clinically and conduct additional testing (CXR if not done). Broad spectrum antimicrobials may be considered in symptomatic patients while awaiting Xpert MTB/RIF test results.
   - 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.

Interpretation of discordant results: Please follow the following guidance for interpretation of discordant results in TB diagnostic work up.

Table 6: Interpretation of discordant results in TB diagnostics

Discordant Situation	Interpretation
Molecular WRD result "MTB detected other than trace", culture negative	• The mWRD result and clinical judgment should have been used to guide the treatment decision. The mWRD result should be considered as bacteriological confirmation of TB, if the sample was collected from a person who was not recently receiving treatment with anti-TB drugs. Cultures from individuals with PTB may be negative for several reasons, including that the patient is being treated for TB (effective treatment rapidly renders MTBC non-viable), transport or processing problems have inactivated the TB bacilli, cultures have been lost to contamination, the testing volume was inadequate, or a laboratory or clerical error occurred. • Re-evaluating the patient for TB, reassessing the possibility of prior or current treatment with anti-TB drugs (including FQ use), evaluating response to therapy, and evaluating the possibility of laboratory or clerical error.
Molecular WRD result "MTB not detected", culture positive.	• Treatment decision should be based on the culture result. If the patient started treatment based on clinical judgment, continue treatment. Record the patient as having bacteriologically confirmed TB. • The culture-positive result should be considered as bacteriological confirmation of TB. The sensitivity of WRDs is lower in PLHIV, children and other specimen types such as CSF. • False-positive cultures can result from a variety of causes, such as cross-contamination in the laboratory or sample labelling problems. Such incidents are usually rare in well-functioning labs. • Re-evaluating the patient for TB, conducting additional testing using WRD test; culturing additional samples, and evaluating the possibility of laboratory or clerical error. If the patient was initiated on anti-TB therapy based on clinical judgment, evaluate the response to therapy.
Molecular WRD result "MTB detected, RIF resistance detected"; RIF susceptible by phenotypic DST.	• Use the molecular WRD result to guide treatment decisions pending additional testing. Certain mutations are known to generate this discordant result, particularly in the BACTEC™ MGIT system (i.e. a false-susceptible phenotypic result). Patients infected with strains carrying these mutations often fail treatment with RIF-based first line regimens. Silent mutations have been observed that generate a false-resistant WRD result, but these are very rare. False RIF-resistant results have been observed with the Xpert MTB/RIF G4 cartridge when the MTB detected result was "very low". Follow-up action may include WRD testing of the culture. • Follow-up actions may include DNA sequencing, FL-LPA, phenotypic DST using solid media and evaluation of the possibility of laboratory or clerical error.
Molecular WRD result "MTB detected, RIF resistance not detected"; RIF resistant by phenotypic DST	• The treatment regimen should be modified based on the results of the phenotypic DST. • False RIF-susceptible molecular WRD results are rare, but have been observed in 1–5% of TB cases tested with the Xpert MTB/RIF test in various epidemiologic settings. Mutations in the region of the rpoB gene sampled by the Xpert MTB tests have been shown to account for 95–99% of RIF resistance. The remainder of RIF resistance arises from mutations outside the sampled region, which produce an Xpert MTB result of "RIF resistance not detected". Follow-up actions may include DNA sequencing, repeating the phenotypic DST and evaluating the possibility of laboratory or clerical error.
Xpert Ultra "MTB detected trace", culture negative	The interpretation of this result must consider patient characteristics, specimen type and whether the person had been previously treated for TB: Cultures may be negative for several reasons, including the patient being treated for TB or treated with FQs, transport or processing problems that inactivated the tubercle bacilli, culture contamination or inadequate testing volume, or laboratory or clerical error. The very small numbers of bacilli in a sample that generates an "MTB detected trace" result may be due to active TB disease, laboratory cross-contamination, recent exposure to (or infection with) tubercle bacilli (incipient TB), and current or past treatment for TB. • For PLHIV and children - The "MTB detected trace" result is considered as bacteriological confirmation of TB (i.e. true positive results) and such patients should have been initiated on therapy based on the Xpert Ultra result. Consider the possibility that the culture result was a false-negative result. • For adult HIV Negative and no recent TB treatment History - "MTB detected trace" results should be considered as bacteriological confirmation of TB (i.e. true positive results) and consider the possibility that the culture result was a false-negative result, if the samples were collected from a person who was not receiving treatment with anti-TB drugs, because of the paucibacillary nature of the sample. • For adults with a history of recent TB treatment: Consider the possibility that the Xpert Ultra "MTB detected trace" result was a false positive result because of the presence of non-viable bacilli. A culture-negative result is consistent with this possibility.

Figure 3: Algorithm for LF-LAM testing to aid in the diagnosis of TB among PLHIV in inpatient settings

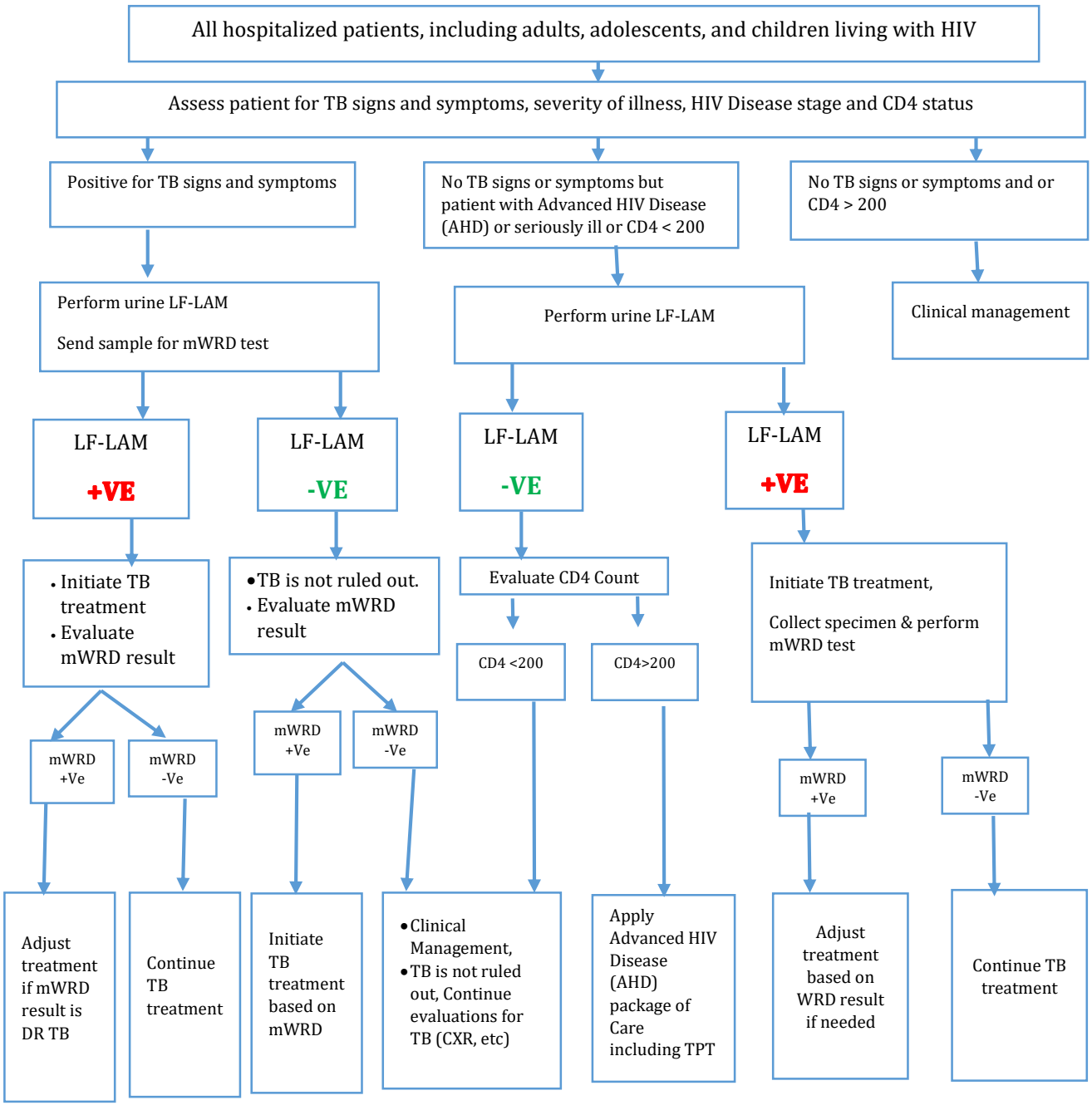
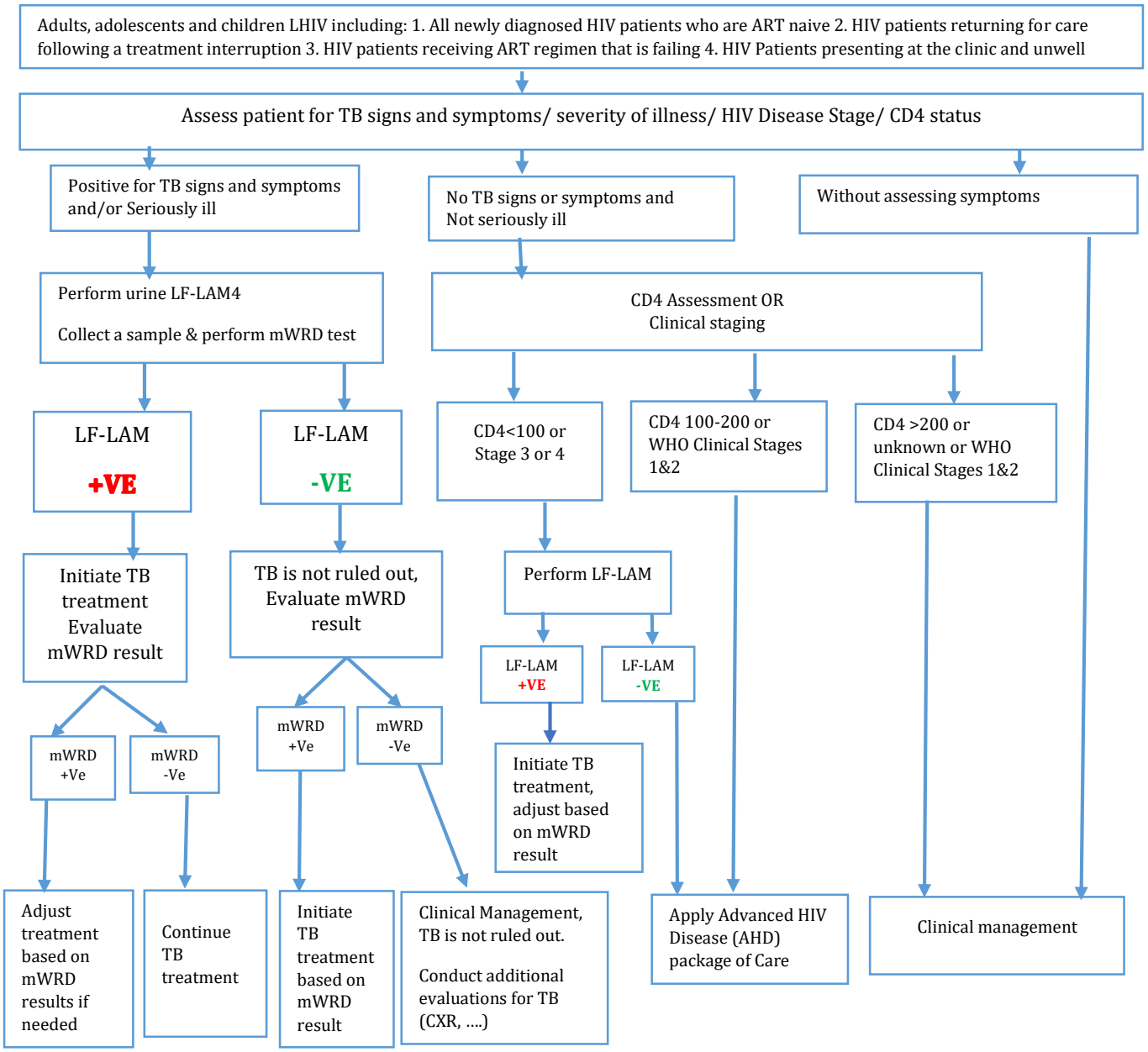


Figure 4: Algorithm for LF-LAM testing to aid in the diagnosis of TB among PLHIV in outpatient settings



Decision pathway for LF-LAM testing to aid in the diagnosis of TB among PLHIV

A. Decision pathway for LF-LAM testing in **inpatient** settings:

1. Evaluate the hospitalized patient for TB, determine HIV status and assess the presence of danger signs for being seriously ill. In PLHIV who are not seriously ill, consider measuring CD4 cell counts, to assess eligibility for testing with the LF-LAM assay.
    a. "Seriously ill" is defined as presenting with any one of the following danger signs: respiratory rate >30 per minute, temperature >39 °C, heart rate >120 beats per minute or unable to walk unaided.
    b. For adults, adolescents and children aged more than 5 years, AHD is defined as CD4 cell count <200 cells/mm3 or WHO stage 3 or 4 event at presentation for care. All children aged under 5 years are considered as having AHD.
2. For hospitalized PLHIV being evaluated for TB, who are positive for signs and symptoms of TB,
    a. Collect a urine specimen and conduct the LF-LAM assay **and** collect a specimen and conduct molecular WRD testing. If the molecular WRD test is available on site, perform the molecular WRD testing in parallel to the LF-LAM testing.
    b. All patients who have a positive LF-LAM result should be initiated on TB treatment immediately, while awaiting results of the molecular WRD test.
    c. TB is not ruled out if the LF-LAM test result is negative. Evaluate the results of the molecular WRD test and follow Figure 2 for interpretation of results.
    d. Treat all patients with a molecular WRD test result of "MTB detected" for TB, regardless of LF-LAM result.
    e. TB is not ruled out if both the LF-LAM result and molecular WRD test results are negative (or if no molecular WRD test is performed). Re-evaluate the patient and conduct additional testing in accordance with national guidelines. Conduct additional clinical evaluations for TB, such as initiating treatment for bacterial infections using broad-spectrum antibiotics. Consider treatment for Pneumocystis pneumonia. Evaluate clinical response after 3–5 days of treatment. If there is clinical worsening or no improvement after 3–5 days of treatment, initiate further investigations for TB and other diseases and, if the patient is seriously ill with danger signs, start presumptive TB treatment. If there is clinical improvement, reassess for TB and other HIV-related diseases. Clinical improvement may occur if the patient has TB and a bacterial infection. If there is high clinical suspicion of TB, use clinical judgment as to whether to initiate TB treatment. All patients should complete the course of treatment for bacterial or Pneumocystis infections.
3. For hospitalized PLHIV being evaluated for TB who do not have signs or symptoms of TB but have AHD or are seriously ill or have CD4 <200 cells/mm^3
    a. Collect a urine specimen and conduct the LF-LAM assay.
    b. If the LF-LAM is negative and the CD4 is <200 cells/mm^3re-evaluate the patient and conduct additional testing in accordance with national guidelines.
    c. If the LF-LAM is negative and the CD4 is >200 cells/mm^3 apply an AHD package of care.
    d. If the LF-LAM is positive, initiate TB treatment based on this result and clinical judgment. Collect a specimen and conduct a WRD test to assess the possibility of rifampicin resistance.

i. If the molecular WRD result is "MTB detected", follow Algorithm for interpretation, testing and treatment recommendations.
ii. If the molecular WRD result is "MTB not detected", treat the patient for TB and conduct additional laboratory testing (e.g. culture and DST) to assess drug resistance.

4. For hospitalized PLHIV without signs or symptoms of TB and whose CD4 is 200 cells/mm3 or above (or is unknown), do not conduct an LF-LAM test.

B. Decision pathway for LF-LAM testing in **Outpatient and Clinic** settings

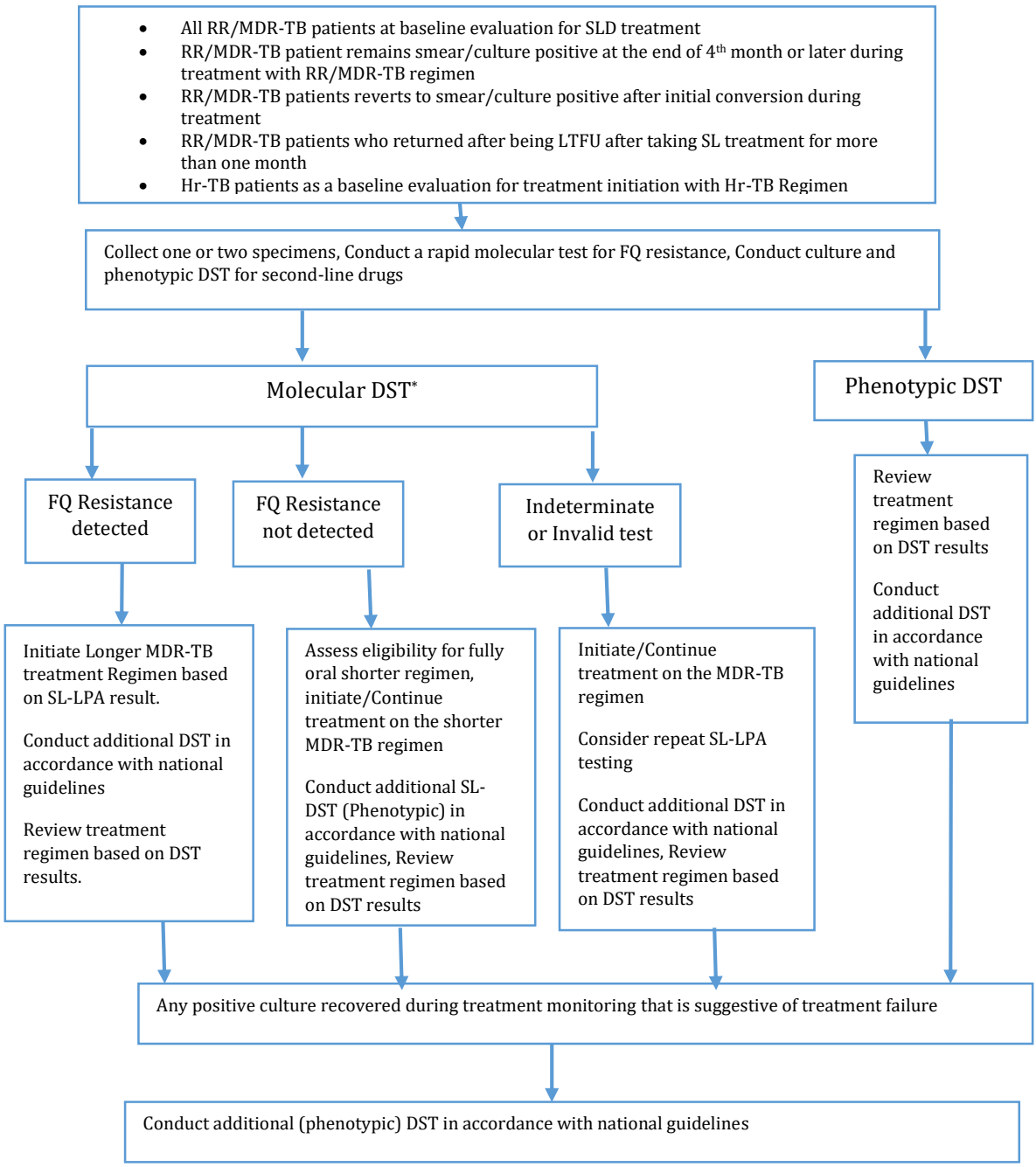
1. PLHIV being evaluated for TB who are positive for signs and symptoms, or who are seriously ill regardless of TB symptoms as an **outpatient**:
    a. Conduct LF-LAM and mWRDs. Initiate anti-TB treatment with FLDs for LF-LAM positive results. Adjust regimen if mWRDs results show resistance.
    b. Negative LF-LAM result will not rule out TB. Evaluate the results of the mWRD test, and follow Figure 2 for result interpretation.
    c. Treat all patients with a molecular WRD test result of "MTB detected" for TB (see the Algorithm indicated in Figure 2), regardless of LF-LAM result.
    d. TB is not ruled out if both the LF-LAM and mWRD test results are negative (or if no mWRD test is performed). Re-evaluate the patient and conduct additional testing. Conduct additional clinical evaluations for TB such as initiating treatment for bacterial infections using broad-spectrum antibiotics. Consider treatment for Pneumocystis pneumonia. Evaluate clinical response after 3–5 days of treatment and follow similar guidance as indicated for inpatient settings.
2. PLHIV being evaluated for TB as an **outpatient** who do not have signs or symptoms of TB, or who are not seriously ill, determine their CD4 count and whether the patient has AHD.
    a. If the CD4 is <100 cells/mm3 , or the patient presents with a WHO stage 3 or 4 event, collect a urine specimen and perform an LF-LAM assay.
        i. If the LF-LAM test is positive, initiate TB treatment immediately. Conduct additional studies to assess drug resistance using mWRDs.
        ii. If the LF-LAM test is negative, apply an AHD package of care.
    b. If CD4 is 100–200 cells/mm3 or Clinical stages 1&2, **DO NOT** perform an LF-LAM assay; apply an AHD package of care.
    c. If the CD4 is >200 cells/mm3 or unknown or Clinical stages 1&2, DO NOT perform an LF-LAM assay; clinically manage the patient.

Treatment follow up of Patients diagnosed using Urine LF-LAM test algorithm

- **Urine LAM test Negative and mWRDs test Negative**: treatment decision can still be made based on other tests e.g. imaging, histopathologic test, etc. If the clinician decides to initiate treatment in such instances, treatment follow up can be made clinically and successful treatment will be documented as 'Treatment Completed'
- **Urine LAM test Positive but mWRDs test Negative**: For both pulmonary and EPTB, monitor patients clinically and report successful treatment outcome as 'Treatment Completed'
- **Urine LAM test Negative but mWRDs test Positive from sputum sample**: Treatment follow up will be by sputum smear test and treatment outcome will be determined in the same way as other bacteriologically confirmed pulmonary TB patients.

If patient diagnosed using the Urine LF-LAM test algorithm and solely based on positive Urine LAM test show worsening of TB symptoms while on TB treatment the patient should be investigated for superimposed infections/illnesses and anti TB drug resistance. In such instances, genotypic DST should be done for identifying Rifampicin resistance. Patient's TB case classification and anti-TB regimen should be modified in case the mWRD test result turns out to be positive and Drug resistance TB is detected.

Figure 5: National Algorithm for DST for SLDs among RR/MDR-TB Patients



**Whenever available/accessible, low complexity automated NAATs such as Xpert MTB-XDR test is preferred for rapid DST of FQs, INH, Ethionamide and Secondline injectable agents.*

The DST Algorithm for SLDs is for further evaluation of patients with RR/MDR-TB or Hr-TB. DST is important for appropriate regimen selection especially for medicines for which mWRDs are available (e.g. RIF, INH and FQs). In addition, there is a need to scale up laboratory DST capacity for medicines for which there are accurate and reproducible phenotypic methods, including BDQ, LZD, clofazimine (CLF) and DLM. As in any potentially life-saving situation, treatment for DR-TB should not be withheld from a patient because of a lack of complete DST results.

1. Patients should be promptly initiated on the DR-TB regimen in accordance with national guidelines.
2. If molecular and phenotypic testing are performed in the same laboratory, one specimen may be sufficient. If testing is performed in two laboratories, two specimens should be collected, and the molecular and phenotypic testing conducted in parallel.
3. It is recommended to get the rapid DST results for FQs before the start of treatment, although this testing should not delay the start of treatment. A new test, the low complexity automated NAAT (Xpert MTB-XDR test), is recommended and is an alternative to SL-LPA as it provides results in under 2 hours, requires minimal hands-on time, can be used at the peripheral level and provides results simultaneously for FQ, INH, Eto and AMK. This test requires a 10-colour GeneXpert instrument unlike the current Xpert MTB/RIF and Xpert Ultra test that use the 6-colour GeneXpert instruments. The use of low complexity automated NAAT to detect FQ resistance does not eliminate the need for conventional culture-based phenotypic DST, which will be necessary for determining resistance to other anti-TB agents and monitoring the emergence of additional drug resistance.
4. Currently, SL-LPA is available and in use for detecting FQ resistance. Diagnostic accuracy of SL-LPA is similar when performed directly on sputum or from cultured isolates. Hence, the national TBL Control program recommends SL-LPA to be used as a direct test irrespective of smear status (on sputum smear-positive or smear-negative specimens). SL-LPA is only recommended for use with sputum specimens or MTBC isolates. The laboratory testing of other specimen types should rely on culture and phenotypic DST.
5. Phenotypic DST should be conducted for each of the drugs included in the treatment regimen for which there are accurate and reproducible methods. Reliable phenotypic DST methods are available for BDQ, FQ, CLF, INH, PZA, DLM and LZD. The initiation of treatment should not be delayed while awaiting the results of the phenotypic DST.
6. For more details regarding RR/MDR-TB regimens, see DR-TB treatment sections below.
7. For FQ-resistant MDR/RR-TB, a specimen should be collected and submitted for phenotypic DST to the WHO Group A and B drugs, if not already being done.
8. If resistance to an individual drug (e.g. BDQ) is suspected and DST for these drugs is not available in the country, laboratories will need to have mechanisms to store the isolate and ship it to a WHO supranational laboratory for DST.

6. DIANGOSIS OF TUBERCULOSIS IN CHILDREN

6.1 Integrated childhood TB care service

TB in young children often present with non-specific clinical presentations making diagnosis challenging. As a result health professionals often overlook TB and repeatedly treat them erroneously as sick child not improving to standard treatment in IMNCI. An important step towards improving the prevention and management of TB in children is the provision of integrated care.

In 2015, NTP in collaboration with child health program launched a national childhood TB roadmap that calls for roll out of an integrated childhood TB care services using IMNCI/ICCM platform and other relevant service delivery points such as MCH/PMTCT clinic, HIV/AIDS service, Nutrition program, etc. [Details provided on the national childhood TB roadmap].

6.2 Characteristic presentations of TB in Children

TB may present in children at any age but most commonly in less than 5 years of age. Pulmonary TB is the commonest form though up to 30-40% may have EPTB. Infants and young children (especially those under 2 years) are at greatest risk of developing severe, disseminated disease and the time between infection and disease can be shorter than in older children. Children under one year of age are more liable to develop disseminated and severe forms of TB, such as Miliary TB or TB meningitis. The presentation and approach to diagnosis of pulmonary TB in older children (> 10 years) and adolescents is similar to that for adults.

After contact with an infectious source case, most immune-competent children present with nonspecific symptoms of a chronic disease. The presentation in infants may be more acute, resembling acute, severe, recurrent or persistent pneumonia. TB should be suspected when there is a poor response to appropriate conventional antibiotics. In such situations, there is often an identifiable source case, usually the mother or primary caregiver. Key risk factors for development of TB in children include:

- Household contact or other close contact with pulmonary TB cases
- Child's age younger than 5 years
- HIV infection; and
- Severe malnutrition.

6.3 Approach to Diagnose TB in Children

The diagnosis of TB can be made with confidence in the majority of children using careful clinical assessment. However, TB in children could easily be over or under diagnosed as obtaining appropriate sputum specimen for pulmonary TB is usually not feasible. Besides the sputum specimen, the national TB control program now recommends the use of alternative specimens such as stool specimen for mWRDs for bacteriological confirmation of TB in children. Bacteriological confirmation should be sought whenever possible by molecular WRDs, microscopy, or culture of respiratory or non-respiratory sample as indicated by the clinical presentation.

A trial of treatment with anti-TB medications is not recommended as a method to diagnose TB in children. The decision to treat a child should be carefully considered and once such a decision is made, the child should be treated empirically with a full course of therapy.

6.3.1 Identification of a child with presumptive TB

Key actions needed for an integrated childhood TB service:

- In the current national primary health care model, health care workers at under-five clinic should routinely screen and be able to diagnose TB at initial or follow-up evaluation of sick child especially among those not improving for standard treatment for pneumonia, malnutrition or malaria.
- Health Extension Workers (HEWs) who are working on ICCM and/or Community level should be able to identify screen and refer exposed children to infectious TB cases during their regular home visit or at time of initial evaluation of a sick child or during follow up.
- Likewise, health care worker at the TB clinic are expected to routinely trace and screen children who are close TB contacts of infectious TB

6.3.2 Evaluation of a child with presumptive TB

Who should be evaluated for TB disease?

- A child with symptoms suggestive of TB, with history of exposure to an infectious pulmonary TB patient;
- A child with pneumonia, pleural effusion, or a cavitary or mass lesion in the lung that does not improve with standard antibiotic therapy;
- Patients with fever of unknown origin, failure to thrive, significant weight loss; severe malnutrition and/or other immunosuppressive conditions (such as measles in the previous 3 months, whooping cough, HIV, being on medication like steroids), or unexplained lymphadenopathy.

Health care workers need to have high index of suspicion of TB in a sick child especially in those who are not improving to standard treatment of common childhood infections or conditions and, for those who have contacts with a source case.

Approaches to diagnose TB in children:

- Careful history (including history of TB contact and symptoms consistent with TB)
- Clinical assessment (including growth assessment)
- Diagnostic tests
    - Bacteriologic confirmatory tests: mWRDs (e.g. Xpert MTB/RIF or Xpert Ultra assay), AFB microscopy, & culture on on expectorated or induced sputum, stool, nasopharyngeal aspirate, gastric aspirate, lymph node aspirate.
    - Chest X-ray
    - HIV testing
    - Histopathology, mainly for suspected EPTB

i. Careful medical history

The most common clinical presentation of PTB is persistent respiratory symptoms and poor weight gain. Note that in at-risk groups such as infants or HIV-infected, PTB can also present as acute pneumonia. The approach to diagnosis of TB in HIV-infected children is similar to that for HIV-uninfected children.

Typical symptoms

- Cough especially if persistent and not improving
- Weight loss or failure to gain weight
- Fever and/or night sweats
- Fatigue, reduced playfulness, less active

Especially if symptoms persist (>2-3 weeks) without improvement following other appropriate therapies (e.g. broad-spectrum antibiotics for cough; anti-malarial treatment for fever; or nutritional rehabilitation for malnutrition)

Atypical clinical presentations of TB in children:

Acute severe pneumonia

- Presents with fast breathing and chest in-drawing
- Occurs especially in infants and HIV-infected children
- Consider PTB if poor response to antibiotic therapy – if HIV infected also consider other HIV-related lung disease e.g. PCP

Wheeze

- Asymmetrical and persistent wheeze can be caused by airway compression due to enlarged Tuberculous hilar lymph nodes
- Consider PTB when wheeze is asymmetrical, persistent, and not responsive to bronchodilator therapy and associated with other typical features of TB.

History of Contact

Young children living in close contact with a source case are at particular risk of acquiring TB infection and further progression to active disease usually within the first year of exposure/infection. A household contact is often found to be the source of infection in children under 5 years of age with TB; infants and young children are especially likely to have contracted TB at home. If no source case is readily identified at home, it is always important to ask for a person in close neighborhood or school with chronic cough. In addition, the identified index case should be assessed for possible case of drug resistant TB (the regimen of TB treatment, adherence and treatment outcome).

NB. If a source is not responding to standardized TB treatment, consider the possibility of drug-resistant TB.

ii. Clinical Assessment (including Growth Assessment)

Physical examination is an important part and parcel of diagnosing childhood TB. There are no specific features on clinical examination that can confirm that the presenting illness is due to PTB. Some clinical signs, although uncommon, are highly suggestive of EPTB.

- Physical signs highly suggestive of extra pulmonary TB:
  - Gibbus, especially of recent onset (resulting from vertebral TB);
  - Non-painful enlarged cervical lymphadenopathy, with or without fistula formation.
- Physical signs requiring investigation to exclude extra pulmonary TB:
  - meningitis not responding to antibiotic treatment, with a sub-acute onset and/ or raised intracranial pressure;
  - pleural effusion;
  - pericardial effusion;
  - distended abdomen with ascites;
  - Non-painful enlarged lymph nodes without fistula formation; Non-painful enlarged joints.

Children who are receiving therapeutic nutritional treatment or nutritional supplementation but are still not gaining weight, or are continuing to lose weight, should be considered as having a chronic disease, such as TB.

iii. Diagnostic tests

All attempts must be made to bacteriologically confirm diagnosis of TB in a child using specimens and laboratory facilities available. Although bacteriological confirmation of TB is not always feasible, it should be sought whenever possible using the available means, such as molecular WRDs including Xpert MTB/RIF assay, or AFB microscopy, or culture. Appropriate clinical specimens include sputum (expectorated or induced), stool, nasopharyngeal or gastric aspirates, and other specimen depending on the site of TB disease. Bacteriological confirmation is especially important for children who have:

- increased risk of acquiring drug-resistant form of TB (such as children who have a history of contact with a confirmed case of DR-TB)
- HIV infection
- complicated or severe cases of TB disease
- uncertainty of the diagnosis
- history of prior TB treatment.

Radiologic examination:

Chest X-ray - remains an important tool for diagnosis of PTB in children for whom bacteriologic confirmation of TB is not possible due to poor sensitivity of the techniques or failure to obtain appropriate biological samples. The abnormalities suggestive of TB include: Enlarged hilar lymph nodes and opacification in the lung tissue, Broad mediastinum due to enlarged mediastinal lymph nodes, miliary mottling in lung tissue, Cavitation (common in older children), effusion in pleural and pericardial spaces. The finding of marked abnormality on CXR in a child with no signs of respiratory distress (no fast breathing or chest in-drawing) is also supportive of TB.

Vertebral X-ray: Spinal X-ray may be normal in early disease, as 50% of the bone mass must be lost for changes to be visible on X-ray. Plain X-ray (PA and Lateral view) of the affected vertebra can show vertebral destruction and narrowed disc space.

Tissue examination: Histological examination to look for caseation and granulomatous inflammation should be performed from specimen collected by FNA or tissue biopsy.

HIV testing: Rapid HIV test should routinely be offered as part of evaluation to all children with presumptive /diagnosed TB

6.3.3 Diagnosis of Tuberculosis in HIV negative Children

In order to reach at diagnosis, efforts should be made to gather evidences from history, physical examination and laboratory and radiologic imaging.

A) Diagnosis of TB based on bacteriologic confirmation

Bacteriologic confirmation of TB is reached if the TB bacilli are detected by m WRDs (e.g. Xpert MTB/RIF), AFB microscopy or culture from any of the biologic specimens listed earlier.

B) Clinical diagnosis of TB based Algorithmic Approach

The diagnosis of TB can be reached safely by using structured algorithm by combining the evidences from clinical features of TB, contact information and supportive evidences from investigations.

C) Clinical diagnosis of TB can also be made if the child has either:

- Radiological picture of Miliary pattern;
- Histopathological findings compatible with TB; or
- Presence of clinical features suggestive of TB, documented contact history and decision to treat TB with help of experienced clinician.

6.4 Diagnosis of Tuberculosis in HIV Positive Children

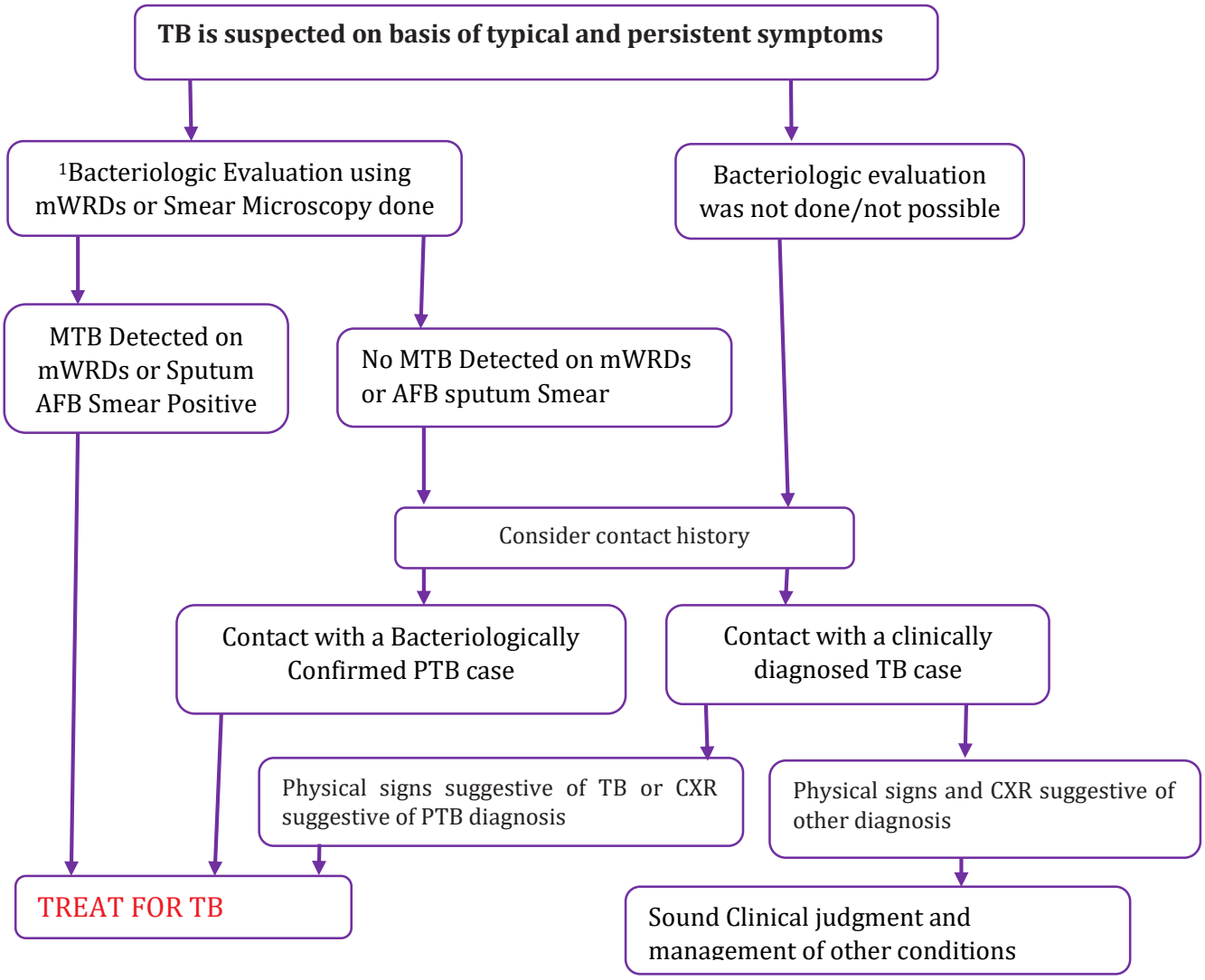
Incidence of tuberculosis in HIV-infected children is much higher compared to HIV negative children. In HIV infected children, tuberculosis is often severe, progressive and likely to involve extra-pulmonary sites. All HIV-exposed and infected children should be screened for TB using symptom based TB screening and appropriate evaluation should be conducted for cases who fulfill the screen positive criteria.

TB Screening in Infants and Children: Children living with HIV who have any one of the following symptoms –poor weight gain , fever, current cough or contact history with a TB case – may have TB and should be evaluated for TB and other conditions. Children living with HIV and who do not have poor weight gain, fever or current cough are unlikely to have active TB.

Algorithmic approach to Diagnose TB among children living with HIV (CLHIV)

The approach to diagnosing TB in children living with HIV is essentially the same as for diagnosis in HIV-negative children. Bacteriologic confirmation of TB is first step for investigation using mWRDs such as Xpert MTB/RIF, or AFB microscopy or culture from biologic specimen. LF-LAM is also recommended as a TB diagnostic aid among CLHIV. Use of the TB diagnostic algorithm is simplified approach recommended to evaluate HIV infected children who fulfill symptom screen criteria to reach to the diagnosis of TB, (see Figure 6 below).

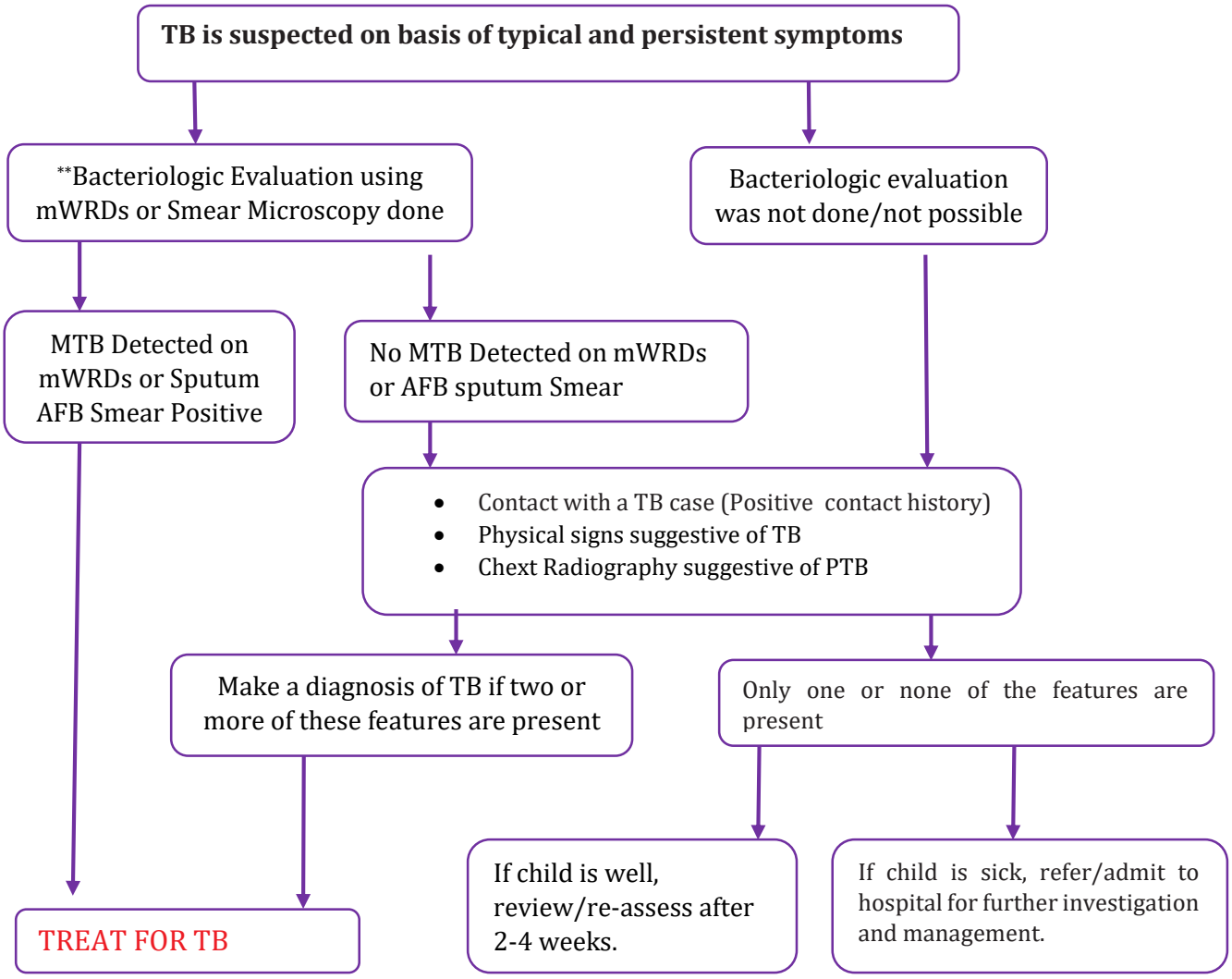
Fig 6 Approach to TB diagnosis in HIV-infected child



[1]For bacteriological evaluation of a child suspected of TB using mWRDs the following biological specimens are recommended: Sputum (expectorated or induced), nasogastric aspirates, stool, nasopharyngeal aspirates, CSF, Lymphnode aspirates

For CLHIV with advanced HIV Disease or seriously ill, urine LF-LAM is also recommended to aid in the diagnosis of TB. Please refer to the LF-LAM algorithms for details.

Fig 7 Approach to TB diagnosis in HIV-negative child



***For bacteriological evaluation of a child suspected of TB using mWRDs the following biological specimens are recommended: Sputum (expectorated or induced), nasogastric aspirates, stool, nasopharyngeal aspirates, CSF, Lymphnode aspirates.*

6.5 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 3 months of treatment
- History of previous TB treatment interruption, treatment failure or retreatment case or recently died from TB

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 first line treatment despite 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 at least for FQs should be performed to guide regimen design.

7. PROGRAMMATIC MANAGEMENT OF LATENT TB INFECTION AND TB PREVENTIVE THERAPY

7.1 Introduction to Latent tuberculosis infection (LTBI)

Latent tuberculosis infection (LTBI) is the persistent immune response to stimulation of *Mycobacterium tuberculosis* (M.TB) antigens without evidence of clinically apparent active Tuberculosis (TB). Estimates show a quarter of the global population is infected with M.tb, where most cases are asymptomatic and non-infectious. Studies show that on average, 5-10% of these latently infected persons have risks of progressing to develop active TB, usually within the first five years of initial infection. However, risks of progression by and large depend on immunological status.

Treatment of LTBI, to prevent progression to active disease, is one of the global key strategies to ending the TB epidemic. Increasingly, eligible targets and treatment options are expanding, with significant implications in the programmatic management of LTBI.

Programmatic Management of TB Preventive Therapy (TPT)

Programmatic management of TPT consists of a set of systematically implemented interventions to identify and treat those with the infection. Three key considerations are addressed in this guideline update:

1. Determination of priority eligible populations in Ethiopia. This is decided based on a national consultation and deliberation on risk, effectiveness, cost, and outcomes in the national context.
2. Clinical (or any other) criteria to identify persons eligible for LTBI treatment, from priority populations, which also considered effectiveness and feasibility of available options in Ethiopia.
3. LTBI treatment options, their effectiveness, cost and practicality in Ethiopia.

This guideline provides recommendations in all these three key aspects of the programmatic management of LTBI. It replaces all previous national recommendations in relation to the management of LTBI, which may also be dubbed as TB preventive therapy (TPT, referring to all the treatment options) or INH preventive therapy (IPT, specifically referring to TPT using isoniazid).

Key updates

- Expansion of eligible groups beyond PLHIV and children under 5 years of age who are household contact of bacteriologically confirmed PTB case.
    - People aged between 5 and 15 who are HIV negative and who have been exposed to an index case with bacteriologically confirmed pulmonary TB
    - Other high risk groups
- New alternatives for TPT regimens have been included
    - 3HP for those aged 2 and over
    - 3HR for those aged under 2
    - WHO 2020 guideline update also recommends other alternative TPT regimen options [one-month daily administration of INH plus Rifapentine (1HP) and Four months daily administered Rifapentine (4R)] however these alternative regimens are not included in this national guidelines till further information is obtained regarding added program benefit, logistic and cost implications.
- Updates to recording and reporting tools to reflect these updated alternative regimens and eligible groups.

7. 2 Consolidated TPT recommendations

Priority populations for TPT in Ethiopia:

A) People living with HIV:

- Adolescents and adults living with HIV who are unlikely to have active TB based on symptom screening should receive TPT as part of a comprehensive package of HIV care. Treatment should be given irrespective of degree of immunosuppression, and also to those on antiretroviral therapy (ART), those who have been previously treated for TB at least 3 years prior, and pregnant women living with HIV.
- Children 12 months or older who are living with HIV and are unlikely to have active TB based on symptom screening should receive TPT as part of comprehensive HIV care package whether they have been in contact with a case of TB or not.
- Infants younger than 12 months who are living with HIV and who have been exposed to an index case of bacteriologically confirmed PTB and are investigated for TB should receive TPT if the investigation shows no active TB.

B) HIV-negative children and adolescents who have been exposed to TB:

- Children aged < 5 years who are household contacts of people with **bacteriologically confirmed pulmonary TB** and who are found not to have active TB on an appropriate clinical and/or radiologic evaluation.
- Children aged ≥ 5 years, adolescents and adults who are household contacts of people with **bacteriologically confirmed pulmonary TB** who are found not to have active TB by an appropriate clinical and/or radiologic evaluation.

C) Other People at Risk:

- Patients initiating anti-TNF therapy, receiving dialysis, preparing for organ or hematologic transplant and patients with silicosis should be systematically tested for LTBI and should receive TPT after excluding active TB disease.
- Systematic LTBI testing and treatment should be considered for prisoners, health workers, immigrants, homeless people and people who use drugs.

Ruling out active TB disease:

- Excluding active TB disease before initiating preventive treatment is one of the critical steps in the LTBI care pathway.
- All priority populations should be screened for TB based on a clinical algorithm and/or chest x-ray to determine eligibility for TPT.
- In general, those risk groups without any of the clinical symptoms and/or abnormality on CXR are unlikely to have active TB and should be provided with TPT.
- Those with symptoms and/or radiologic abnormality on CXR should be evaluated for TB (see updated national TB diagnostic algorithms) and others diseases that cause such symptoms. If subsequent evaluation excludes TB, they should be offered TPT along with any other appropriate treatment.

Testing for LTBI

- LTBI testing using Tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can possibly be used whenever feasible to identify certain individuals at highest risk for developing active TB. However, it is not required in PLHIV or in household contacts aged < 5 years. If it is available, the test can be performed for HIV-negative household contacts aged 5 years and more and in other risk groups, but their unavailability should not be a barrier to treat people who were judged to be at higher risk.
- The use of TST and IGRA, Chest X-Ray, or other TB diagnostic tests is not recommended for diagnosis of LTBI in order to initiate TPT. However chest radiography may be offered to people living with HIV on ART and preventive treatment be given to those with no abnormal radiographic findings provided that it is easily accessible and doesn't incur out-of-pocket cost on the client (e.g. available for free or covered with health insurance, etc.),
- Confirmation of LTBI using either IGRA or TST is desirable if the tests are easily available. In situations where these tests are not accessible or available for free, TB preventive treatment should not be withheld from eligible people if active disease has been excluded on clinical grounds alone.
- Clinical screening using symptom-based criteria can safely be used to identify those eligible for TPT. Therefore, chest radiography may be added as an additional investigation **ONLY** if it does not pose a barrier to the provision of preventive treatment for PLHIV. It should not be a requirement for initiating preventive treatment.

Identification of those eligible for TPT

- Adults and adolescent PLHIV who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should receive TPT.
- Infants <12 months of age living with HIV who do not report any of the symptoms of poor weight gain, fever, or current cough, and who do not have history of contact with an index PTB case are unlikely to have active TB or LTBI and should not receive TPT.
- Children ≥ 12 months of age living with HIV who do not report any of the symptoms of poor weight gain, fever, or current cough, are unlikely to have active TB and should receive TPT regardless of the contact history.
- Infants and children who have been exposed to an index PTB case and who do not report any of the symptoms of cough, fever, not eating well/anorexia, weight loss/failure to thrive, fatigue, reduced playfulness or decreased activity are unlikely to have active TB and should receive TPT.
- Adolescents (< 15 years of age) who have been exposed to an index PTB case and who do not report any of the symptoms of cough, haemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath or fatigue are unlikely to have active TB and should receive TPT.
- Patients initiating anti-TNF therapy, receiving dialysis, preparing for organ or hematologic transplant and patients with silicosis who do not report any of the symptoms of cough, haemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath or fatigue are unlikely to have active TB and should receive TPT.
- Systematic LTBI screening and treatment may be considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and injection drugs users.
- All adults and children living with HIV who have successfully completed treatment for TB disease should receive TPT. The national recommendation for the timing of TPT in such instances should be three years after the completion date of the last course of TB treatment.

TPT Regimens in Ethiopia

- Currently, the recommended TPT regimens in Ethiopia are: **3HP, 3RH and 6H**;
- Three months of weekly isoniazid plus rifapentine (3HP) is the preferred TPT regimen for all PLHIV > two years age who are not receiving protease inhibitor or NVP based regimen, and who do not have any other contraindication for 3HP.
- Six months of isoniazid preventive therapy (**6H**) is the recommended regimen for children, adolescents and adults living with HIV who are receiving ART regimen with protease inhibitor or existence of other contraindication for 3HP.
- Three months of weekly isoniazid plus rifapentine (3HP) is also the preferred regimen for TPT in eligible HIV-negative children and adolescents (2- 14 years of age).
- Three months of daily isoniazid plus rifampicin (**3HR**) is the preferred regimen for eligible HIV-negative children < 2 years of age.
- Six months of isoniazid preventive therapy (IPT) should be offered to HIV-exposed infants taking nevirapine-based prophylaxis who are also exposed to pulmonary TB case
- IPT may be used for all eligible individuals if 3HP or 3HR are not available or contraindicated.

Preventive Treatment for household contacts of MDR-TB index patient

There is a conditional recommendation for preventive therapy in selected high-risk household contacts of patients with MDR-TB to be considered based on individualized risk assessment and a sound clinical justification by WHO. However, due to the capacity limitations and challenges in ruling out active TB among the DR-TB contacts as well as limitations to perform (have access to) quality-assured testing for drug susceptibility (in the presumed source case), the national TB Control program does not recommend the use of chemoprophylaxis for close contacts of RR/MDR-TB patients. Close contacts of DR-TB patients, instead, should receive careful clinical follow-up every 3 month (with CXR screening at least once) for a period of at least two years.

7.3 National TPT Algorithms

The national algorithms to be used for the provision of TPT in Ethiopia are indicated below (see figures 8,).

Figure 8: Algorithm for initiating TPT in adults and adolescents ≥15 years living with HIV.

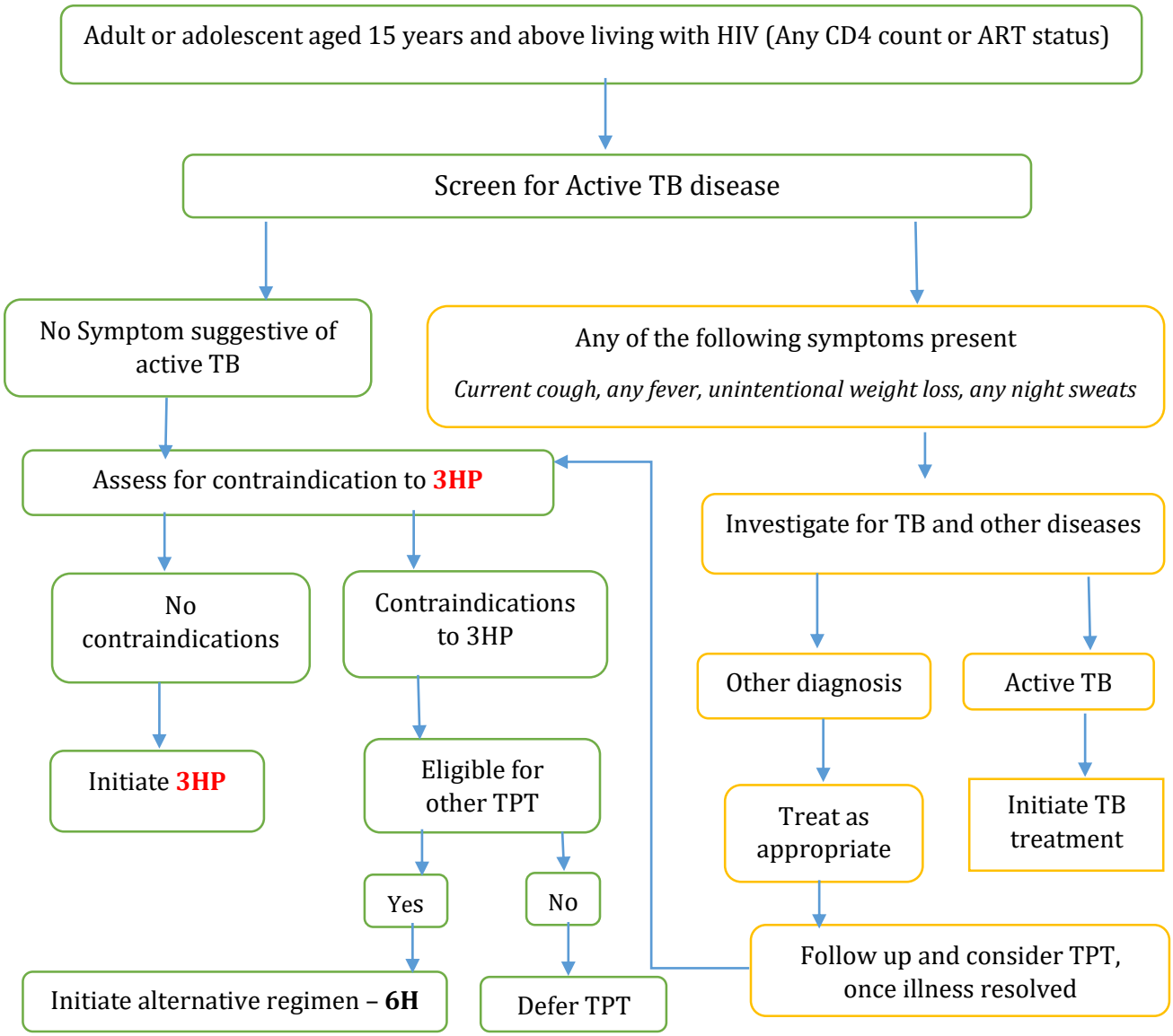


Figure 8. Children < 15 years living with HIV and without household TB exposure

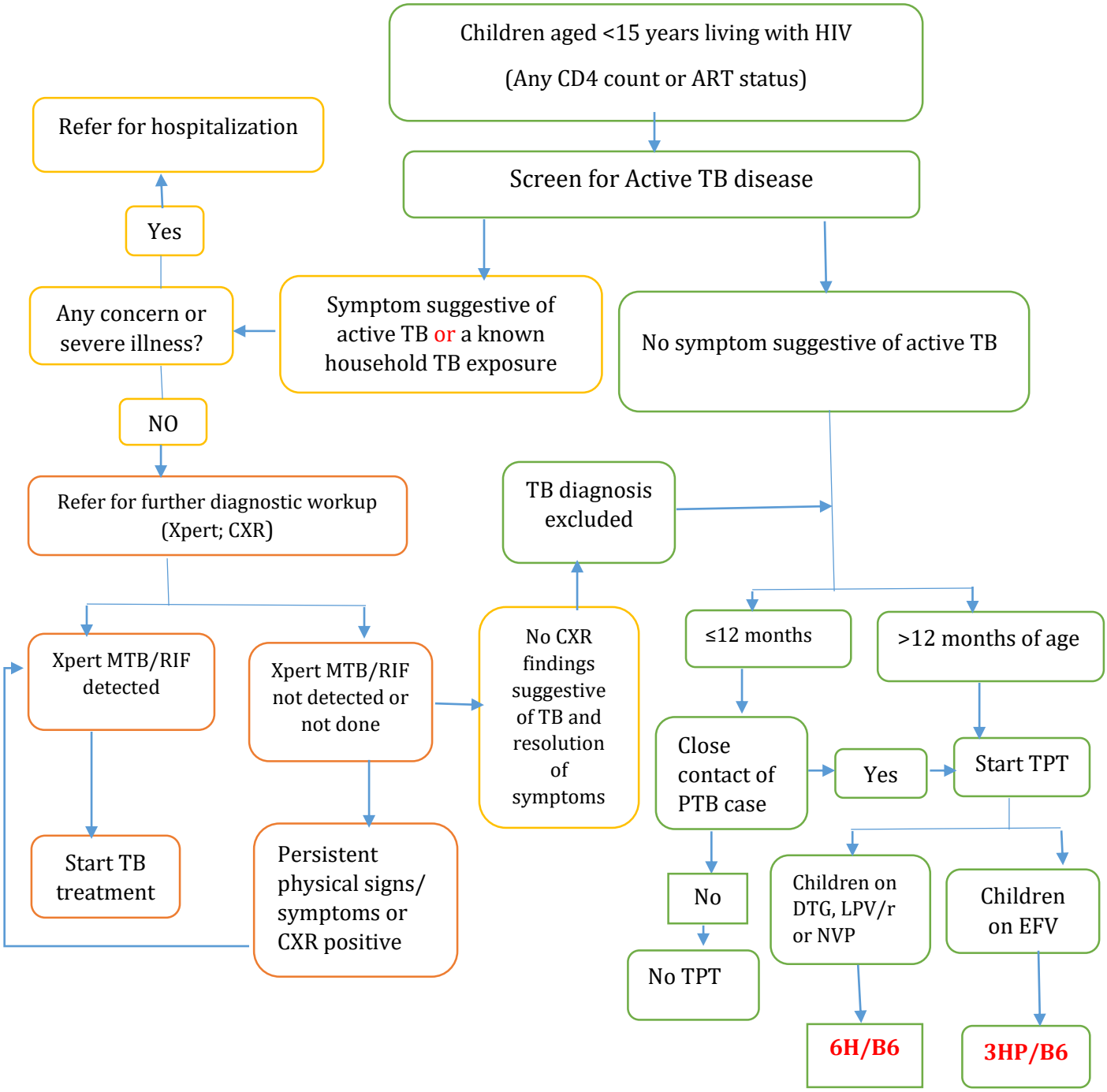
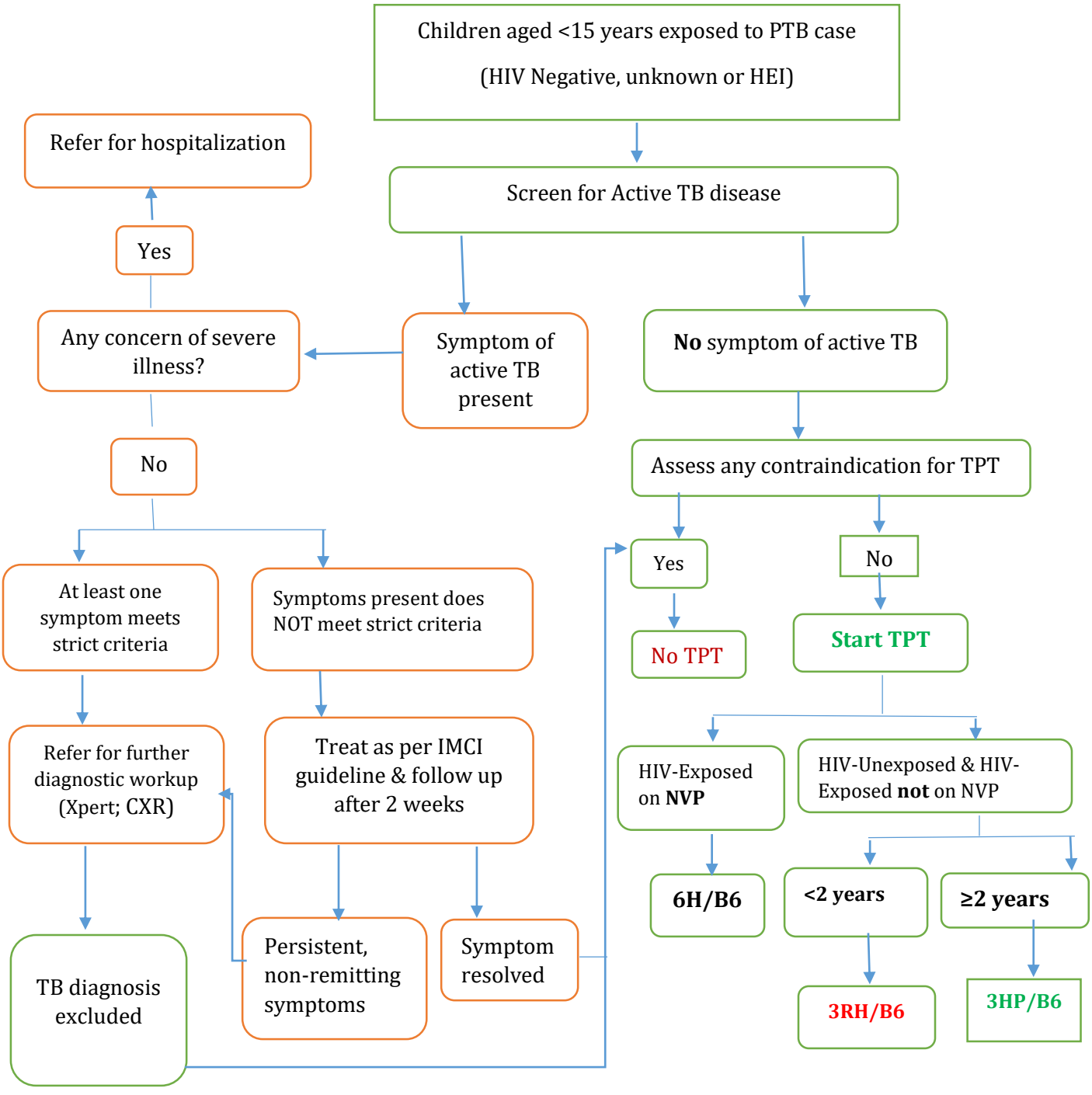


Figure 10: HIV negative and HIV-exposed Children < 15 years of age with household exposure to PTB case



7.4 Regimen and dosage for TB Prevention Treatment

Table 7. Regimen for TB Prevention Treatment.

Population group	Age group and ART regimen	Selection of TPT regimen	
		Preferred regimen	**Alternative regimen**
Persons living with HIV	Adults, adolescents, children and infants of all ages taking a **PI-based ART regimen**	Daily isoniazid preventive treatment (IPT) for 6 months	
	Children and adolescents aged <15 years taking a **DTG-based ART regimen**	Daily isoniazid preventive treatment (IPT) for 6 months	
	Children and adolescents aged between 2-14 years taking a **EFV-based ART regimen**	Weekly isoniazid Plus rifapentine for 3 months (3HP).	- Daily rifampicin Plus isoniazid for 3 months (3RH). - Daily isoniazid preventive treatment (IPT) for 6 months.
	Adolescents and adults living with HIV (≥ 15 years of age) taking **non-PI based ART regimen**	Weekly isoniazid Plus rifapentine for 3 months (3HP).	- Daily isoniazid preventive treatment (IPT) for 6 months.
HIV-negative persons	Infants and children <2 years of age)	Daily rifampicin Plus isoniazid for 3 months (3RH).	- Daily isoniazid preventive treatment (IPT) for 6 months
	Eligible adolescents, children aged between 2-14 years (refer to eligibility criteria specified above) and adults (HH contacts of Bacteriologcally confirmed PTB cases)	Weekly isoniazid Plus rifapentine for 3 months (3HP).	- 3RH will be used as alternative to 3HP - Daily isoniazid preventive treatment (IPT) for 6 months

Notes:

1. *If any of the preferred TPT regimens are unavailable, IPT may be used.*
2. *Safety and pharmacokinetics of 3HP and DTG co-administration was studied only among PLHIV >14 yrs old. So the evidence is not yet known among PLHIV aged < 15 years, which is why 3HP will not be used in this group.*
3. *3HP should be taken with food to prevent GI upset; if patients are unable to swallow tablets (due to age or illness), the tablets can be crushed and added to a small amount of semi-solid food.*

Table 8. Dosage of medicines for treatment of LTBI.

Medicine	Formulation	Weight bands for patients 2-14 years					Comments
		10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg	
Isoniazid	**100 mg**	**3**	**5**	**6**	**7**	**7**	**adult 300 mg tab. can reduce pill burden**
Rifapentine	**150 mg**	**2**	**3**	**4**	**5**	**5**	
Isoniazid+ Rifapentine FDC	**150 mg /150 mg**	**2**	**3**	**4**	**5**	**5**	

Medicine	Formulation	Weight bands for patients >14 years					Comments
		30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg	
Isoniazid	300 mg	3	3	3	3	3	
Rifapentine	150 mg	6	6	6	6	6	
Isoniazid + Rifapentine FDC	300 mg / 300 mg	3	3	3	3	3	

Dosing of 3RH:

Dose per Kg body weight	# of tablets	Maximum dosage
INH Adults: 5mg/Kg Children: 10mg (7-15mg)/Kg **Rifampicin** Adult: 10mg/Kg Children: 15mg (10-20 mg)/Kg	**RH 75/50mg tablet FDC** 4-7 Kg = 1 tab 8-11 Kg = 2 tabs 12-15 Kg = 3 tabs 16-24 Kg = 4 tabs 25 Kg and above = As adults	INH = 300 mg Rifampicin = 600 mg

Dosing of IPT:

Weight Ranges(kg)	Dose Given (mg)	Tablets of INH(of 100mg) per Dose
< 5 Kg	50 mg	½ tab
5.1 – 9.9 Kg	100 mg	1 tab
10 – 13.9 Kg	150 mg	1 ½ tab (or ½ adult tab)
14 – 19.9 Kg	200 mg	2 tabs
20 – 24.9 Kg	250 mg	2 ½ tabs
25 Kg and above	300 mg	1 adult tablet

7.5 Treatment initiation, monitoring and clinical care

Treatment initiation

The selection of treatment options for LTBI should consider the characteristics of the clients who are to receive treatment and acceptability of treatment for higher completion rate. The benefits of all the treatment options outweigh the potential harm. All the treatment options can be self-administered.

Clinicians should follow the TPT algorithms for initiation and selection of regimen for the specific population groups eligible for TPT as indicated above.

Drug-drug interactions with antiretroviral medicines

Caution is necessary in using rifampicin and rifapentine in persons who are receiving antiretroviral treatment (ART), due to drug-drug interactions. Both rifampicin and rifapentine should not be administered in persons who are receiving nevirapine or Protease Inhibitor (PI) based regimen. A three-month weekly rifapentine plus isoniazid can safely be used in patients receiving efavirenz-based antiretroviral regimen without the need for dose adjustment. Studies show that co-administration of rifapentine with raltegravir and dolutegravir based regimen is both safe and well tolerated in HIV infected adults and adolescents aged ≥ 15 years.

Monitoring adverse events

Routine clinical monitoring of persons on TPT is necessary to ensure adherence and continuity of care. Adverse effects, including those considered as medically "minor", may be a barrier for adherence in a person who is otherwise well. TPT related adverse events (AEs), identified during the course of treatment should be properly monitored, managed and reported per national recommendation, using health facilities reporting systems.

Table 9: Likely adverse events with drugs used for TPT

TPT drugs	Known adverse events	Rare adverse events
Isoniazid	Asymptomatic elevation of serum liver enzyme concentrations Hepatitis Peripheral neuropathy (paraesthesia, numbness and limb pain) Skin rash Sleepiness and lethargy	Convulsions Pellagra (Niacin or Vitamin B3 deficiency characterized by dementia, diarrhea and dermatitis) Arthralgia Anaemia Lupoid reactions
Rifampicin	Gastrointestinal reactions (abdominal pain, nausea, vomiting) Hepatitis Generalized cutaneous reactions Thrombocytopenic purpura Discolouration of body fluids	Osteomalacia Pseudomembranous colitis Pseudoadrenal crisis Acute renal failure Shock Haemolytic anaemia Flu-like syndrome
Rifapentine	Gastrointestinal reactions (abdominal pain, nausea, vomiting) Hypersensitivity reactions (flu-like symptoms) Hepatitis Discoloration of body fluids	Hypotension/syncope Decrease in white blood cell and red blood cell count Decreased appetite Hyperbilirubinemia

Management of adverse events

Individuals receiving TPT do not have active disease and therefore their risk for AEs during treatment must be minimized. Moreover, the regimen can be withheld while an AE is assessed, and there is time for the regimen to be recommenced and completed if safe to do so. Overall, 3HP is a safe and effective treatment for latent TB infection. Clinically significant drug reactions are rarely experienced by patients taking 3HP, and even less commonly require discontinuation of treatment. Severe reactions are particularly rare. Nonetheless, healthcare workers should be familiar with the important drug reactions so that they can recognize rare occurrences and manage them appropriately.

Therefore, *if an AE occurs while a patient is taking TPT, they should be advised not to take any further doses and contact the ART providers and TB focal persons of the health facilities as appropriate.*

Drug reactions	• The most common drug reactions with 3HP are Flu-like reactions (more common than for IPT). Liver toxicity and peripheral neuropathy are less common than for IPT. • Drug reactions are usually mild and self-limiting, but occasionally they can be severe. • Children usually tolerate 3HP very well and have much lower rates of drug reactions.
Baseline assessment	• Active TB must be ruled out before commencing TPT regimens. • 3HP is currently not recommended in Pregnancy and children with age <2 years. • Information on baseline liver function is important in the following: o PLHIV (done as part of ART assessment) o Age >35 years o Patuient having daily alcohol consumption o Patient with Liver disorders including viral hepatitis o Pregnant mothers or immediate Postpartum period (≤3 months after delivery) o Patients with Concomitant use of other hepatotoxic substances • Individuals at higher risk of peripheral neuropathy should be offered vitamin B6 (pyridoxine) supplementation with 3HP; if B6 is not available this should not delay starting a course of TPT including 3HP.
Counselling for AEs	• Red/orange discoloration of urine and other body fluids while taking rifamycin based regimens (3RH, 3HP) is normal and completely harmless. • If patients experience any symptoms concerning for an AE: o Do not take any further doses of 3HP o Contact a healthcare provider for advice • Only continue taking 3HP if advised to do so by a healthcare provider Individuals should be alert to the following symptoms: o Weakness, fatigue, loss of appetite, persistent nausea (early symptoms of hepatotoxicity) o Flu-like, or other acute symptoms appearing shortly after taking a dose of 3HP o Symptoms of active TB

Reporting of adverse events

Adverse events associated with the TPT drugs should be reported using either the standardized adverse event reporting format (yellow form) or electronically on e-reporting of ADR available on the apps or website of EFDA (www.fmhaca.gov.et) by health care providers and public health programs. Please refer to the details under pharmacovigillance section of this guidelines.

General Reporting approach and Timeline for aDSM in TPT

All Serious Adverse Events (SAEs) that occure in a patient taking TPT regimens should be reported to EFDA within 24 hours of awareness. Pregnancy detected while on TPT regimen is also an immediately reportable event.

The following conditions are considered as **Adverse Events of Interest (AEIs)** for a client on TPT regimen and should be recorded on the Adverse events line listing form and reported using the yellow form/online systems on monthly basis.

Adverse Events of Interest (AEIs) in TPT:

- Severe hypersensitivity or flu like reactions
- cutaneous reaction
- Hepatitis
- Peripheral neuropathy
- Elevated liver enzymes (AST ≥3x UNL)

Other Adverse events leading to medication change or otherwise considered medically significant are also reported using the yellow form/online reporting system at least monthly.

Adherence support and monitoring

Adherence to the TPT course and treatment completion are important determinants of clinical benefit, both at individual and population levels**.** Irregular or inadequate treatment reduces the protective efficacy of TPT regimen. It is known that the efficacy of TPT is greatest if at least 80% of the doses are taken within the duration of the regimen. The total number of doses taken is also a key determinant of the extent of TB prevention*.*

Completion of course of preventive treatment - 80% of recommended dose consumed within 120% of planned TPT duration, or 90% of recommended dose consumed within 133% of planned TPT duration*.*

The national TB Control program recommends that eligible patients to take all the recommended total doses with the specified period of time for each of the TPT regimens. The following table guides the TPT completion criteria in Ethiopia.

Table 10: Preventive TB treatment completion

Regimen	Total duration (months)	Expected number of doses (100%)	Extended time for treatment Completion (treatment duration +33% additional time)	Remark on completion criteria for TPT Regimens in Ethiopia
3HP	3	12	120 days (4 months)	Completion of the 12 doses within 4 months period
3RH	3	84	120 days(4 months)	Completion of the 84 doses within 4 months period
6H	6	168	240 days (8 months)	Completion of the 168 doses within 8 months period.

Adherence support should be part of comprehensive care provided to patients on TPT during scheduled facility visits and/or at home by adherence case managers, HEWs or family supporters. They should have monthly scheduled follow up that is coordinated with other services, such as HIV care, child and maternal health services, as necessary.

Individuals on TB preventive treatment should be monitored routinely at monthly encounters with healthcare providers, who should explain the disease process and the rationale of the treatment and emphasize the importance of completing it.

At each follow-up visit, the healthcare provider should:

- Educate clients and their families about the benefit of TPT, potential side effects, and importance of returning back to a health facility for new symptom/sign or any concern.
- Evaluate and counsel clients on importance of treatment adherence and completion. Case managers, adherence supporters, and HIV care and child health service providers should support treatment adherence and monitoring, as part of comprehensive HIV care and child health services.
- Evaluate and routinely monitor drug side effects, including hepatitis, peripheral neuropathy or rash. Stop TPT if serious adverse effect is identified and manage the patient.
- Evaluate for signs and symptoms of active TB, other opportunistic infections (OIs) or diseases.
- Stop TPT, if active TB is diagnosed, which requires immediate start of anti-TB treatment.

Contraindications to TPT

Individuals with any one or more of the following conditions should not receive TPT:

- Symptoms compatible with tuberculosis even if the diagnosis isn't yet confirmed;
- Active hepatitis (chronic or acute);
- Regular and heavy alcohol consumptions;
- Prior allergy or intolerance to medicine(s) in the regimen and
- Symptoms of peripheral neuropathy.

In addition, rifapentine is not currently indicated for children below 2 years, PLHIV receiving PI or NVP based ART regimen, pregnant women and breast feeding mothers.

Patient management after treatment interruption

TPT is said to be completed when a person took the full course of treatment within the specified period. If a patient has interrupted TPT without medical personnel advice, the client should be traced by health extension workers (HEW) or through the index person or other family member who is already enrolled in care, and treatment must be resumed. It is important to identify barriers and support treatment adherence. However, concern of adherence should not be a barrier to the use of TPT.

The detailed guidance on recommended actions in the management of TPT regimen interruptions is provided in the following table.

Table 11: Management of interruptions in TB preventive treatment

TPT regimen	Duration of treatment interruption	Recommended Actions
3HR, 6H	Less than 2 weeks	• Resume preventive treatment immediately upon return and add the number of days of missed doses to the total treatment duration. • Do not change the scheduled date of the next follow-up visit but the last follow-up visit will be postponed by the number of extra-days to compensate for missed doses (e.g. If a child on 3HR missed 3 days of treatment, continue preventive treatment for a total duration of 3 months + 3 days from the date of start).
	More than 2 weeks	• If treatment interruption occurred after more than 80% of doses expected in the regimen were taken, no action is required. Continue and complete the remaining treatment as per original plan. • If less than 80% of doses expected in the regimen were taken, and the treatment course can still be completed within the expected time for completion, i.e. treatment duration + 33% additional time, no action is required. Continue and complete the remaining treatment as per original plan. • If less than 80% of doses expected in the regimen were taken, and the treatment course cannot be completed within the expected time for completion, consider restarting the full TPT course.
3HP	Weekly schedule of one dose Missed	• If the missed dose is remembered within the next 2 days, the person can take the dose immediately. Continue the schedule as originally planned (i.e. continue to take remaining doses following the same schedule). • If the missed dose is remembered more than 2 days later, the person can take the missed dose immediately and change the schedule for weekly intake to the day the missed dose was taken until treatment completion. This will avoid two weekly doses being taken less than 4 days apart.
	More than 1 weekly doses of 3HP missed	• If 1-3 weekly doses are missed, treatment is continued until all 12 doses are taken, thus prolonging the treatment duration to a maximum of 16 weeks. • If, however, 4 or more weekly doses are missed, consider restarting the full TPT course. • If adherence to a weekly routine is not possible, consider discontinuing 3HP and offering an alternative (daily) regimen.

7.6 Provision of TPT for special populations

TPT among pregnant and postpartum women

Pregnant women living with HIV are at higher risk for TB during pregnancy and postpartum, which can have severe consequences for both the mother and the infant. Pregnancy should not disqualify women living with HIV or HIV-negative pregnant women who are eligible for receiving TPT since isoniazid and rifampicin, the medicines commonly used in preventive treatment, are considered safe for use in pregnancy (classified as Pregnancy Category C by U.S. Food and Drug Administration). Therefore, TPT should be started during the antenatal and postnatal periods along with due care. Routine LFT is not indicated when TPT is given during pregnancy unless there are other hazards. Vitamin B6 supplementation should be given routinely to all pregnant and breastfeeding women on TPT. Rifampicin is generally considered safe for use during pregnancy, and no dose adjustment is needed although no safety or efficacy data are available specifically for pregnant and postpartum women. There are limited data on the efficacy and safety of rifapentine in pregnancy and therefore 1HP and 3HP should not be used in pregnancy until more safety data are available. Until such data become available, IPT may be used for TPT among pregnant and postpartum women with HIV with due supportive care and monitoring.

Preventive treatment using isoniazid and or rifampicin can be safely given to breastfeeding women. Supplemental pyridoxine (vitamin B6) should be given to the infant who is taking isoniazid or whose breastfeeding mother is taking isoniazid.

Women receiving oral or hormonal contraceptives

Rifampicin and rifapentine interact with oral and hormonal contraceptive medications with a potential risk of decreased contraceptive efficacy. Women receiving oral contraceptives while on rifampicin or rifapentine should either:

- change the oral contraceptive pill and use an alternative (such as depot medroxyprogesterone acetate (DMPA) every eighth week or higher dose oestrogen (50µ)) in consultation with a clinician; or
- use another form of contraception, a barrier contraceptive or intrauterine device.

In women having hormonal contraceptive implants, the interval for replacing the implants may need to be shortened from 12 weeks to eight weeks (ACTG study A5338).

Renal failure

Isoniazid and rifampicin/rifapentine are eliminated by biliary excretion. These drugs, therefore, can be given in standard dosages to patients with renal failure. Patients with severe renal failure should receive isoniazid with pyridoxine (vitamin B6) to prevent peripheral neuropathy.

TB preventive treatment in New born

Once a pregnant woman with TB has been on treatment for TB for several weeks before delivery, it is less likely that the baby will become infected. The risk is highest if a mother is diagnosed at the time of delivery or shortly thereafter. If a pregnant woman is found to have pulmonary TB shortly before delivery, then the baby, and if possible, the placenta, should be investigated for evidence of congenital TB infection. If the result is positive, the new born should be treated accordingly. If

asymptomatic, the new born should receive TB preventive treatment followed by BCG immunization. Breastfeeding can be safely continued during this period.

Management of babies born to mothers with TB disease:

- Assess the newborn. If the newborn is not well, refer to a specialist/paediatrician. It is important to ensure that the mother receives effective TB treatment so that she is no longer infectious. Also, ensure that infection control measures are in place in the nursery, especially if the baby is in an inpatient facility for care when preterm or small at birth.
- If the newborn is well (absence of any signs or symptoms presumptive of TB), provide TPT and delay bacille Calmette-Guérin (BCG) vaccination until TPT is complete. Administer pyridoxine at 5–10 mg/day.
- If the infant is HIV-exposed (mother is HIV infected) and on nevirapine, IPT should be started. TPT with RH and HP cannot be given along with nevirapine prophylaxis since rifamycins decrease nevirapine levels and may result in increased mother-to-child transmission of HIV.
- At the end of TPT, perform TST or IGRA. If test for TB infection is negative or not available, give BCG (unless the baby is HIV-positive).
- If the mother is taking anti-TB drugs, she can safely continue to breastfeed. Mother and baby should stay together, and the baby may be breastfed while on TPT.
- Infant breastfeeding from a mother on either TB treatment or TPT should receive pyridoxine for the duration of the mother's treatment.

7.7 Program management, monitoring and evaluation of TPT

Preventive therapy for HIV negative under-fifteen children should be administered and monitored for completion in the TB clinic, and additional information on comprehensive registration, monitoring and follow-up of those receiving preventive therapy should be recorded on TB contact investigation and LTBI follow up register. Preventive therapy for PLHIV should be part of a comprehensive care for HIV positive individuals; therefore, patients should be initiated preventive therapy and monitored at ART clinic and relevant information should be documented in the patient follow up card, Pre-ART/ART register, smartcare and performance data will be reported using HMIS reporting formats.

The key indicators for monitoring of TPT include:

- Initiation of TPT among eligible groups (disaggregated by HIV status, contact status, sex, age and regimen type)
- Completion of TPT among eligible groups (disaggregated by HIV status, contact status, sex, age and regimen type)

In addition to monitoring treatment initiation and completion, a number of unfavorable outcomes are proposed that could be used to trigger a review of case management and, in some instances, changes to treatment (see list below).

- **Failed** – development of TB disease any time while on TPT
- **Died** – death for any reason while on TPT
- **Lost to follow-up** – TPT interrupted by person for eight consecutive weeks or more for 6H, four consecutive weeks or more for 3HP and 3HR.
- **TPT discontinuation due to toxicity –** by clinician due to adverse events or drug–drug interactions, with or without restart or switching of regimen
- **Not evaluated** – such as records lost, transfer to another health facility with record of TPT Completion

8. DEFINITION OF TERMS AND PATIENT REGISTRATION

8.1 Case Definitions

The below definitions are based on the level of certainty of the diagnosis, laboratory confirmation, and susceptibly status to standard TB drugs as well as presence of TB symptoms and/or signs suggestive of TB.

i) Case definitions for Drug susceptible TB

Presumptive TB case: Any person who presents with symptoms and/or signs suggestive of TB. 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). Presumptive TB case also includes any person with chest X-ray abnormality suggestive of TB with or without other symptoms/signs suggestive of TB.

Case of TB: refers to a patient in whom TB has been bacteriologically confirmed or clinically diagnosed without bacteriologic confirmation (by clinician decision).

Bacteriologically confirmed TB case: Refers to a patient from whom at least one biological specimen is positive for mmycobacterium tuberculosis by either smear microscopy, Xpert MTB/RIF, culture or other WHO approved bacteriologic detection tests.

Clinically diagnosed TB case: A patient who does not fulfil the criteria for a bacteriologically confirmed case but, has been diagnosed with active TB by a clinician and is decided to be given, a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extra-pulmonary cases diagnosed without confirmation of mycobacterium TB.

NB: Clinically diagnosed cases subsequently found to be bacteriologically confirmed (before or after starting treatment) should be reclassified as bacteriologically confirmed.

ii) Case definitions for Drug resistant TB:

Presumptive DR-TB case: refers to a person who presents with clinical features suggestive of TB or actual diagnosis of active TB and is among either medium or high- risk group for drug resistant TB.

Bacteriologically confirmed DR-TB: refers to those cases with documented laboratory DST (phenotypic or molecular) results showing resistance to at least one antituberculosis medicine.

Clinically diagnosed DR-TB case: refers to a person who is diagnosed to have DR-TB without documented DST result showing resistance to at least one antituberculosis medicine but the clinical panel team decided to empirically treat with SLD regimen.

8.2 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.

8.2.1 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 extrapulmonary TB should be classified as a case of PTB. Miliary TB is classified as PTB because there are lesions in the lungs. A patient with both pulmonary and extrapulmonary 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. Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB.

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.

8.2.2 History of previous treatment:

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

Previously treated: patients who have received anti-TB drugs for one or more months in the past and again diagnosed with Tuberculosis. They are further classified by the outcome of their most recent course of treatment as *Relapse, Treatment after failure, treatment after loss to follow up, other previously treated patients*.

8.2.3 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.
- **Multidrug- or rifampicin-resistant TB (MDR/RR-TB):** is the term used to group MDR-TB and RR-TB cases together as MDR/RR-TB; both MDR-TB and RR-TB cases are eligible for treatment with MDR-TB regimens. MDR/RR-TB usually refers to all patients affected by either MDR-TB or RR-TB.
- **Isoniazid-resistant TB (Hr-TB):** TB caused by Mycobacterium tuberculosis strains resistant to isoniazid and susceptible to rifampicin.
- **Pre-XDR-TB:** TB caused by Mycobacterium tuberculosis strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone.
- **Extensively drug-resistant TB (XDR-TB):** TB caused by Mycobacterium tuberculosis strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone and at least one additional Group A drug (Bedaquiline or Linezolid).

8.2.4 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.

8.2.5 Registration group for DS/DR TB patient

New TB: patients that have never been treated for TB or have taken anti-TB drugs for less than one 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 irrespective of the duration previous TB treatment completion.

Treatment after failure: refers to patients who were declared treatment failure in their most recent course of treatment as per national protocol and is now decided to be treated with full course of TB treatment.

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 in to continue treatment at a given reporting unit after starting treatment in another reporting unit irrespective of the duration of treatment at the initial reporting unit.

8.3 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 per patient per treatment course.

The treatment outcome definitions differ between DS-TB and DR-TB cases. Please refer to the following tables for the specific treatment outcome definitions of DS-TB and DR-TB patients.

Further, inline with the recent changes in the diagnosis and treatment of DR-TB, WHO conducted an online consultation to revise the TB/DR-TB treatment outcome definitions towards end of 2020 and has proposed new treatment outcome definitions following the consultations. The propsed new TB/DR-TB outcome definitions are indicated in ***Box 1*** below. The national TBL control program is considering the adoption of these new definitions for implementation along with the revised DHIS2 TBL indicators and recording tools.

Table 12: Definitions of Treatment Outcome for Drug Susceptible TB

Outcome	Definition
Cured	A pulmonary TB patient with bacteriological confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy and was smear- or culture- negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum or culture results in the last month of treatment were negative, either because tests were not done or because results are unavailable .
Treatment failure	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Died	A TB patient who died (for any reason) before starting TB treatment (after registration) or during the course of TB treatment.
Lost to follow up(LTFU)	A patient whose treatment was interrupted for eight or more consecutive weeks after getting registered at a TB treatment center/reporting unit or who did not start anti-TB treatment for for eight or more consecutive weeks.
Not Evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Moved to DR-TB	TB Patients who were found to have DR-TB(Hr-TB, RR-TB or MDR-TB) before the fifth month of treatment and who were referred to a DR TB unit and started on a full DR-TB treatment regimen (i.e. patient is moved to the second-line treatment register).
Treatment success	A sum of cured and completed treatment.

Note that patients found to have DR-TB (Hr-TB, RR-TB or MDR-TB strain) at any point in time during treatment for drug susceptible TB should be excluded from the main Drug susceptible TB cohort when calculating treatment outcomes and included only in DR-TB cohort analysis. These patient should be assigned as "Moved to DRTB" as an outcome not as a failure case considering this as misclassification as Drug susceptible TB while having resistant strains.

Table 13: Outcome definitions in 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 other group A second line drugs, **or**, Adverse drug reactions.
Died	A patient who died during the course of TB treatment.
Lost to follow up(LTFU)	A patient whose treatment was interrupted for two 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.
Treatment adapted	A RR-/MDR-TB patient registered to second line TB treatment and whose current empirical treatment regimen was ended due to DST results showing resistance to second-line drugs and therefore rendering the current treatment sub-optimal or ineffective prior to end of intensive phase/prior to the last 12 months of treatment for patients on longer regimens.

Notes:

- *[**]For Treatment failed, lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of intensive phase applied by the programme. If no maximum duration is defined, an 8-month cut-off is used. For regimens without a clear distinction between intensive and continuation phases, a cut-off 8 months after the start of treatment is suggested to determine when the criteria for Cured, Treatment completed and Treatment failed start to apply.*
- ***Conversion (to negative):** culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.*
- ***Reversion (to positive)**: culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining Treatment failed, reversion is considered only when it occurs in the continuation phase.*

Box 1: Proposed new definitions for TB/DR-TB Treatment outcomes by WHO

- **Treatment failed**: A patient whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy.
- **Cured**: A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriological response and no evidence of failure.
- **Treatment completed**: A patient who completed treatment as recommended by the national policy, whose outcome does not meet the definition for cure or treatment failure.
- **Died**: A patient who died before starting treatment or during the course of treatment.
- **Lost to follow-up**: A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
- **Not evaluated**: A patient for whom no treatment outcome was assigned.
- **Treatment success**: The sum of cured and treatment completed.

Notes on new outcome definitions:

Reasons for the permanent treatment regimen change include:

- no clinical response and/or no bacteriological response (see below);
- adverse drug reactions; or
- evidence of additional drug resistance to medicines in the regimen.

"Bacteriological response" refers to bacteriological conversion with no reversion.

- "**Bacteriological conversion**" describes a situation in a patient with bacteriologically confirmed TB where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, are negative.
- "**Bacteriological reversion**" describes a situation where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB.

9. TREATMENT OF DRUG SUSCEPTIBLE TB (DS-TB)

9.1 Objectives of TB treatment

The aims of treatment of Tuberculosis are:

- To cure the patient from TB
- To prevent death from TB disease and its late effects
- To prevent relapse of TB
- To prevent the development of acquired drug resistance, and
- To decrease TB transmission

The Anti-TB drugs grouping and rational use of these agents to construct TB regimen considers the relative effectiveness of the TB drugs (i.e. bactericidal activity, sterilizing activity and the ability to prevent drug resistance) and the safety of TB drugs in the treatment of TB, (see table 14).

Table 14: Medicines Recommended for the Treatment of DS-TB

Groups	Drug Name	Comment
Drugs First line TB drugs	Rifampicin(R)	The most bactericidal and potent sterilizing agent
	Isoniazid(H)	Highly bactericidal especially in the first few days
	Pyrazinamide(Z)	Bacteriostatic and only active in acidic environment and bacilli inside macrophages.
	Ethambutol(E)	Bacteriostatic and effective to prevent drug resistance when administered with other potent drugs

9.2 Essential properties of Tuberculosis treatment

In order to achieve the desired aim of treatment, an anti-TB treatment regimen needs to be administered:

- in appropriate combination of drugs
- in the correct dosage
- regularly taken by the patient, and
- For a sufficient period of time.

9.3 Dosing of anti-tuberculosis drugs

The essential anti-TB drugs and their recommended doses are indicated in the following table.

Table 15: The Essential Anti-TB Drugs and Their Recommended Dosages

TB Drug	Recommended Adult dosage		Recommended pediatric Dosage [a]	
	Daily Dose range (mg/kg body weight)	Maximum (mg)	Daily Dose range (mg/kg body weight)	Maximum (mg)
Isoniazid	5(4-6)	300	10 (7-15)	300
Rifampicin	10(8-12)	600	15 (10-20)	600
Pyrazinamide	25(20-30)	-	35 (30-40)	-
Ethambutol	15(15-20)	-	20 (15–25)	-
[a] *Children weighing 25kg and more can be treated using recommendation for adults.*				

9.4 Standardized TB treatment

Standardized TB treatment means that patients with diagnosis of TB in a defined group receive the same treatment regimen. Choosing standardized treatment regimen in TB have multiple benefits including: less complicated for drug supply management and suitable for decentralized implementation, easy to train HCWs and reduces chance of error in regimen construction, and minimizes the need for sophisticated culture and DST laboratories.

To facilitate procurement, distribution and administration of treatment to patients, the daily dosage of First line TB treatment is also standardized based on patients' weight band ranges – for instance 20-29kg, 30–39 kg, 40–54 kg and over 55 kg, and packed as TB patient kits for treatment of adults, see table 16.

All TB patients on treatment need daily pyridoxine (Vitamin B6) 50 mg supplement to prevent neuropathy which is common side effect on patient taking Isoniazid.

Table **16**: First line TB Treatment Adult Dosing Chart Using Patient's Body weight Bands

Patients weight band (Kg)	Treatment regimen and Dose	
	Intensive phase: 2(RHZE) RHZE (150/75/400/275mg), tabs	Continuation Phase:4(RH) RH (150/75mg), tabs
20-29	1 ½	1 ½
30-39	2	2
40-54	3	3
≥55	4	4
Note: all TB patients on treatment need daily Pyridoxine 50mg tablet supplement.		

Likewise, the national program procures first line Pediatric FDC of RHZ 75/50/150 and RH 75/50 as it is the most appropriate formulations recommended for use in the treatment of TB in the pediatric groups weighing below 25kg, see table 17.

All TB pediaric patients on treatment need daily pyridoxine supplement to prevent neuropathy which is common side effect on patient taking Isoniazid.

Table 17: First line TB Treatment Pediatric Dosing Chart Using Body Weight Bands

Child's Weight band	**Treatment regimen and doses**		
	Intensive phase: 2 (RHZ)E		continuation phase: 4(RH)
	RHZ 75/50/150 tabs	E 100mg tabs	RH75/50 tabs
4-7kg	1	1	1
8-11kg	2	2	2
12-15kg	3	3	3
16-24kg	4	4	4
25+kg	Adult dosages recommended		
Note: all pediatric TB patients on treatment need daily Pyridoxine 50mg tablet supplement			

9.5 Standardized Treatment regimen for drug susceptible TB (DS-TB)

New Pulmonary patients presumed or known to have drug-susceptible TB:

Generally, selection of standardized anti-TB treatment regimen should be guided by rapid DST results. Standard first line treatment regimen with 2(RHZE)/4(RH) is recommended for New DS-TB patients. For patients who have developed active TB after known contact with a patient with a documented drug-resistant TB; treatment should be decided based rapid DST result. While awaiting DST result, the patient may be initiated treatment with the DR-TB regimen based on the DST of the presumed source case as they are likely to have a similar drug resistance pattern.

Previously treated pulmonary TB patients presumed or known to have drug-susceptible TB:

In all previously treated TB patients who require re-treatment, specimen for rapid molecular-based drug susceptibility testing for first line TB drugs should be obtained at or before the start of treatment to inform the choice of appropriate treatment regimen.

While awaiting the DST result, the standard first line treatment regimen 2(RHZE)/4(RH) is recommended for previously treated TB patients. Please see section 9.8.1 below for detailed guidance for recommended actions for previously treated patients.

Note that, re-treatment regimen for eight months with addition of streptomycin should no longer be prescribed for patients coming to receive treatment for repeated TB episode.

9.5.1 Phases of chemotherapy and Daily dosing frequency

DS-TB treatment is administered in two phases:

Intensive (initial) phase: aims to render the patient non-infectious by rapidly reducing the bacillary load in the sputum and brings clinical improvement in most patients receiving effective treatment.

Continuation phase: aims to sterilize the remaining semi-dormant bacilli and is important to ensure cure/ completion of treatment and prevent relapse after completion of treatment.

Intensive phase treatment	Continuation phase treatment
Two months of HRZE	Four months of HR

Dosing frequency: daily administration of all doses of the six months (or more for CNS and Osteoarticular TB) TB treatment should be implemented under supervised treatment. Intermittent dosing frequency is not recommended.

Note: One month is four weeks /28 days/ in TB treatment.

9.6 Treatment of Extra-pulmonary TB (EPTB)

Extra-pulmonary tuberculosis (EPTB) is generally treated with the same regimen as pulmonary tuberculosis. The guiding principles for patient registration, regimen designing, monitoring of treatment and outcome definitions are similar to patients with pulmonary TB.

Additional considerations in EPTB Treatment:

- Treat patient with extra-pulmonary TB involving any site for six-month with standardized first-line regimen with the exception of CNS TB(meningitis, tuberculoma) and Osteoarticular TB (including vertebral bones, joint and osteomyelitis)
- CNS TB and Osteoarticular TB treatment require prolongation of the continuation phase for 10 months: 2RHZE/10RH.
- An initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8weeks should be used for patients with **Tuberculosis meningitis and/or pericarditis** to improve outcome and reduce complications. Adults (>14 years) should start treatment with dexamethasone 0.4 mg/kg/24 hours with a tapering course over 6 to 8 weeks. Children (<14 years) should be given prednisolone 4mg/kg/24 hrs (or equivalent dose dexamethasone: 0.6 mg/kg/24 hrs) for 4 weeks, followed by a tapering course over 4 weeks.

9.7 Treatment of Drug susceptible TB in Children

Treatment outcomes in children are generally good provided that effective treatment is initiated promptly.

In Treatment of children for TB:

- Ethambutol is safe in children at a dose of 20 mg/kg (range 15– 25 mg/kg) daily.
- Children receiving treatment must be weighed at least every month
- Children weighing 25 kg and more should be treated with Adult dosage
- Treatment doses should be adjusted as soon as a child changes weight bands

- Monitor nutritional status/response during treatment using growth chart
- Check tablet strengths regularly to avoid toxicity
- Adverse events are less common in children than in adults.
- A child who is not responding to anti-TB treatment should be referred for further assessment and management.

9.8 Pre-treatment Evaluation and preparation for treatment

Before starting TB treatment, it is important to conduct baseline evaluation of the patient. The baseline evaluation shall focus on the following:

- Checking how diagnosis of TB has been made and for confirmatory bacteriologic information
- Determining the site of TB Disease (Pulmonary or Extra pulmonary, multi-system involvement)
- HIV Status including offering HIV tests
- Assessment for risk of drug resistance including testing for at least Rifampicin Resistance
- Assessment for co-morbid conditions like pregnancy, renal or liver disease.
- Classification of the TB type and assignment of patient the registration group
- Identification of appropriate treatment supporter
- Initiation of contact screening and provide adherence counseling for the patient and supporter.

9.8.1 Selecting appropriate treatment regimens for Drug susceptible TB

Guidance on how to select the standardized First line TB treatment regimens in Ethiopia are given in the following table 18.

Table 18: Selecting a TB Treatment Regimen

TB patient type		**Recommended TB Treatment regimen**	**Additional Action(s)**
New	With confirmed Susceptibility to Rifampicin (Known baseline Xpert MTB RIF Test or other mWRD)	2(RHZE)/4RH	
	Baseline Xpert MTB RIF Test not known/not done, but patient is from Low DR-TB Risk Group.	Initiate Treatment with 2(RHZE)/4RH.	Do rapid DST at least for RIF as a baseline or within a week of treatment initiation.
	Baseline Xpert MTB RIF Test not known/not done, patient is a contact of known/ presumed DR-TB case.	Do rapid DST before making decision on the appropriate regimen. If RIF Susceptible, initiate treatment with 2(RHZE)/4RH.	If patient is not clinically stable (too sick to wait for DST result), refer the patient to RR/MDR-TB treatment Center for possible initiation with DR-TB regimen based on the DST results of the source case.
Previously treated	Relapse, Treatment after Loss to follow up, Treatment after failure of New regimen, Other previously treated	Initiate Treatment with 2 (RHZE) / 4(RH) for all with RIF Susceptible DST results.	Do rapid DST (at least for RIF) for all patients in this group prior to initiation of treatment. Wait the DST result for a maximum of one week if patient is clinically stable. Initiate first line anti-TB regimen if

			patient is not clinically stable while awaiting DST result. If DST confirms DR-TB, refer/link patient to DR-TB treatment center. Additional DST for possible INH-Resistant TB (Hr-TB) is required if RIF Susceptible. If DST confirms Hr-TB, initiate Hr-TB regimen as per the guidelines.
	Failure after 2nd course of FLD regimen	Treatment regimen to be based on DST results.	Perform rapid DST/GeneXpert If patient is not clinically stable, refer patient to TIC for possible initiation of RR/MDR-TB treatment regimen by the MDR TB panel team decision while awaiting DST results. Additional DST for possible INH-Resistant TB (Hr-TB) is required if RIF Susceptible. If DST confirms Hr-TB, initiate Hr-TB regimen as per the guidelines.
Transfer in		Continue the same treatment regimen.	Assess the treatment response to decide on the need for DST.

9.8.2 Adherence to treatment

Supervision of the administration of treatment through directly observed treatment (DOT) has been the core strategy by the TB program. Cognizant of the multidimensional barriers that TB patients, in particular the vulnerable and marginalized population, might face, treatment supervision alone is not likely to be sufficient to ensure good TB treatment outcomes. Hence, additional treatment adherence interventions need to be provided.

A package of the other treatment adherence interventions also needs to be offered to patients on TB treatment. The interventions should be selected on the basis of an assessment of the individual patient's needs, provider's resources and conditions for implementation (see the details in Section 13).

9.8.3 Directly Observed Treatment

Directly observed treatment (DOT) means that an observer watches the patient swallowing their tablets, in a way that is sensitive and supportive to the patient's needs. This ensures that a TB patient takes the right anti-tuberculosis drugs, in the right doses, at the right intervals. National TB program recommends supervision of treatment to be made by a trained health worker, Health extension worker or a trained TB treatment supporter.

Supervision of treatment can take place at a hospital, a health center or health post, the patient's workplace, resident institution or home as per the agreement reached during adherence preparation (see the details in Section 13).

9.9 Monitoring treatment responses

Appropriate monitoring of response to TB treatment is important to ensure that all patients are responding to the prescribed treatment and achieve favorable treatment outcome. All TB patients receiving standard first line treatment should be monitored using clinical parameters during treatment. Besides, bacteriologically confirmed pulmonary TB patients need additional AFB microscopy for monitoring response to the treatment.

A. Clinical Monitoring of TB patients:

During scheduled visit, a patient receiving TB treatment should be checked for:

- Persistence or reappearance of clinical feature of TB, including weight monitoring*
- Treatment adherence by reviewing the "treatment supporter card" or UNIT TB register
- Risk for developing acquired drug resistance, and need for DST screening
- Occurrence of Adverse drug reaction, and
- Development of TB complications.

*Weight is a useful indicator of clinical improvement especially in children and should be monitored monthly.

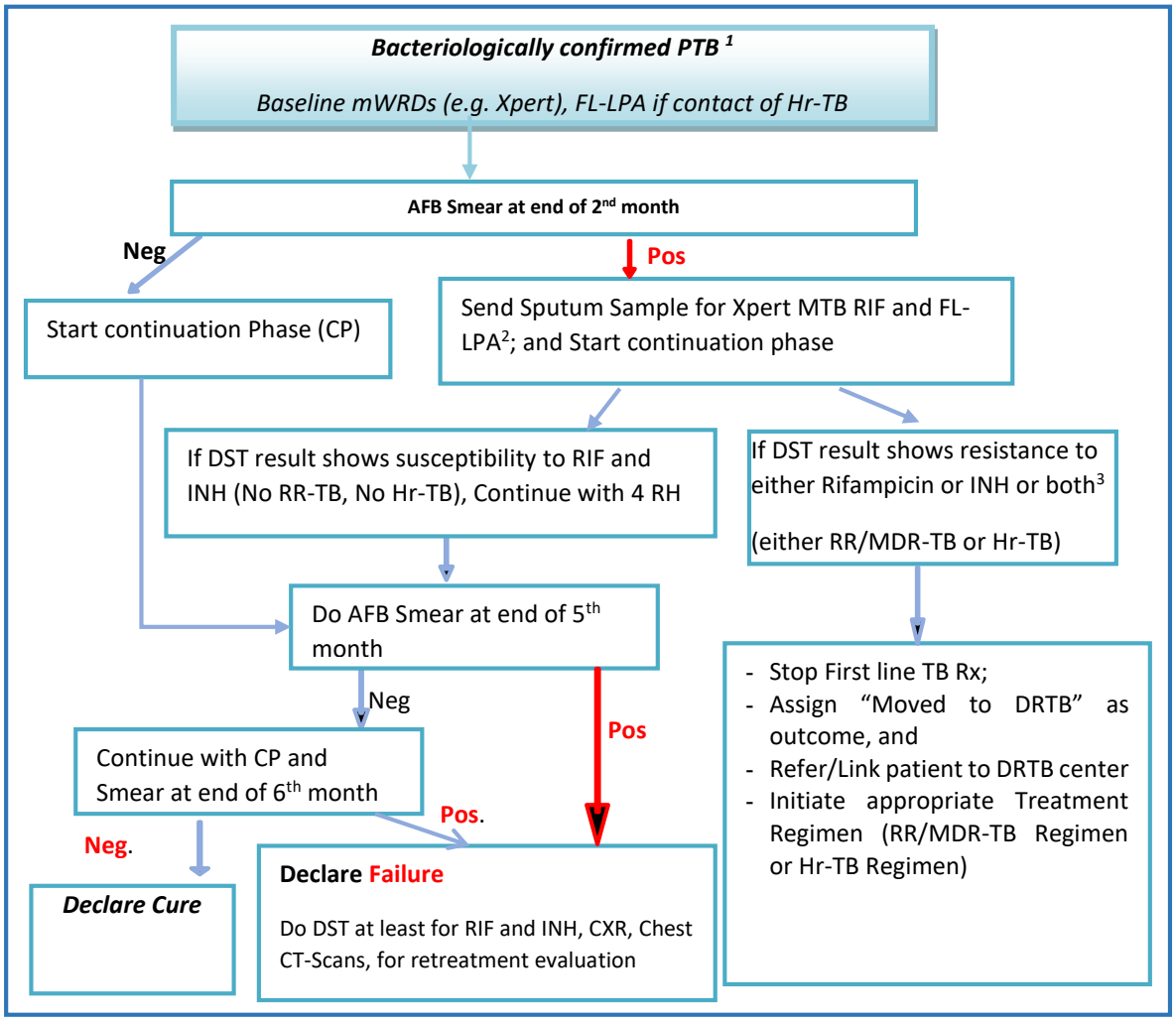
Unsatisfactory response to treatment beyond two months of treatment should alarm the possibility of drug resistance or alternative diagnoses.

B. Bacteriologic monitoring of Bacteriologically confirmed pulmonary TB patients:

Besides the clinical monitoring, bacteriologically confirmed pulmonary TB patients (i.e. those diagnosed by identification of bacilli by smear microscopy, Xpert MTB/RIF assay, other mWRDs or culture) need their sputum specimen to be checked using AFB microscopy. TB Care Provider (TB focal at the HF) should request sputum for AFB microscopy **at the end of 2nd, 5th, and 6th months of therapy**, (See flow chart for follow up of bacteriologically confirmed Pulmonary TB patients in figure 11 below). Clinically diagnosed Plumnary TB patients with poor clinical response or with no improvemet require bacteriologic evaluation and their sputum needs to be checked using AFB microscopy.

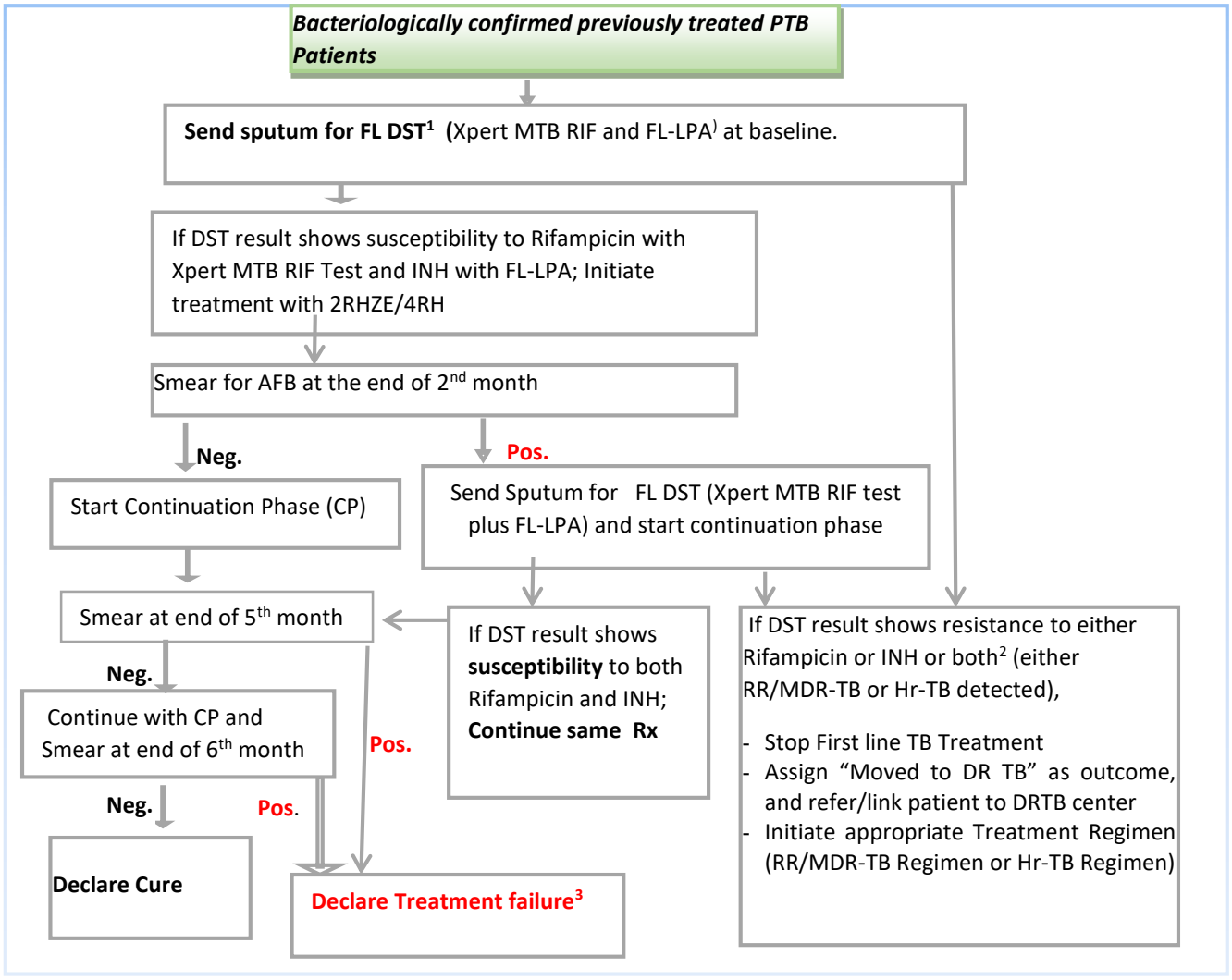
Molecular techniques like Xpert MTB/RIF assay are not recommended for monitoring response to TB treatment.

Figure 11: Sputum AFB Follow-up for Bacteriologically Confirmed PTB Patients



[1]Bacteriolgically confirmed TB patients include those diagnosed by positive result on either mWRDs (e.g. Xpert MTB/RIF Assay), AFB microscopy, or culture. [2]DST may be performed from one sputum sample using Xpert MTB/RIF, LPA or conventional DST based on availability. Information on Rifampicin may be enough to decide on Next Action. [3]if DST result shows resistance to INH but susceptible to Rifampicin; treat with Hr-TB Regimen.

Fig 12. Flow Chart for Sputum AFB Follow-up for bacteriologically confirmed *previously treated* PTB Patients



[1]DST may be performed from one sputum sample using Xpert MTB/RIF, LPA or conventional DST based on availability. Information on rifampicin and INH DST may be enough to decide on Next Action.

[2]If DST result shows resistance to INH but susceptible to Rifampicin; treat with Hr-TB Regimen.

[3]A patient who has failed second course of full TB treatment requires further evaluation and consultations. Such patients require chest imaging, Full DST for FLDs, and further workup to establish the cause for treatment failure. Referral to DR-TB TICs and/or consultations are required in such cases.

C. Management of adverse reaction to First line Anti-TB drugs

Generally first line anti TB drugs have fewer side effects. However, the health workers should regularly monitor for occurrence of side effects to the Anti-TB drugs administered to the patient (Details on ADR management is provided on section 12).

9.10 Management of Treatment Interrupters

If a TB patient misses a scheduled appointment during treatment, the health care worker must promptly initiate tracing using the patient's and his/her treatment supporter. Upon retrieval of absentees:

- Assess the patient (and his/her supporter) to understand the reasons for missing appointment or treatment interruption
- Assess the patient for common adherence barriers in the locality
- Advice on the consequence of treatment interruption and need for optimal adherence
- Assist them to overcome the identified barrier
- Agree on corrective action to improve adherence
- Arrange follow up visit to re-assess the patient, and
- Resume TB treatment using the general guidance indicated below

Subsequent management decision for patients who have interrupted treatment is complex and takes several variables into consideration including immune status, degree of remission of the disease with the previous treatment and drug susceptibility. A simplified decision tree is suggested in the table 19 below.

Table 19: Management of New Pulmonary TB Treatment Interrupters[a]

Length of treatment	Duration of interruption[b]	Sputum result at return	Treatment action and registration
<1 month	2-7 weeks	Not needed	Re-start treatment
	≥8weeks	Smear +Ve Smear -Ve	Re-start Rx, perform DST (Xpert test, FL-LPA and/or conventional DST)
1-2 month	2-7weeks	Smear +Ve	Re-start Rx, perform DST (Xpert test and FL-LPA/or conventional DST)
		Smear -Ve	Continue treatment at the point it was stopped
	≥ 8weeks	Smear +Ve Smear -Ve	Start re-treatment, perform DST (Xpert test and FL-LPA/or conventional DST) and Re-register the patient
> 2 month	2-7 weeks	Smear +Ve	Start re-treatment, perform (Xpert test and FL-LPA/or DST)) and register for TB treatment
		Smear -Ve	Continue treatment at the point it was stopped
	≥ 8weeks	Smear +Ve Smear -Ve	Start re-treatment, perform DST (Xpert test and FL-LPA or conventional DST. Re-register.

[a]*Adapted from "Tuberculosis: practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries; 2014 edition, MSF/PIH"*

[b]*Patients who interrupted treatment for less than 2 weeks must continue treatment at the point it was stopped.*

Note that clinically diagnosed TB cases should be managed in consultation with trained clinician; the missed doses should be supplemented at the end of each phases of treatment.

Table 20: Management of Retreatment Patients Who Interrupted Treatment for 2 Weeks or more[a]

Length of treatment	**Duration of interruption**	**Sputum result at return**	**Treatment action and registration**
<1 month	2-7 weeks	Not needed	Re-start retreatment
	≥ 8weeks	Smear +Ve Smear -Ve	Re-start retreatment, perform DST (Xpert test and FL-LPA/or conventional DST), and re-register the patient.
> 1 month	2-7 weeks	Smear +Ve	Re-Start retreatment, perform (Xpert test and FL-LPA/or conventional DST)
		Smear -Ve	Continue treatment at the point it was stopped, perform (Xpert test and FL-LPA/or conventional DST)
	≥ 8weeks	Smear +Ve Smear -Ve	Start retreatment, perform DST ((Xpert test and FL-LPA/or conventional DST) and re- register the patient.

[a]*Adapted from "Tuberculosis: practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries; 2014 edition, MSF/PIH" (see table 14).*

[b]*Patients who interrupted treatment for less than 2 weeks must continue retreatment at the point it was stopped.*

10. TREATMENT OF DRUG RESISTANT TB

10.1 Commonly used terms and key definitions in drug-resistant TB treatment

Term	Definition
Drug susceptibility testing (DST)	Refers to in vitro testing using either molecular, genotypic techniques to detect resistance-conferring mutations, or phenotypic methods to determine susceptibility to a medicine.
Extensive (or advanced) TB disease	Refers to the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography. Extensive parenchymal damage is defined when more than 1 lobe on both sides (at least 2/3rd of the lung) are involved, or bilateral cavitary lesions present.
Severe extrapulmonary TB	Refers to the presence of miliary TB, TB meningitis, TB pericarditis, disseminated TB, Adrenal TB, bilateral massive pleural effusion, renal TB and TB hypersensitivity reaction. In children aged under 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered as severe.
A shorter MDR-TB regimen	Refers to a course of treatment for MDR/RR-TB lasting less than 12 months, which is largely standardized
Longer MDR-TB regimens	Used for treatment of MDR/RR-TB, last at least 18 months and are designed using a hierarchy of recommended medicines, to include a minimum number of TB medicines considered to be effective based on drug-resistance patterns or patient history.
Empiric treatment	Refers to the initiation of treatment before laboratory confirmation of the drug resistance pattern. Empiric regimens can be either standardized (in which the composition and duration are to a large extent fixed) or individualized (i.e. adapted to the local epidemiological situation or specific needs of a particular patient or patient group).
The likelihood of effectiveness of a medicine	Judged on the basis of one or more of the following: confirmed susceptibility in the individual patient; confirmed susceptibility in the presumed source case; no known resistance to another drug that has cross-resistance to the medicine; rare use of the drug in a geographical area or setting (possibly supported by low drug-resistance levels from surveillance activities); and no previous use of the medicine in a regimen that failed to cure the individual patient.
Off-label use	Refers to the use of a pharmaceutical agent for an indication, age group, dosage, duration or route of administration that differs from what was approved by a national drug regulatory authority.
An adverse event	Any untoward medical occurrence that may present in a TB patient during treatment with a pharmaceutical product, but that does not necessarily have a causal relationship with the treatment. Please refer to (see EFDA ADR reporting tool).
A serious adverse event	An adverse event that leads to: 1. death or 2. life-threatening experience, 3. hospitalization or prolongation of hospitalization, 4. persistent or significant disability, or 5. a congenital anomaly. 6. Otherwise medically significant as defined as adverse events that do not immediately result in one of these outcomes but that require an intervention to prevent such an outcome from happening are included.

10.2 Key Considerations in Drug Resistant TB Treatment

10.2.1 Access to DST

- There is a need for access to reliable, quality assured DST, to inform the use of the recommended DR-TB regimens. In particular, DST for at least rifampicin and fluoroquinolones are required given the importance of the DST results of these agents for selecting the most appropriate initial regimen.
- National TB drug resistance surveillance (DRS) data also provides accurate estimates of the frequency of resistance to at least rifampicin and isoniazid in new patients, and to fluoroquinolones among MDR/RR-TB cases to help guide regimen design.
- Rapid molecular DST is recommended as the initial test to detect drug resistance before the initiation of appropriate therapy for all TB patients, including new patients and patients with a previous history of TB treatment.
- If rifampicin resistance is detected, rapid molecular tests for resistance to at least fluoroquinolones should be performed promptly, to inform the decision on which regimen to use for the treatment.
- Further DST for all TB medicines for which there are now agreed reliable and reproducible methods (e.g. Bdq, Lnz, Clz, Dlm and Z) is also required.
- The inability to undertake DST routinely in all patients despite all possible efforts should not be a barrier to starting patients on a potentially life-saving MDR-TB regimen, but should always be considered in a context of the potential risk of prescribing ineffective treatment and amplifying drug resistance, with a subsequent decrease in the likelihood of a successful treatment outcome.
- If DST for second-line TB medicines is not yet available, the clinician should base decisions on the likelihood of effectiveness of the medicines used, informed by the patient's history of use of second-line TB medicines, the drug-resistance pattern of the contact or index case, and recent representative drug-resistance surveillance data. Therefore, a reliable clinical history of exposure to second-line TB medicines should be considered when designing a treatment regimen, but this should not be the primary source of evidence to guide clinical judgement.
- For paediatric patients, it is not always possible to obtain a DST result, owing to the difficulty of obtaining an adequate specimen or the lack of bacteriological confirmation; hence, the treatment design is usually based on the drug resistance pattern of the index case.
- In the absence of individual DST, relevant population surveillance data are essential to inform the choice and design of MDR-TB treatment regimens.
- If DST is not routinely available for individual patients, storage of M. tuberculosis isolates collected at baseline or during treatment monitoring can be considered for performing whole genome sequencing in case of treatment failure.

10.3 Principles of Dug Resistant Tuberculosis Treatment

- DR-TB diagnosis needs to be confirmed preferably 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 at least for FQs using 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 irrespective of smear status.
- 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 an all oral Bdq containing shorter 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, an all oral Bedaquiline based 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).
- It is essential to 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 adjunct 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 2 weeks period.
- Ambulatory model of care is recommended approach except for those with severe diseases and/or complication warranting in-patient care.

10.4 DR-TB treatment regimen options

DR-TB Treatment Regimen options in Ethiopia

A. RR/MDR-TB Regimens

1. **Shorter, All-Oral, Bdq Containing Regimen: 4–6 Bdq(6 m)-Lfx-Cfz-Z-E-Hh-Eto / 5 Lfx-Cfz-Z-E**
2. **Fully Oral Longer Regimen: 18 Bdq(6 m)-Lfx/Mfx-Lzd-Cfz-Cs**
3. **Individualized Longer Regimens**

B. Regimen for isoniazid-resistant TB (Hr-TB Regimen): **6 (H)RZE-Lfx**

C. BPaL Regimen (only under Operational Research conditions): 6–9 Bdq-Pa-Lzd

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

Summary Recommendation:

- 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.

10.5.1 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.
- It is not advisable to give a regimen for Hr-TB unless isoniazid resistance is confirmed or highly suspected (e.g. TB patient who is the close contact of a documented Hr-TB case).
- 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 2 weeks of TB treatment initiation (regardless of CD4 count). 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.

Table 21: 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

10.5.2 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 Hr-TB regimen. In patients with cavitary disease and with persistent positivity on sputum smear or culture, prolongation of (H)REZ-Lfx beyond 6 months could be considered through consultations.
- Levofloxacin is the preferred fluoroquinolone for Hr-TB regimens, for two reasons: first, exposure to moxifloxacin decreases markedly when it is combined with rifampicin and secondly, levofloxacin appears to cause less QT interval prolongation than moxifloxacin.
- Levofloxacin is included in Hr-TB regimens except when rifampicin resistance cannot be tested for, or 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.
- The dosage of other first-line agents in the Hr-TB regimen is the same as in the standardized first-line 2HREZ/4HR regimen. 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.
- 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.

10.5.3 Considerations for implementation of HR-TB Regimen

- The regimens recommended for treatment of Hr-TB do not have an intensive and a continuation phase. 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.
- Majority of the Hr-TB occurs among new TB cases and testing to detect Hr-TB should focus on new cases. Previous TB treatment is not a strong indicator of risk of Hr-TB.
- 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.

10.5.4 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. 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 the 6(H)REZ-Lfx regimen is not usually required.
- 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, but a DSM is not mandatory.
- 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.

10.6 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.

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

The shorter all-oral bedaquiline containing MDR-TB treatment regimen may be offered to 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:

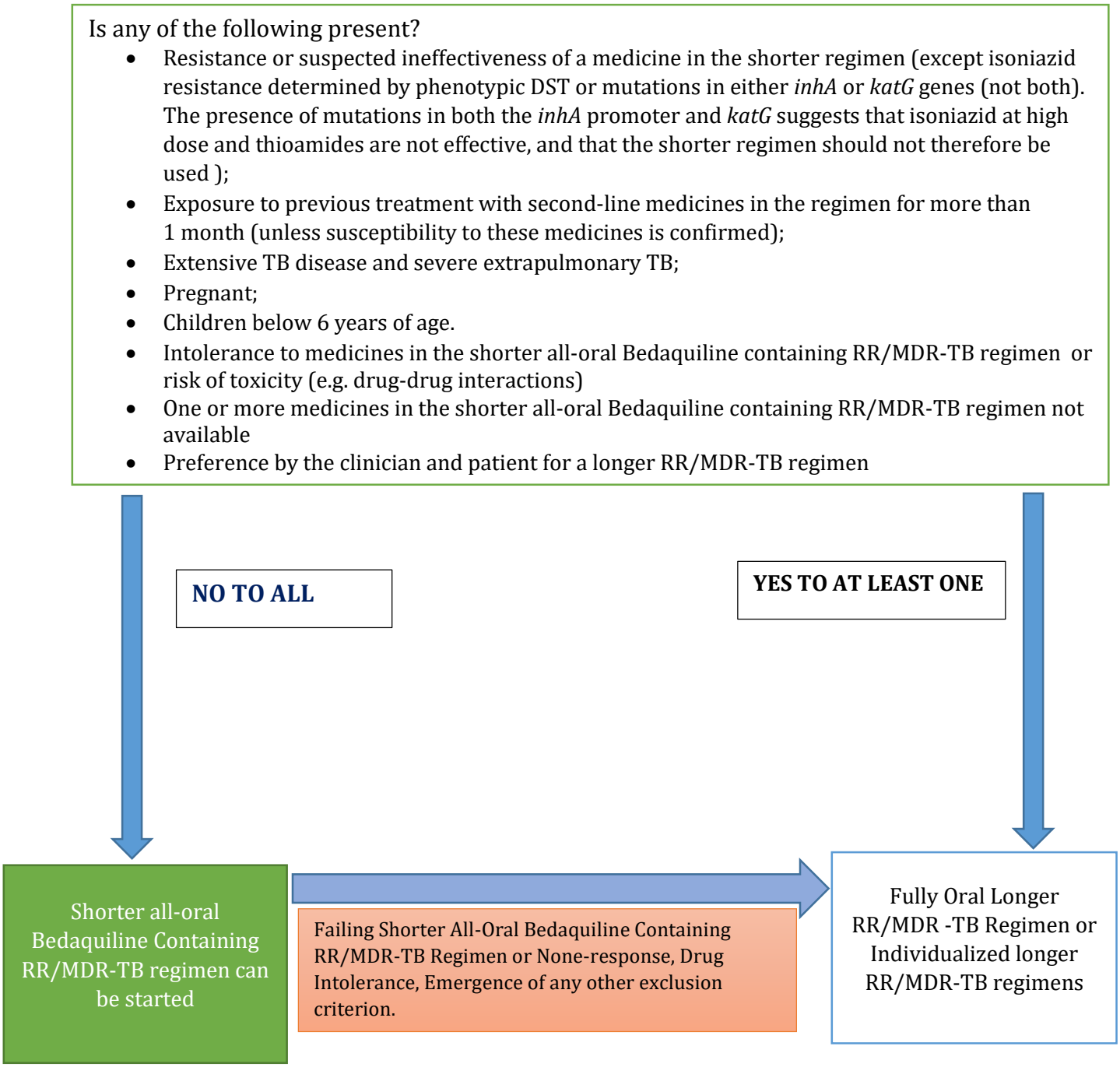
- No resistance or suspected ineffectiveness of a medicine in the shorter regimen (except isoniazid resistance determined by phenotypic DST or mutations in either *inhA* or *katG* genes (not both). The presence of mutations in both the *inhA* promoter and *katG* suggests that isoniazid at high dose and 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 extrapulmonary TB;
- Not pregnant;
- Children 6 years old and above.

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 or individualized longer regimen.

Assessment of extent of TB disease: Extent of TB disease is important to determine the regimen options, in addition to the DST. Please refer to the definitions of extensive TB disease and severe extrapulmonary TB provided under section 10.1.

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.

Figure 13. Eligiblity Criteria for shorter all-oral Bedaquiline Containing RR/MDR-TB regimen



10.6.2 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.
- All medicines should be taken once a day on all days of the week, except for bedaquiline, which should be taken every day for the first 2 weeks, followed by three times a week in the remaining 22 weeks.

The regimen can be 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 and 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. 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.
- 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. 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.

10.6.3 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 provided that other eligibility criteria are met.
- There is 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 bedaquiline exposure, 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 and close monitoring is advised.
- Importantly, ART regimens need to be initiated early. Patients receiving the shorter all-oral bedaquiline containing regimen who also have HIV infection will need prophylactic medication for opportunistic infections, support for TB and antiretroviral medication adherence, and close monitoring of the biomarkers of immune status.

2. Children:

- The shorter all-oral bedaquiline-containing regimen may 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 by WHO, 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:

- Pregnant mothers are not eligible for treatment with an all-oral Bdq containing shorter RR/MDR-TB regimen.
- The regimen contains ethionamide, which is usually contraindicated in pregnancy because animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans.
- Individualized longer regimens need to be designed to avoid known toxicities until better safety profiles are established.

4. Rifampicin-resistant TB without MDR-TB:

- All patients – children over 6 years of age or adults – with rifampicin-resistant TB in whom flouroquinolone resistance is not confirmed may be treated with the shorter all-oral bedaquiline-containing MDR-TB treatment regimen provided the eligibility criteria are met.

5. Patients with extensive disease or Severe extrapulmonary TB disease:

- Extensive TB disease or severe extrapulmonary TB disease is an exclusion criteria for the use of all-oral Bdq containing shorter regimen and preference should be given to the longer regimens.

6. Patients with diabetes mellitus:

- There are no data on the use of the shorter all-oral bedaquilinecontaining 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.

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

Table 22: Dosages for all-oral bedaquiline-containing shorter regimen (Patients older than 14 Years)

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 or Protionamide	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 23: Dosages for all-oral bedaquiline-containing shorter regimen (Patients below 15 Years)

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients below 15 years of age							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 or Protionamide	15–20 mg/kg	125 mg dt (Eto)	1	1	2	3	4	4	(>14 y)	1 gm
			250 mg tab (Pto/Eto)	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 week (e.g. Monday, Wednesday, Friday dosing) for the remaining 22 weeks.

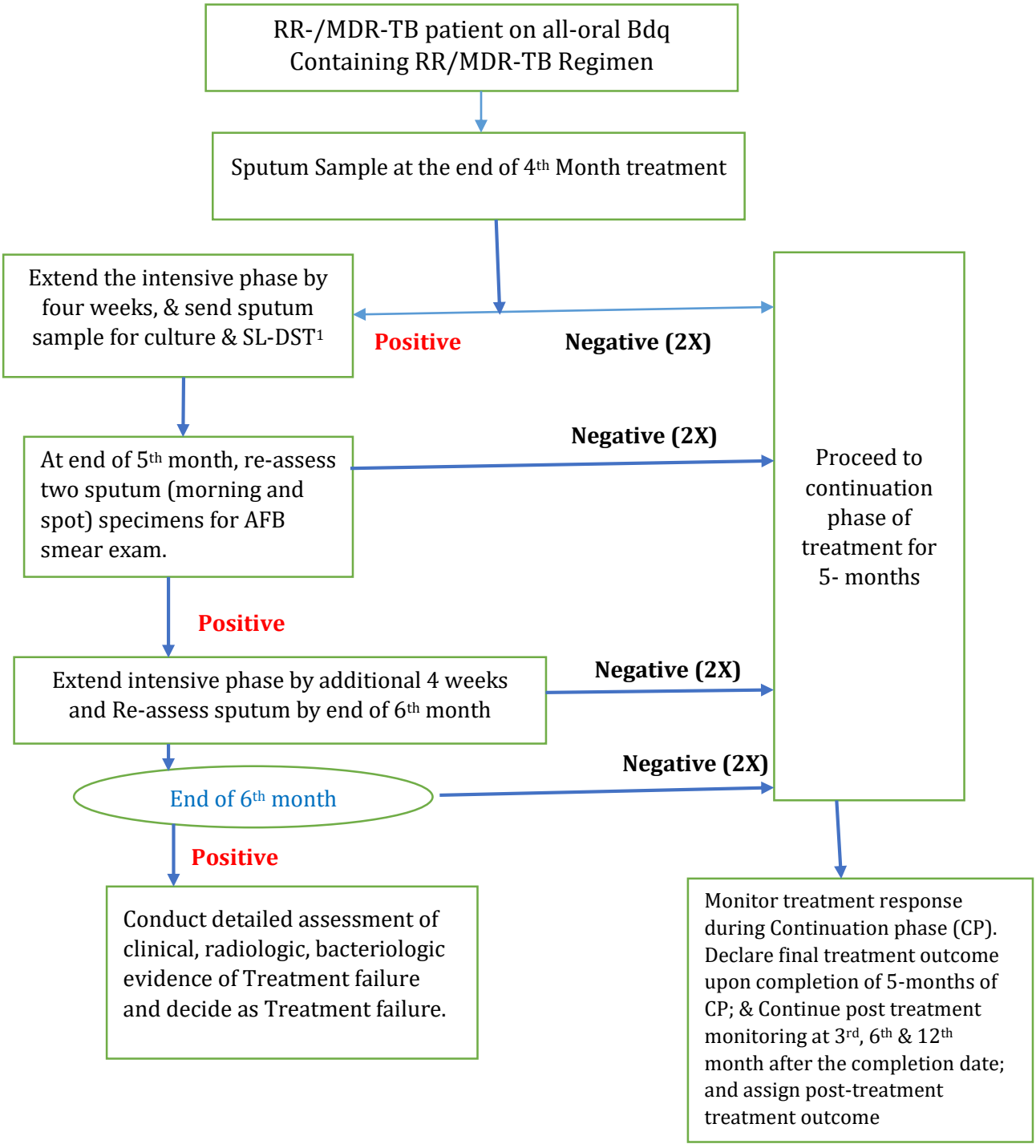
10.6.5 Treatment monitoring for all-oral Bedaquiline containing MDR/RR-TB Regimen

- The shorter all-oral bedaquiline-containing MDR-TB regimen may need to be switched to a longer MDR-TB regimen when:
  - reliable DST results show resistance to key medicines in the shorter all-oral bedaquiline-containing MDR-TB regimen;
  - 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).

10.6.6 Monitoring treatment response and outcome assignment

- Response to treatment is monitored on the basis of monthly sputum smear microscopy, as well as culture, ideally at the same frequency. This is similar to the schedule used in patients on the longer all oral MDR-TB regimen.
- 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 14: Treatment Monitoring Chart for patients on all-oral shorter MDR/RR-TB Regimen



10.6.7 Monitoring safety

- The shorter all-oral bedaquiline-containing regimen is generally well tolerated, but 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 – requires the monitoring for additive cardiotoxicity (using ECG) for these drug combinations than it is for other drug combinations.
- Any adverse events for patients on treatment need to be reported primarily to the national pharmacovigilance center, within the framework of aDSM. A functional aDSM system is a requirement for the use of the shorter all-oral bedaquiline containing MDR/RR-TB regimen. All TICs are required to apply the aDSM principles in patient management as per this guidelines (Please refer to section 12 for details on aDSM).
- 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.

10.6.8 Using modified all-oral shorter MDR-TB regimens under operational research

At present, there is little evidence to support modified all-oral shorter MDR-TB regimens that are designed using the hierarchy of TB medicines (in Table 24). The national TBL Control program in Ethiopia will support the implementation of such pilot studies of modified all-oral shorter MDR-TB regimens only under operational research conditions.

10.7 Longer regimens for MDR/RR-TB

All MDR/RR-TB patients may be treated with longer regimens; however, the longer regimen is preferably given to those MDR/RR-TB patients who are not eligible for shorter all-oral regimens, including those with quinolone resistance.

10.7.1 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 feature the medicines to be used to compose longer MDR-TB regimens. Under programmatic conditions, only these medicines (Groups A–C) have a role in MDR-TB longer treatment regimens. Table 24 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 24. Therefore, Clinicians should be guided by these new recommendations in designing treatment regimen.

Table 24. Medicines recommended for the treatment of RR/MDR-TB[1]

Group	Name of medicine	Abbreviation
Group A: **Include all three medicines**	Levofloxacin Or Moxifloxacin	Lfx Mfx
	Bedaquiline [2,3]	Bdq
	Linezolid [4]	Lzd
Group B: **Add one or both medicines**	Clofazimine	Cfz
	Cycloserine or Terizidone	Cs 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 Meropenem [7]	Ipm Mpm
	Amikacin (or Streptomycin) [8]	Am (or S)
	Ethionamide or Prothionamide [9]	Eto Pto
	Para-aminosalicylic acid [9]	PAS

[1] This table is intended to guide the design of longer MDR-TB regimens (the composition of the recommended shorter MDR-TB regimen is largely standardized). 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.

[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.

10.7.2 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 13 above regarding the patient triaging criteria to initiate either of the regimens.
- 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 can no longer 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. The capacity for DST for new and repurposed second-line drugs needs to be developed as well.

Rifampicin-resistant TB: Any patient with rifampicin-resistant TB – whether a child or an adult – in whom isoniazid resistance is absent or unknown, needs to be treated with a recommended MDR-TB regimen. The regimen could be a shorter all-oral bedaquiline-containing regimen or a longer MDR-TB regimen if the former cannot be used. High-dose isoniazid has also been shown to be an important component in paediatric regimens. Although high-dose isoniazid is not included in Groups A–C, it may still be used in patients with confirmed susceptibility, or in the presence of mutations that do not usually confer complete resistance to isoniazid.

10.7.2 Composition of Longer RR/MDR-TB Regimens

A stepwise approach guides the design of longer MDR-TB regimens. 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 fluoroquinolones 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.

All patients should have a laboratory confirmed diagnosis of MDR/RR-TB before embarking on a regimen using second-line medicines. The diagnosis of resistance additional to MDR-TB may present at baseline, or may be uncovered after MDR-TB treatment has started.

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 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.

The clinicians may consider continuing bedaquiline for longer than 6 months, as no additional safety concerns are documented when bedaquiline was used for longer than 6 months.

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.

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).

Other tests for resistance to agents such as pyrazinamide, and for mutation patterns commonly associated with resistance to isoniazid and the thioamides, may help to inform the composition of the regimen. Currently, there is no validated rapid test for pyrazinamide susceptibility, and phenotypic testing may require several weeks to produce a reliable result; a decision to include or replace pyrazinamide should not delay the start of treatment.

10.7.3. Steps in longer MDR/RR-TB Regimens Design

The step-by-step directions to be applied in designing an effective longer MDR/RR-TB regimen is indicated below (Table 25).

Table 25: 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 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. ▪ 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. ▪ If Eto/Pto have 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. extrapulmonary TB 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.

Individualized longer RR/MDR-TB Regimen design

- 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 (Table 26 below).
- 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:
    1. If 4 Group A and B agents are included and there is confidence in all of them then Group C agents are not needed.
    2. 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.

3. 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.

- Moxifloxacin, a later-generation fluoroquinolone, may still be effective at high dose when the fluoroquinolone MIC is below the clinical breakpoint. If the MIC is elevated, then fluoroquinolones are not used, and additional Group C agents will be needed.

Table 26: Longer MDR/RR-TB Regimen composition under different situations of known resistance/contraindication 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	1 medicine	Not usually needed	18 Bdq$_{(6\ m\ or\ longer)}$-(Lfx or Mfx)-Lzd-(Cfz or 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 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 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 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 or 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

10.7.4 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. Doing so risks reversion even after culture conversion.
- In 2019, new evidence on the safety profile of the prolonged use of bedaquiline became available that supports its safe use beyond 6 months in patients who receive appropriate schedules of baseline and follow-up monitoring. The added benefit of the use of bedaquiline beyond 6 months remains unclear. Treatment should therefore be extended at the clinical discretion of the prescribing doctor under appropriate monitoring. Use of Bdq and Dlm beyond 24 weeks should follow best practices in 'off-label' use.
- 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.
- Both Bdq and Dlm 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. Given the serious consequences that patients with MDR/RR-TB with fluoroquinolone resistance face under such circumstances, clinicians may opt to use bedaquiline and delamanid together or beyond 6 months on a case-by-case basis. Such conditions require consultation with national or regional CRC.

10.7.5 Dosage of medicines used in longer MDR-TB regimen

Dosages of individual medicines are often determined by body weight separately for adults and children. Suggested weight-based dosing schemes are provided in Table 27.

Doses may need to be adjusted because of accompanying medicines or comorbidities. In situations where there is a limited possibility of adjusting the dose because of the drug formulation (e.g. delamanid in children aged 3–5 years), the general principle is to consider inclusion of the medicine if the benefits are expected to outweigh the harms, and to aim for a dose that achieves the therapeutic range. Patients should then be monitored closely for adverse events, which should be managed as quickly and as effectively as possible if they occur.

All TB medicines can be started at the full dose. The emergence of drug reactions may also require the interruption – temporary or permanent – of an agent or changes to its dosage. If tolerance is an issue, cycloserine, ethionamide and PAS can start at a low dosage and then be increased (i.e. ramped up) gradually over a 2-week period.

Most experience with the use of clofazimine in both shorter and longer regimens has been with a *fixed* daily dose throughout treatment; empirical evidence to support starting with a loading dose in MDR-TB regimens is lacking. Clofazimine appears to act primarily as a sterilizing agent, implying that its role is less important in the first part of treatment. A high initial dose may also increase the risk of adverse reactions particularly given its relatively longer half-life, with cardiotoxicity being a particular concern.

Table 27: Dosing of medicines used in longer DR-TB regimens

A. Dosing of medicines used in second-line multidrug-resistant-TB regimens by weight band (patients 15 years or older)

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients older than 14 years					Usual Upper daily dose	Comments
				30-35 Kg	36-45 Kg	46-55 Kg	56-70 Kg	>70 Kg		
A	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		
	Moxifloxacin	Standard Dose	400 mg tab	1	1	1	1	1	400 mg	
		High-dose	400 mg tab	1 or 1.5	1.5	1.5 or 2	2	2	800 mg	
	Bedaquiline		100 mg tab	4 tabs daily for first 2 weeks; then 2 tabs od M/W/F for 22 weeks					400 mg	
	Linezolid		600 mg	(<15 Y)	(<15 Y)	1	1	1	1.2 g	
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	
	Cycloserine or Terizidone	10-15 mg/Kg	250 mg Cap	2	2	3	3	3	1g	
C	Ethambutol	15–25 mg/kg	400 mg tab	2	2	3	3	3		
	Delamanid		50 mg Tab	2 BID	2 BID	2 BID	2 BID	2 BID	200 mg	
	Pyrazinamide	20–30 mg/kg	400 mg tab	3	4	4	4	5		
			500 mg tab	2	3	3	3	4		
	Imipenem-cilastatin		500 mg + 500 mg powder for injection, vial (10 mL)	2 vials (1 g + 1 g) bd						To be used with clavulanic acid.
	Meropenem		1 g powder for injection, vial (20 mL)	1 vial 3 times per day or 2 vials bd						To be used with clavulanic acid.
	Amikacin	15–20 mg/kg	500 mg/2 mL solution for injection, ampoulef	2.5 mL	3 mL	3-4 Ml	4mL	4mL	1 gm	
	Streptomycin	12–18 mg/kg	1 g powder for injection, vial	Calculate according to the dilution used					1 gm	
	Ethionamide or prothionamide	15–20 mg/kg	250 mg tab	2	2	3	3	4	1 gm	Once daily dose advised but can start with 2 divided doses until tolerance improves.
	P-aminosalicylic acid	8–12 g/day in 2–3 divided doses	PAS sodium salt (equivalent to 4 g PAS acid) sachet	1 BID	1 BID	1 BID	1 BID	1 to 1.5 BID	12 gm	
			PAS acid (4 g) sachet	1 BID	1 BID	1 BID	1 BID	1 to 1.5 BID		
Other medicines	Isoniazid	4–6 mg/kg (standard dose)d	300 mg tab	2/3tab	1	1	1	1		100 mg isoniazid tablet can facilitate the administration of certain dosages. Pyridoxine is given with isoniazid in patients at risk (e.g. those with HIV or malnutrition).
		10–15 mg/kg (high dose)d	300 mg tab	1.5	1.5	2	2	2		
	Clavulanic acid		125 mg clavulanic acid as amoxicillin/ clavulanate, 500 mg/ 125 mg tabh	1 BID	1 BID	1 BID	1 BID	1 BID		Only to be used with carbapenems.
	Pretomanid		200 mg tab	1	1	1	1	1	200 mg	Only to be used as part of the BPaL regimen, together with bedaquiline and linezolid.

Table 28: Dosing of medicines used in longer DR-TB regimens (Age below 15 years)

B. Dosing of medicines used in second-line multidrug-resistant TB regimens by weight band (patients under 15 years)a

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients below 15 years of age							Usual Upper daily dose	Comments
				5-6 Kg	7-9 Kg	10 -15 Kg	16–23 Kg	24–30 Kg	31–34 Kg	>34 Kg		
A	Levofloxacin	15–20 mg/kg	100 mg dispersible tab (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	
	Moxifloxacin	10–15 mg/kg	100 mg dt	0.8	1.5	2	3	4	(>14 y)	(>14 y)	400 mg	Use 10 mg/kg in <6 months
			400 mg tab	1 or 1.5	1.5	1.5 or 2	2			2	400 mg	
	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		–	Only in patients aged >5 years (lower dose from 15–29 kg; higher dose from >29 kg).
			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		–	
	Linezolid	15 mg/kg od in <16 kg	20 mg /mL susp	4 mL	6 mL	8 mL	11 mL	14 mL	15 mL	20 mL	600 mg	
		10–12 mg/kg od in >15 kg	600 mg	0.25	0.25	0.25	0.5	0.5	0.5	0.75		
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	Give on alternate days if dose in mg/kg/day is too high
			100 mg Cap or Tab	M/W/F	M/W/F	1 alt days	1 alt days	1	(>14 y)	(>14 y)	100 mg	
	Cycloserine or Terizidone	15–20 mg/kg	125 mg mini capsule (cycloserine)c	1	1	2	3	4	(>14 y)	(>14 y)	1g	
			250 mg Cap	4–5 mL	5–6 mLc	7–10 mLc	2	2	2	(>14 y)	1g	
C	Ethambutol	15–25 mg/kg	100 mg dt	1	2	3	4	_	_	(>14 y)		
			400 mg tab	2	2	3	3			3		
	Delamanid		50 mg Tab	–	–f	–f	–f	1 BID	1 BID	2 BID	200 mg	Only in patients aged >2 years (25 mg bd in 3–5 years; 50 mg bd in 6–11 years; 100 mg bd in 12–17 years).
	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)		
	Imipenem-cilastatin		500 mg + 500 mg powder for injection, vial (10 mL)	–	–	–	–	–	–	–		Not used in patients aged <15 years (use meropenem)
	Meropenem	20–40 mg/kg iv every 8 hours	1 g powder for injection, vial (20 mL)	2 mL	4 mL	6 mL	8–9 mL	11 mL	(>14 y)	(>14 y)	–	To be used with clavulanic acid.
	Amikacin	15–20 mg/kg	500 mg/2 mL solution for injection, ampoulef	0.4 mL	0.6 mL	0.8–1.0 mL	1.2–1.5 mL	2.0 mL	(>14 y)	(>14 y)	1 g	
	Streptomycin	20–40 mg/kg	1 g powder for injection, vial	Calculate according to the dilution used					(>14 y)	(>14 y)	1 gm	
	Ethionamide or prothionamide	15–20 mg/kg	125 mg dt (ethionamide)	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	
	P-aminosalicylic acid	200–300 mg/kg in 2 divided doses	PAS acid (4 g) sachet	0.5–0.75 g bd	0.75–1 g bd	1–2 g bd	2–3 g bd	3–3.5 g bd	(>14 y)	(>14 y)		Full dose can be given once daily if tolerated.
			PAS sodium salt (equivalent to 4 g PAS acid) sachet	0.5–0.75 g bd	0.75–1 g bd	1–2 g bd	2–3 g bd	3–3.5 g bd	(>14 y)	(>14 y)		
			(9.2 g; equivalent to 4 g PAS acid) sachet	1.5 g bd	2–3 g bd	3–4 g bd	4 or 6 g bd	6 or 8 g bd	8–12 g bd	8–12 g bd		
Other medicines	Isoniazid	15–20 mg/kg (high dose)	50 mg/5 mL soln	8–10 mL	15 mL	20 mL	–	–	–	–		300 mg isoniazid tablet can be used in patients >20 kg. Pyridoxine is always given with high-dose isoniazid in children (12.5 mg od in those aged <5 years and 25 mg od in those aged >4 years).
			100 mg tab	1	1.5	2	3	4	4	(>14 y)		
	Clavulanic acid		62.5 mg clavulanic acid as amoxicillin/ clavulanate, 250 mg/62.5 mg, powder for oral solution, 5 mL	2 mL bdi	3 mL bdi	5 mL bdi	8 mL bdi	10 mL bdi	(>14 y)	(>14 y)		Only to be used with carbapenems.

Most agents are given in a single daily dose. Cycloserine and PAS may be given in split doses to reduce the likelihood of adverse reactions (ethionamide/prothionamide displays concentration-dependent killing of M. tuberculosis, so twice daily dosing should be avoided). Linezolid is usually given once daily. Bedaquiline and delamanid are taken together with the other medicines in the MDR-TB

regimen; the second dose of delamanid is usually taken alone, so treatment supervision needs to factor this in too. Injectable agents (if absolutely needed) are also usually given intramuscularly once daily and the dose should not be split (with the exception of imipenem-cilastatin and meropenem, which are given intravenously in divided doses).

Ideally, all medicines are taken with food, given that a light meal promotes absorption.

Oral agents are usually given every day of the week. Bedaquiline is given daily for the first 2 weeks and three times weekly for the following 22 weeks.

Regarding missed doses, in general, if all the medications due on a given day are missed, then treatment is resumed the following day and an extra day of treatment is added to the end of the regimen. However, if a dose is missed during the first 2 weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule. This means that they should not add the missed dose at the end of the 2-week period. From the third week onwards, if a 200 mg dose is missed, patients should take the missed dose as soon as possible, and then resume the three-times a-week regimen.

If a delamanid dose is missed, patients should take it as soon as possible after it has been missed. However, if it is close to the time for the next scheduled dose, then the missed dose may be skipped, and the patient should not take a double dose to make up for a forgotten tablet.

Table 29. Summary of MDR/RR-TB Regimens to be used under programmatic conditions in Ethiopia

Regimen Type	**Regimen Composition**	**Remarks on its use**
All-Oral Bdq Containing Shorter MDR/RR-TB Regimen, 9-12 months	4–6 $Bdq_{(6\ m)}$ -Lfx-Cfz-Z-E-Hh-Eto / 5 Lfx-Cfz-Z-E	Refer to the eligibility criteria for its use.
All-Oral Longer MDR/RR-TB Treatment Regimen (LTR), 18-20 months *	18 $Bdq_{(6\ m\ or\ longer)}$-Lfx-Lzd-Cfz-Cs/ Lfx-Lzd-Cfz-Cs	Preferred regimen for MDR/RR-TB patients not eligible to be treated with all-oral Bdq containing Shorter regimen.
Individualized LTR, 18-20 months, but could be extended up to 24 months **	Individualized	Recommended when construction of a LTR with at least 3 group A and 2 group B drugs is not possible due to intolerance to the medicines, acquired additional resistance, etc.

* 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 with fully oral LTR. If patient is shown to be FQ resistance (preferably prior to initiation of treatment), then Dlm would be used instead of the FQ.

** 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. Examples of Individualized LTR by type of patient are shown in the following Table 30, below.

Table 30: 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 ("Simple MDR"; 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 despite good programmatic conditions (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, or nephrotoxicity	All-Oral LTR (with Bdq or Dlm substituted for the injectable) if patient was on STR All-Oral Bdq Containing Shorter Regimen may be initiated if other criteria are met for its use.	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
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 fluoroquinolones and other group A drug ("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 $Bdq_{(6m\ or\ longer)}$-$Dlm_{(6m\ or\ longer)}$-Cfz-Cs-PAS (if Lnz resistant but Bdq Susceptible) 18 $Dlm_{(6m\ or\ longer)}$-Lzd-Cfz-Pto-Cs (if Bdq resistant but Lnz Susceptible) 18 $Bdq_{(6m\ or\ longer)}$-$Dlm_{(6m\ or\ longer)}$-Cfz-Cs-PAS-Mfx^{HD} 18 $Dlm_{(6m\ or\ longer)}$-Lzd-Cfz-Pto-Cs-Ipm/Cln-Amx/Clv

10.7.6 Duration of longer MDR/RR-TB regimens

Recommendations

- In MDR/RR-TB patients on longer regimens, a 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.

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

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 31: 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	$Dlm_{(6m\ or\ longer)}$, PAS, Pto/Eto
	FQ-Resistant	18 Lzd-Cfz-Cs-$Dlm_{(6m\ or\ longer)}$	Add one of $Dlm_{(6m\ or\ longer)}$, 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

Adapted from Management of Drug-Resistant Tuberculosis in Children: A Field Guide. Boston, USA: The Sentinel Project for Pediatric Drug-Resistant Tuberculosis; November 2018, Fourth edition

The table outlines a possible approach to regimen design based on different age groups and the presence or absence of fluoroquinolone resistance.

The age groups were selected based on the presence of pharmacokinetic and safety data to support the use of the medications.

- 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 forms of DR-TB including 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 and imipenem-cilastatin. Seizures may be more common in children with meningitis treated with imipenem-cilastatin (meropenem is preferred for meningitis cases and children).

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 32: 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:

TB in pregnancy is associated with poor outcomes, including an increased risk of preterm birth, low birth weight, intrauterine growth restriction, and perinatal death.

All pregnant women should be started on treatment as soon as possible. However, the decision to initiate treatment for DR-TB and the construction of a DR-TB regimen must consider the gestational age of the fetus, and should weigh the risks of the teratogenicity against potential benefit to the mother.

The teratogenic effects of anti-tuberculous treatment mainly occur during the first trimester. Therefore, treatment may be deferred until the second trimester in selected cases where the clinical condition of the mother is stable and where there is minimal radiological disease. This strategy, however, must be accompanied by close clinical follow-up as DR-TB in pregnancy, especially in the context of HIV coinfection, can have an accelerated course.

Aminoglycosides, such as amikacin are FDA class D agents. These should be excluded from TB treatment regimens during pregnancy because of the risk of ototoxicity and fetal malformation, especially within the first 20 weeks of gestation.

Knowledge about the safety of bedaquiline and delamanid in pregnancy and during breastfeeding is still sparse. Bedaquiline may be used as it is likely safer (FDA pregnancy risk category B) and animal reproduction studies have not demonstrated risk to the fetus. Delamanid, however, should not be used in pregnancy until more safety data become available since animals studies have demonstrated potential teratogenic effects.

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.

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 33: 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.[1] 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.

[1] Jaspard M, Elefant-Amoura E, Melonio I, De Montgolfier I, Veziris N, et al. Bedaquiline and linezolid for extensively drug-resistant tuberculosis in pregnant woman. *Emerg Infect Dis* 2017; 23(10). doi: 10.3201/eid2310.161398.

HIV Infection:

The composition of the treatment regimen for MDR-TB does not usually differ substantially for people living with HIV. A few drug-drug interactions may be avoided with careful attention (e.g. bedaquiline and efavirenz). See table below for recommendations for HIV infected patients and other co-morbidities.

Table 34 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.

10.7.8 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 Clinical Review Committee is always available for case-by-case advice.

Table 35 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	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.
Ipm/Cln, Mpm	Patients with central nervous system disorders	Use with caution as carbapenems have been associated with seizures. Use Mpm in preference to Ipm.

Drug-Drug interactions

Table 36 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 37 Drug-drug interactions between ARVs and medicines used in RR/MDR-TB regimen

	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 an 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.[2]

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

[2] Mallikaarjun S, Wells C, Petersen C, Paccaly A, Shoaf SE, et al. Delamanid coadministered with antiretroviral drugs or antituberculosis drugs shows no clinically relevant drug-drug interactions in healthy subjects. Antimicrob Agents Chemother, 2016; 60(10): 5976-85.

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.[3]

Table 38 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).[4]		

[3] endTB Medical Review Board. Beta-blocker use in MDR-TB patients, ver 2.0. 17 January 2017.

[4] Woosley RL, Black K, Heise CW, Romero K. CredibleMeds.org: What does it offer? *Trends Cardiovasc Med*, 2017. pii: S1050-1738(17)30114-7.

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

Recommendation:

- In MDR/RR-TB patients on longer regimens, the performance of sputum culture in addition to 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 41 below. Details on adverse events detection and management is indicated in section 12 of this guidelines. Treatment monitoring should be carried out in the context of mainly ambulatory care, using a decentralized model of care.

10.8 The bedaquiline, pretomanid and linezolid (BPaL) regimen for MDR-TB with additional fluoroquinolone resistance

Recommendation:

- A treatment regimen lasting 6–9 months, composed of bedaquiline, pretomanid and linezolid (BPaL), may be used under operational research conditions in multidrug-resistant tuberculosis (MDR-TB) patients with TB that is resistant to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks.

The bedaquiline, pretomanid and linezolid (BPaL) regimen, which was used in the Nix-TB study, may not be considered for routine programmatic use worldwide until additional evidence on efficacy and safety has been generated. However, in individual patients for whom the design of an effective regimen based on existing WHO recommendations is not possible, the BPaL regimen may be considered as a last resort under prevailing ethical standards.

The evidence reviewed supports the use of this regimen in certain patient subgroups, such as PLHIV.

BPaL regimen: 6–9 Bdq- Pa-Lzd

The BPaL regimen is to be used under operational research conditions conforming to WHO standards, which include:

- Research subject to ethical approval,
- Patient-centred care and support,
- Pre-defined eligibility criteria,
- Patient informed consent,
- Implementation according to the principles of good clinical practice,
- Active drug safety monitoring and management,
- Treatment monitoring, outcome evaluation, and comprehensive, standardized data collection.

Pretomanid is a novel medicine that has recently been studied as part of the BPaL regimen for the treatment of MDR-TB with additional fluoroquinolone resistance. Pretomanid possesses activity against both replicating and non-replicating M. tuberculosis. In vitro, preclinical and clinical data support a role for pretomanid as part of the BPaL regimen (6–9 Bdq-Pa-Lzd). Because there is no experience of the use of this medicine in other combinations, pretomanid is not recommended for use outside the context of the BPaL regimen. Safety signals related to pretomanid include hepatologic, gastrointestinal, dermatologic and reproductive adverse effects.

10.8.1 Eligibility

A patient is eligible for treatment with the BPaL regimen if he or she:

- is diagnosed with bacteriologically confirmed pulmonary TB and has laboratory-confirmed resistance to rifampicin and fluoroquinolones with or without resistance to injectable agents; and
- is aged at least 14 years at the time of enrolment; and
- weighs 35 kg or more; and
- is willing and able to provide informed consent to be enrolled in the operational research project and to adhere to the follow-up schedule (signed or witnessed consent if the patient is illiterate, signed or witnessed consent from a child's parent or legal guardian); and
- if the patient is a premenopausal woman, is not pregnant or breastfeeding and is willing to use effective contraception; and
- has no known allergy to any of the BPaL component drugs; and
- has no evidence in DST results of resistance to any of the component drugs, or has not been previously exposed to any of the component drugs for 2 weeks or longer; and
- has no extrapulmonary TB (including meningitis, other CNS TB, or TB osteomyelitis).

Patients who are not eligible for the BPaL regimen can benefit from the individualized longer treatment regimen that is composed of medicines using the priority grouping of medicines.

Contraindications:

There are no absolute contraindications for the use of any drug in the treatment of MDR-TB and MDR-TB with fluoroquinolone resistance (a disease that poses serious risk of death or debilitation to the patient if treated inadequately). However, there are relative contraindications for the BPaL regimen, and some of the most relevant of these are listed in Table 39. If the clinician judges that the potential benefits outweigh the potential risk (also taking into account alternative treatment options), then treatment may proceed with caution. In these situations, advice should be sought from the national CRC.

Table 39: Relative contraindications to the use of the BPaL regimen for treatment of patients with MDR/RR-TB with additional fluoroquinolone resistance

Relative contraindication	Notes
Concurrent use of medications that have known interactions or overlapping toxicities with BPaL component drugs	Inducers of CYP450 enzymes: ○ Efavirenz ○ Rifamycins ○ Antiepileptics Inhibitors of CYP450 enzymes: ○ Ritonavir-boosted PIs ○ Fluconazole or itraconazole ○ Clarithromycin or erythromycin Drugs that prolong the QT interval Drugs that increase serotonin level
High risk of cardiac arrhythmia	Baseline QTcF >500 ms History of syncopal episodes, ventricular arrhythmias, heart failure or severe coronary artery disease Family history of long-QT syndrome
Severe anaemia, thrombocytopenia or leukopenia	Haemoglobin level < 8.0 g/dL Platelet count < 75 000/mm3 Absolute neutrophil count < 1000/mm3
Severe hepatic failure	AST/ALT > 3.0 × ULN Total bilirubin > 2.0 × ULN Albumin < 32 g/L
Severe renal failure	Serum creatinine > 3.0 × ULN Owing to limited experience with the use of this regimen, caution should be exercised in patients with severe renal failure
Severe neuropathy	Peripheral neuropathy of grade 3 or grade 4

10.8.2 Composition and duration of the BPaL regimen

The BPaL regimen comprises three components – bedaquiline, pretomanid and linezolid – that are used as a package. Bedaquiline and linezolid are used in longer regimens and bedaquiline is also used in the shorter all-oral regimen.

Pretomanid is a new medicine, and its safety and effectiveness have not been established for its use in combination with medicines other than bedaquiline and linezolid as part of the BPaL regimen. Pretomanid is a nitroimidazole (i.e. in the same chemical class as delamanid) and is a prodrug that is metabolically activated by a nitroreductase, producing various metabolites that are responsible for its therapeutic action. Pretomanid inhibits cell wall biosynthesis and, under anaerobic conditions, it causes respiratory poisoning of the bacterial cell through the release of reactive nitrogen species.
Pretomanid possesses activity in both replicating and non-replicating M. tuberculosis bacilli. In vitro, preclinical and clinical data support a role for pretomanid as part of the BPaL regimen. Because there is no experience of the use of this medicine in other combinations, pretomanid is not currently recommended for use outside the context of the BPaL regimen. Pretomanid is currently being further tested as part of combination regimens for the treatment of both drug susceptible and drug-resistant TB.
The most common adverse reactions observed in patients treated with pretomanid in combination with bedaquiline and linezolid included damage to the nerves (peripheral neuropathy), acneiform dermatitis, anaemia, nausea, vomiting, headache, increased liver enzymes (transaminases and gamma-glutamyltransferase), indigestion (dyspepsia), rash, pruritus, increased pancreatic enzymes (hyperamylasemia), decreased appetite, increased transaminases and gamma glutamyl transpeptidase, visual impairment, low blood sugar (hypoglycemia), abdominal pain, musculoskeletal pain and diarrhoea.
Data from the animal model study also suggested the side-effect of infertility related to pretomanid. Infertility is a serious issue because it affects both patients and their families; given this potential side-effect, the balance of the desirable and undesirable effects of the treatment needs to be carefully discussed with the patient, who should be involved in the treatment decision.
The BPaL regimen comprised pretomanid administered at 200 mg once daily, bedaquiline administered at 400 mg once daily for the first 2 weeks of treatment (days 1–14) and then 200 mg three times a week thereafter, and linezolid at 1200 mg per day.
Table 40: BPaL Regimen drugs dose chart

Drug	Dose
Bedaquiline (100 mg tablet)	400 mg once daily for 2 weeks, then 200 mg 3 times per week afterwards
Pretomanid (200 mg tablet)	200 mg once daily
Linezolid (600 mg tablet)	1200 mg once daily (adjustable)

Dose modifications for bedaquiline and pretomanid are not allowed. Linezolid high dose (1200 mg once daily) in the BPaL regimen can be reduced after the first month of treatment in patients with Lnz-induced peripheral neuropathy or myelosuppression.
Following the regimen used in the Nix-TB study, the linezolid dosage is 1200 mg per day. Dose reduction to 600 mg daily and further to 300 mg daily or temporary cessation of linezolid was permitted for up to 35 consecutive days for any known linezolid adverse reactions of myelosuppression, peripheral neuropathy and optic neuropathy. If toxicity prohibited further treatment with linezolid, then patients could remain on bedaquiline and pretomanid provided that they had received the 1200 mg per day dose for at least the first 4 consecutive weeks, were sputum smear negative or had only trace or scanty results, and were responding to treatment based on clinical monitoring and follow-up. Missed doses of linezolid were not made up during the Nix-TB study, and dose modifications for bedaquiline and pretomanid were not allowed.

With the experience of linezolid use in the Nix-TB study, the following modifications of linezolid dosing in the management of adverse events may be considered for the BPaL regimen:

- Linezolid can be temporarily interrupted, or the dosage can be reduced after the first month.
- The dose of linezolid can be reduced from 1200 mg once daily to 600 mg or 300 mg once daily.

The BPaL regimen is given for a duration of 6–9 months. The standard treatment duration is 6 months. If the sputum culture taken after 4 months of treatment is positive, patients can receive an additional 3 months of treatment (total 9 months).

The full BPaL regimen can be temporarily interrupted for a maximum of 35 consecutive days. Any missed days will be made up by extending the duration of the regimen by the number of days missed, but this must not be more than 35 days.

Sub-group Considerations in BPaL:

Children	• Children (0–13 years) were excluded from the Nix-TB study; therefore, no analysis specific to this subgroup of patients could have been performed. • It is recommended that children with pulmonary MDR/RR-TB with additional resistance to fluoroquinolones be given the same consideration for longer treatment regimens as adults, to include components with a safety profile that is better established.
PLHIV	• PLHIV were eligible to enroll in the Nix-TB study if they had a CD4 count of more than 50 cells/uL and if they were using permitted antiretroviral medications • It is important to note drug–drug interactions when administering TB and HIV medications in combination, including the documented interactions between bedaquiline and efavirenz. • There are two important drug–drug interactions between antiretroviral drugs and bedaquiline: o Efavirenz induces metabolism of bedaquiline – its co-administration with bedaquiline may result in reduced bedaquiline exposure and loss of activity, and it is therefore not recommended; and o Ritonavir may increase bedaquiline exposure, which could potentially increase the risk of bedaquiline-related adverse reactions, so the combination of bedaquiline with ritonavir should be avoided or be administered with caution. • ART regimens should be modified to avoid these drugs for an HIV-positive patient treated with a BPaL regimen. Efavirenz also reduces pretomanid exposures significantly; therefore, an alternative antiretroviral agent should be considered if pretomanid or the BPaL regimen is to be used. Regimens including zidovudine should be used with special caution because both zidovudine and linezolid may cause peripheral nerve toxicity and are known to have myelosuppression cross-toxicity.
Pregnant and lactating women	• Safety of the BPaL regimen in pregnant and lactating women has not been established. In such cases, it is recommended that a longer regimen be individualized to include components with a safety profile that is better established. The safety of pretomanid in pregnant and lactating women has not been established. • The use of bedaquiline in pregnancy has been shown to be associated with infants born with a lower mean birth weight than infants whose mothers did not take bedaquiline; however, this did not appear to be a clinically significant finding when infants were followed over time. Breastfeeding is not recommended for women taking BPaL.
EPTB	• Patients with extrapulmonary TB were excluded from the Nix-TB study. Therefore, the WHO recommendations for longer MDR-TB regimens apply to patients with extrapulmonary disease, including for those with TB meningitis. There are few data on the CNS penetration of bedaquiline or pretomanid.
Patients with very limited treatment options	• In some instances, patients will have extensive drug resistance profiles that may make it difficult (or impossible) to construct a regimen based on existing recommendations. In such situations, the patient's life may be endangered. Therefore, for individual patients for whom it is not possible to design an effective regimen based on existing recommendations, the BPaL regimen may be considered as a last resort under prevailing ethical standards

10.8.3 Implementation Considerations for BPaL Regimen

The implementation of the BPaL regimen should be in the context of operational research only. This implies that:

- a study protocol needs to be developed and submitted to a national ethics board or any other ethics approval committees;
- pre-specified inclusion and exclusion criteria are in place;
- an appropriate schedule of safety monitoring and reporting is in place (including aDSM):
- a pre-defined schedule of clinical and microbiologic monitoring is in place, preferably including post-treatment completion follow-up;
- individual patient informed consent is obtained;
- patient support is provided; and
- a standardized reporting and recording system is used, including for adverse events.

Patients should be fully informed about the regimen, and especially that it includes a new compound, pretomanid. Individual patient informed consent is necessary but should not be overly burdensome for patients – consent forms should be adapted, contextualized and streamlined so that they are easy for patients to understand. As part of the informed consent process, patients should be advised of the reproductive toxicities seen in animal studies and advised that the potential effects on human male fertility have not been adequately evaluated.
A medication guide is available as part of the pretomanid product label, and it may be used when informing patients. In any operational research study involving the BPaL regimen, the principles of good clinical practice should apply. All efforts need to be made to carefully select eligible patients and then, once patients are enrolled, to provide effective patient support to enable adherence to treatment and close monitoring for adverse events and response to treatment.

DST is an important implementation consideration, which will need further enhancement given the increasing potential use of bedaquiline and linezolid (even for longer regimens for MDR/RR-TB) and the inclusion of new medicines – such as pretomanid – in MDR-TB treatment regimens.
Baseline DST will confirm eligibility for the BPaL regimen; therefore, the establishment and strengthening of DST services will be a vital implementation consideration. For patients with confirmed MDR/RR-TB, the MTBDRsl assay is considered as the initial test, in preference to culture and phenotypic DST, to detect resistance to fluoroquinolones and, if necessary, to the second-line injectable drugs. If DST is available for bedaquiline or linezolid, it is highly desirable that this is also carried out at baseline. DST for pretomanid is being developed.
Patients with strains resistant to any of the medicines used in the BPaL regimen should commence treatment with a longer MDR-TB regimen.
Preventing treatment interruption is important to increase the likelihood of treatment success. Measures to support patient adherence tailored to patient needs are important to retain patients on treatment and to ensure good treatment outcomes, such as a relevant model of care, DOT provided in the community or at home and by a trained treatment supporter, social support and digital health interventions for communication with the patient.

10.8.4 Treatment monitoring of BPaL Regimen

- Response to treatment is monitored on the basis of monthly sputum smear microscopy and culture (ideally at the same frequency). This is similar to the schedule used in patients on longer MDR-TB regimens.

- While awaiting updated definitions, the treatment outcome definitions and reporting framework for patients on the shorter MDR-TB regimen are the same as those for patients on longer MDR-TB regimens.
- Treatment must be administered under closely monitored conditions to enable optimal drug effectiveness and safety, and to monitor for the acquisition of emerging drug resistance, should it arise.
- Given that the BPaL regimen is a new and shorter regimen that includes a novel medicine and is being implemented under operational research conditions, it is also important to follow up patients after the completion of treatment, to ensure that there is no relapse.
- Monitoring after completion of treatment to be carried out monthly for months 1–3, then at 3-monthly intervals thereafter. Follow-up after treatment completion needs to be for a total of 24 months.
- Safety for patients who receive BPaL needs to be actively monitored, following the aDSM framework.
- Patients need to be tested at baseline and then monitored during treatment using schedules of relevant clinical and laboratory testing.
- Active pharmacovigilance should be performed, as well as proper management of adverse events and prevention of complications from drug–drug interactions.

10.8.5 Modification or discontinuation of treatment with BPaL Regimen

- Safe management of adverse events may warrant dose reduction or discontinuation of the component drugs.
- Modification of the regimen through early discontinuation or replacement of any of the component drugs may result in poor treatment outcomes.
- Although dose modification of bedaquiline and pretomanid is not allowed, dose modification of linezolid is acceptable after the first month of treatment in cases of adverse events.
- The BPaL regimen may need to be discontinued in some patients. In such cases, patients need to be evaluated and treatment switched to an individualized longer regimen, based on the WHO guidelines for regimen design using priority grouping of medicines.
- The most common situations in which the regimen may be discontinued are the following:
    - **Intolerable toxicity** – One or more drugs may need to be suspended permanently owing to severe toxicity. In such cases, the clinician (or, preferably, clinical committee or consilium) should review the medical history and assess the patient carefully to determine what regimen should be prescribed.
    - **Treatment failure** – If clinical and bacteriological responses to treatment are poor, a change in the treatment regimen should be considered. DST should be repeated, whether or not the regimen is changed, to inform future management decisions.
    - **Resistance to drugs in the BPaL regimen** – For patients who submit a sputum sample for culture based second-line DST at the beginning of treatment, results may not be available until after treatment has started. If resistance to BPaL component drugs is discovered after treatment is initiated, it will be necessary to discontinue the regimen.
    - **Pregnancy during treatment** – For patients who become pregnant during treatment, it will be necessary to discontinue the BPaL regimen.
- Regarding the discontinuation of any component of the BPaL regimen due to severe toxicity, the following factors should be taken into account:
    - If either bedaquiline or pretomanid needs to be discontinued, the entire BPaL regimen should also be discontinued.

- If linezolid is permanently discontinued during the initial 4 consecutive weeks of treatment, the entire regimen should be discontinued.
- Temporary cessation of linezolid (due to a linezolid-specific toxicity) or of the full regimen is allowed for suspected drug-related toxicity. Re-introduction of the regimen could be considered after a cessation of no more than 35 consecutive days.
- If linezolid needs to be permanently discontinued at a later stage of the regimen, when the patient has already completed the initial 4 consecutive weeks of treatment with the linezolid 1200 mg daily dose, clinicians should assess patient status and consider discontinuing the regimen or continuing administration of bedaquiline and pretomanid for the rest of the regimen.

10.9 Treatment Initiation, Patient Monitoring and Clinical Care

RR-/MDR-TB patients who are to be initiated on second line anti-TB drugs are required to have a thorough pre-treatment evaluation and, after initiation of treatment are to have regular scheduled follow-up evaluations (clinical and laboratory). Patients should be evaluated on emergency basis when they develop adverse effects to treatment or any other concomitant illness.

10.9.1 Pre-treatment evaluation and treatment initiation

Before the patients are started on any MDR/RR-TB treatment regimen, the following must be done at the time of diagnosis:

- Counsel and educate the patient and family member
- Ensure that all relevant information is provided to the patient concerning the drugs in the regimen, preferably with a signed informed consent
- Address any concerns raised by the patient
- Verify the patient's residential and work address
- Do all the required baseline clinical assessments, including laboratory investigations
- Adherence preparation
- Enquire about close contacts at home or work
- Arrange for screening and testing of all contacts

The pre-treatment assessment should be systematically conducted on all patients in order to decide the preferred regimen, identify patients at greater risk of adverse effects, poor outcomes, and to establish baseline levels for monitoring. It is mandatory to understand the patient's psychosocial and economic situation and identify potential barriers to treatment before initiation of treatment.

The pretreatment evaluation should include a thorough medical history, physical examination, and laboratory investigations. The patient must be evaluated for other co-morbidities as it affects the initial treatment regimen or other important management decisions. All baseline clinical and laboratory evaluation must be conducted before treatment initiation.

Once patients complete the pretreatment evaluation, the appropriate treatment regimen should be selected and designed.

10.9.2 Treatment Monitoring and patient Follow Up

Every MDR/RR-TB patient should undergo regular follow-up during and after treatment, including clinical evaluation, bacteriological and laboratory testing as described in the following table (Table 41). The baseline visit refers to the beginning of the treatment with the respective MDR/RR-TB treatment regimen. The monitoring schedule should be applied to all patients who receive treatment for MDR/RR-TB, regardless of the composition of the regimen.

Each MDR-TB patient should be monitored closely for signs of both treatment efficacy and adverse effects of the medications. The success of the treatment depends on the intensity and quality of monitoring and supervision activities. Patients should be seen by a doctor or experienced Health Officer at monthly intervals until the end of treatment after discharge from the DR-TB Centre. The responsible clinician should assess clinical, microbiological, and radiological 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.

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

Treatment monitoring should follow the standard assessment format and schedule:

a) **Clinical history**:
   - Resolution or worsening of symptoms of TB (cough, sputum production, haemoptysis, chest pain, respiratory distress, fever and weight loss).
   - Assess for adherence (missed PO doses, missed injections, reasons)
   - Symptoms of drug adverse events
   - Systematic assessment for co-morbid illnesses
   - Reproductive age women: Assess for Pregnancy, assess FP need.

b) **Physical examination**: To be done as per the monitoring schedule (refer to the below table).

c) **Laboratory monitoring:** Laboratory monitoring and other investigations are important for documenting response and identifying complications early. Laboratory tests should be done regularly based on the monitoring schedule, and when necessary based on clinical indication, as shown in the table below.

Additional remarks:

- The laboratory and ECG follow-up should be continued at monthly intervals for the full duration of treatment with bedaquiline and/or delamanid (i.e. this may be for longer than 6 months in cases where Bdq and/or Dlm is prolonged beyond 24 weeks)
- More frequent monitoring may be advisable in specific categories of patients, such as the elderly, patients living with HIV, patients affected by HBV- or HCV-related hepatitis, diabetics, patients with moderate to severe hepatic or renal impairment, or receiving specific drug combinations (i.e. Bdq and Dlm).
- In case of electrolyte disturbances or ECG abnormalities, more frequent monitoring should be performed as described in the chapter on clinical management of adverse events of interest.
- More frequent albumin monitoring (i.e. monthly) may be indicated during treatment with Dlm in specific cases, e.g. in patients with Grade 2 or worse hypoalbuminemia (<30 g/L) at baseline, or in patients experiencing QT_c interval prolongation.
- If sputum culture positive at month 4 of treatment, baseline and month 4 sputa specimens should be sent to the National and/or Supranational TB Reference Laboratory to perform comprehensive first- and second-line DST.

Table 41: **Monitoring schedule for patient follow-up**

	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	

10.9.3 Post treatment monitoring

Post treatment monitoring is important to:

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

Once the patient has completed the course of treatment, the post-treatment follow-up assessments should be performed every three months for a period of at least one year.

The assessment should include the following examination:

- Clinical history and 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 one year. The assessment should include the above recommended steps.

If during any post-treatment follow-up assessment, the patient shows evidence of active TB disease, the patient should be fully re-evaluated and managed accordingly.

10.10 Adjuncts to MDR-TB treatment

10.10.1 Surgery in treatment of M/XDR-TB

Recommendation:

- In patients with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant TB (MDR-TB), elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen.

Surgery is considered as an adjunct to treatment with effective chemotherapy for patients with indications as it improves quality of life and chance of cure.

Surgery should be considered in patients with localized pulmonary disease that cannot be cured by medical treatment alone or when there are life-threatening complications (pulmonary hemorrhage, non-resolving pleural empyema, or extensive necrosis).

The best treatment outcomes are achieved with partial unilateral lung resections.

All care providers should identify patients requiring surgical interventions and communicate the program to access the service. (See Annex 3 for details on surgery in TB and DR-TB).

Chest CT Scans, pulmonary function testing and quantitative lung perfusion or ventilation may have a role in the preoperative work-up.

Resection surgery should be timed to give the patient the best possible chance of cure with the least

risk of harm. Thus, the timing of surgery may be earlier in the course of the disease when the patient's risk of morbidity and mortality are lower (e.g. when the disease is still localized to one lung or one lung lobe). Generally, at least 2 months of therapy should be given before resection surgery, to decrease the bacterial infection in the surrounding lung tissue. Prognosis appears to be better when partial lung resection is performed after culture conversion. Even with successful resection, the total duration of treatment and the duration of treatment after culture conversion should be guided by the recommendations in Annex 3.

Partial lung resection for patients with MDR/RR-TB is only to be considered when good surgical facilities, staffed by trained and experienced surgeons, are available.

RR/MDR-TB patient may also need none-TB related surgical care. Any DR-TB patient who needs emergency surgery services (such as Ceaserain Section, appendectomy, cholecystectomy, etc) should be provided by optimizing Personal protection for HCWs in the general hospital care setting. National and regional CRC members could provide advises when needed.

10.10.2 Corticosteroids

Corticosteroids may be beneficial as an adjunctive therapy in DR-TB patients with severe respiratory insufficiency, central nervous system or pericardial involvement. Corticosteroids may also alleviate symptoms in DR-TB patients with an exacerbation of chronic obstructive pulmonary disease. Prednisone is commonly used, started at approximately 1 mg/kg of body weight with gradual tapering dosage over one to two weeks. When a more immediate response is needed, injectable corticosteroids are often used. Avoid use of corticosteroids in pregnancy and PLHIV unless the benefit outweighs.

10.10.3 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 regimen should receive daily oral pyridoxine 50mg tablet, while patients receiving cycloserine containing regimens receive 50mg of pyridoxine for every 250mg of cycloserine administered.

11. TREATMENT OF TB/DR-TB IN SPECIAL CONDITIONS

11.1 TB treatment in special situations and conditions

The management of TB/DR-TB in patients with special conditions and concomitant co-morbid diseases requires additional considerations that the managing clinician should take precautions in the development of individual care plan to avoid further damages to the organs affected and also prevent the occurrence of adverse drug events due to the inappropriate administration of a medicine or its dosages. Most essential first line drugs are usually safer for use in clinical treatment of patients while the use of many second line TB drugs in management of patient with Rifampicin resistance and beyond needs to be vigilant as many are not only toxic but also used in higher doses that might harm the various organ system of the patient. Summary of the general recommended management precautions and considerations for patients with special situations is indicated below.

Pregnancy, Breastfeeding and Contraceptives Use

Conditions	Management precautions and considerations
Pregnancy and Breastfeeding	• See detailed guidance under the RR/MDR-TB Regimens in section 10 above for preganancy. • Both first and second line anti-TB drugs are considered safe during lactation even though data is limited for SLDs. • Continue to breast feed the baby while administering Anti-TB treatment as it is the most feasible feeding option for most infants in Ethiopia, with adequate precaution to prevent airborne TB transmission from the mother.

Contraceptives use	• Rifampicin, a potent liver enzyme inducer, reduces serum level of estrogen and hence effect of the combined oral contraceptive (COC) against pregnancy.
	• Advice females in the child-bearing age to use another form of contraception:
	  ○ Medroxyprogesterone (Depo-Provera) administered every 12 weeks.
	  ○ IUCD or implants (e.g. Implanon) are preferred.
	  ○ Dual protection with use of Condoms protects against Sexually transmitted diseases

TB/DR-TB Treatment and Diabetes Mellitus

- DR TB and Diabetes have bidirectional interaction, one adversely affecting the outcome of the other.
- Ethionamide and PAS affect the control of blood sugar especially in patients on oral hypoglycemic agent
- Patients with diabetes usually have some underlying chronic diabetic nephropathy. This increases the risk of injectable nephrotoxicity if patient is on injectable:
    - Creatinine and potassium levels should be monitored frequently.
    - Consider ACE-I in patient with advanced diabetes to prevent
- Consider the use of longer regimens in RR/MDR-TB patients with DM.
- Metformin may exaggerate gastrointestinal side effects when coadministered with anti-tuberculous agents such as ethionamide, PAS, and clofazimine, and can rarely cause lactic acidosis.
- Caution is advised when using nephrotoxic agents and neurotoxic agents in patients with established diabetes.
- QTc monitoring is advised when using hypoglycemic agents such as sulphonylureas and glinides concurrently with bedaquiline and/or delamanid.
- Furthermore, caution is also advised when using bedaquiline concurrently with potentially hepatotoxic antidiabetic agents such as thiazolidinediones.
- Oral hypoglycemic drugs can be used during the treatment of DR-TB but may require higher doses due to drug-drug interactions.
- Insulin might be preferred over oral hypoglycemic agents.
- Administer pyridoxine to reduce occurrence of Peripheral neuropathy in diabetic patients that may be exacerbated by treatment with SLDs.
- Conduct regular monitoring of blood glucose levels and other important markers of diabetes management: Goal for fasting blood glucose levels are 70-140 mg/dL

Treatment of TB/DR-TB in patients with Renal Insufficiency

- Chronic kidney disease is common in TB and DR-TB patients. Etiologies include renal TB disease, damage due to previous use of injectable, diabetes mellitus, and HIV-associated nephropathy.
- Anti-TB drugs that are excreted by the kidney can accumulate to toxic levels in patients with renal dysfunction.
- Rifampicin and Isoniazid are eliminated almost entirely by biliary excretion, so no dose adjustment is required.
- Haemodialysis often leads to elimination of most anti-TB drugs and medications are recommended to be given after dialysis.
- Careful monitoring of patients is essential as side effects (mainly neuropsychiatric problems, hepatitis and optic neuropathy) are noted to occur at higher levels in patients with renal failure and especially those on dialysis.
- The treatment of TB in patients with mild renal impairment, and with glomerular filtration rate (GFR) between 30-60ml/min, should be individualised using standard drugs in dose ranges in the

lower range of usual recommendations for patients with normal renal function, with careful monitoring of side effects.

- There is significant renal excretion of ethambutol and metabolites of pyrazinamide. Adjust dose to three times per week at recommended dosage of pyrazinamide (25 mg/kg), and ethambutol (15 mg/kg), or treat with **2 HRZ/4HR**.
- Administer pyridoxine supplementation with INH.
- FQs also require renal adjustment. Assess Renal functional status by calculating creatinine clearance and adjust doses accordingly (See Annex 1).
- In a patient with HIV, TDF can further aggravate renal insufficiency. Substitute by AZT.

TB Treatment of TB/DR-TB in Liver Disease

- In patient with Hepatitis virus infection, a past history of acute hepatitis and current excessive alcohol consumption, but with no clinical evidence of chronic liver disease Treat with standard TB/DR-TB regimen.
- In patients with unstable or advanced liver disease, do baseline liver function tests; If the serum alanine aminotransferase(ALT) level is more than 3 times normal, the following regimens should be considered for DS-TB:
    - 2SERH/6(RH) or 9(RH)E or 2SEH/10(EH) or
    - 18–24 months of streptomycin, ethambutol and a fluoroquinolone with expert consultation and under strict supervision not to amplify resistance, or
    - Treat with Isoniazid & Rifampicin plus Ethambutol for eight months.
- Note that, if the patient has acute hepatitis, defer TB treatment until it resolves.
- Generally SLDs are better tolerated than FLD:
    - Ethionamide, prothionamide, and PAS may cause hepatotoxicity
    - Hepatitis occurs rarely with the flouroquinolones

TB Treatment in patients with neuropsychiatric disorders

Seizure disorders	• If the seizures are not under control, initiation or adjustment of anti-seizure medication will be needed before the start of drug-resistant TB therapy. • Cycloserine should be avoided in patients with seizure disorders. • Other drugs to avoid are high-dose Isoniazid, Imipenim or Meropinim. • Seizures that present for the first time during DR-TB therapy are likely to be the result of an adverse effect of the anti-tuberculosis drugs usually cycloserine or Hh.
Psychiatric disorders	• High baseline incidence of depression and anxiety in patients with DR-TB is often connected with the chronicity DR-TB and socioeconomic stress factors. • The use of cycloserine is not absolutely contraindicated for the psychiatric patients but better to avoid its use in such patients. • Adverse effects from cycloserine may be more prevalent in the psychiatric

	patient, but the benefits of using this drug may outweighs the risk. • Close monitoring is recommended if cycloserine is used in patients with psychiatric disorders. • Patients with psychosis, suicidal ideation or other psychiatric emergencies require urgent psychiatric consultation.
Substance dependence	• Adherence to treatment may be affected. • Drug versus substance interactions could worsen adverse reactions e.g. alcohol may worsen peripheral neuropathy and hepatitis. • Cycloserine will have a higher incidence of adverse effects in patients dependent on alcohol or other substances, including a higher incidence of seizures. • Encourage patients to abstinence from alcohol or other substances.

12. MANAGEMENT OF ADVERSE EFFECTS AND PHARMCOVIGILANCE

Treatment of Tuberculosis with regimen comprised of any of the TB medicines warrants the institution of patient safety measures to optimize treatment adherence, treatment outcome and to improving quality of care during the treatment period. The recommended measures rely on the provision of information on prevention, early identification and proper management of adverse effects caused by TB drug(s). It also introduces pharmacovigilance of anti-TB drugs, both spontaneous and active drugs safety monitoring in the management of drug- resistant TB programs, particularly in treatment centers providing treatment service using newer anti-TB drugs.

12.1 General approaches in early identification and management of adverse effects

Adverse of effects of second line drugs could be frequent and seriously life threatening warranting routine screening using both clinical and laboratory investigation based recommended interval. The general approach in early identification and prompt management of any adverse effect, however, applies to all patients taking TB medicines:

- Educate every patient the potential for adverse drug effects before starting treatment:
  - Review the common adverse effects associated with each drug in the regimen.
  - Inform patients to anticipate that untoward adverse effects of the medicines and advice on how to recognize them.
  - Instruct the patient on how to notify a health care provider, if they develop any concerns about their health while on treatment.
  - Make stress on early warning signs of important complications requiring immediate medical attention. Remember to reassure the patient that the majority adverse effects are temporary and will improve over time.
  - Engage treatment supporter/family members on early reporting.
- Conduct baseline need assessment for additional psychosocial support.
- Prevent/Minimize occurrence of potential adverse effects ADR through: Pretreatment screening of patients for possible concomitant illnesses, avoiding use of drugs known to have overlapping toxicities or potential interactions.
- Arrange for additional close monitoring and management of ADRs in patients with conditions such as: pregnancy, diabetes mellitus, renal insufficiency, acute or chronic liver disease, thyroid disease, mental illness, drug or alcohol abuse and HIV infection.
- At every DOT visit, conduct systematic screening of every patient for adverse effects, and continue supporting them to early recognize and report if they are experiencing them. Give more attention for patients taking second-line drugs.
- Conduct scheduled laboratory monitoring tests as recommended
- Evaluate patients for common ADRs weekly during the intensive phase and at least monthly while in the continuation phase of treatment should be evaluated for ADRs.
- Document every event on the DR-TB treatment card, and report SAEs to EFDA as per national guidance.

12.2 Management Approaches of Adverse effects during treatment

Treatment with first-line drugs is usually safe. The most common disabling adverse reaction is related to hepatotoxicity which requires proper management.

The adverse effects of a number of second-line drugs are highly dose-dependent. Reducing the dosage of the offending drug is another method of managing adverse effects where the reduced dose is still expected to produce adequate serum levels and not compromise the regimen. With cycloserine and ethionamide, for example, a patient may be completely intolerant at one dose and completely tolerant at a slightly lower dose. However, every effort should be made to avoid under dosing.

Temporary suspension of medications can also be used if an adverse effect is particularly resistant to dose adjustment. Complete discontinuation of drugs, however, should be avoided if possible.

Decision to suspend a drug must be made while weighing the risk of continued side effects against the benefit of improving the chances of cure.

Administration of Pyridoxine (vitamin B6), at dose of 50 mg for every 250 mg of cycloserine prescribed to prevent neurological adverse effects.

Adverse effects may be classified according to their severity, as mild, moderate or severe, and their recommended management approach (see table 42 below).

Table 42: Classification and Management of ADRs

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 need to be given. • No need for patient referral to higher level, unless persistent.	• Patient counselling 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 should 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 till recovery. • After recovery of patients' condition, and the offending agent may be substituted with alternative drugs or it may be re-introduced as needed.
Severe	• The common conditions include severe hepatitis, nephrotoxicity, acute psychosis, suicidal ideation or a generalized hypersensitivity reactions • 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.

12.3 Clinical Management of Common Adverse Events of Interest

The clinical management of adverse events of interest, the likely responsible anti-TB drugs and suggested management strategies are presented below. Upon detection of specific adverse events, it should be graded for severity according to the criteria provided in table 45 below.

1. Peripheral neuropathy

- **Possible anti-TB drug causes**: Lzd, Cs/Trd, H, S, Km, Cm, H, FQ, Pto/Eto, E
- **Possible other causes**: d4T, ddI
- Peripheral neuropathy is a common adverse event of MDR-TB treatment caused by drug toxicity to the nerves of the peripheral nervous system.
- All patients taking isoniazid should receive 50 mg of pyridoxine daily; all patients taking Cs/Trd should receive 50 to 100 mg of pyridoxine (doses greater than 100 mg of pyridoxine may cause peripheral neuropathy and therefore lower doses than previously recommended are now the norm).
- Peripheral neuropathy is extremely common in patients taking linezolid. In one clinical trial of linezolid, 55% of the patients experienced clinically significant peripheral neuropathy.
- Skin punch biopsies, nerve conduction studies, or other specialized tests are the gold standard but are not necessary for a diagnosis.
- According to the ACTG Brief Peripheral Neuropathy Screen (BPNS), a patient can be diagnosed with peripheral neuropathy if he/she reports typical symptoms (numbness, tingling, burning, pain) plus decreased vibration sense in the big toes or decreased ankle tendon reflexes. (Please refer to aDSM SOPs for details on clinical testing procedures).
- When assessing the patient's symptoms with the BPNS (See Step 1 of the BPNS description), assess whether his/her symptom is suggestive of neuropathic pain. Although difficult to define and variable for each individual, neuropathic pain is often described as "burning", "electric", "tingling", and "shooting" in nature. It can vary from a constant pain to intermittent sharp shooting pains. As described, the pain is most often present without associated stimulation, but can be exacerbated by stimuli.
- Peripheral neuropathy can be difficult to assess in young children. Symptoms of peripheral neuropathy in young children may include crying when walking or using hands, rubbing or slapping of hands and feet, crying when putting on sock and/or shoes, and difficult walking, grasping, or handling toys. Younger children should have monofilament or pin testing of their hands and feet at each visit and reflexes should be assessed as well.
- After a diagnosis of peripheral neuropathy, the subjective sensory neuropathy score from the BPNS should be used for grading.
- **Management strategy**:
    1. Many patients experience improvement when the offending drugs are suspended, especially if the symptoms are mild.
    2. The neuropathy associated with linezolid is common after prolonged use and often extremely painful and irreversible. For this reason, linezolid should be immediately stopped and not reintroduced when symptomatic neuropathy develops (grade 2 or above). Consider additional anti-TB drugs to reinforce the regimen.
    3. In HIV co-infected patients, avoid use of d4T or ddI in combination with cycloserine/terizidone or linezolid because of an increased risk of peripheral neuropathy.

4. Symptomatic relief:
    - Non-steroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms.
    - Tricyclic antidepressants have traditionally been used to treat neuropathic pain; however, due to their QT prolonging characteristics (and because they may increase the risk of arrhythmias) are best avoided when using all-oral regimens that contain drugs that may also prolong the interval. Tricyclic antidepressants should also be avoided in patients taking linezolid to avoided due to potential risk of serotonergic syndrome.
    - Carbamazepine may also be effective in relieving pain and other symptoms of peripheral neuropathy. Carbamazepine is a strong inducer of CYP3A4 and should not be used with bedaquiline or delamanid.

2. Myelosuppression (anemia, thrombocytopenia, or neutropenia)

- Possible anti-TB drug causes: Lzd
- Possible other causes: AZT, cotrimoxazole
- The mean corpuscular volume (MCV) may be helpful to assess whether anemia is normocytic versus microcytic versus macrocytic. Macrocytic anemia is more likely to be due to AZT, but AZT can also induce a normocytic anemia.
- If the patient has thrombocytopenia or neutropenia, this is more likely to be due to linezolid. AZT can do this, but it is rare.
- Myelosuppression is very common in patients receiving linezolid. In one clinical trial of linezolid, approximately 18% of patients taking linezolid experienced clinically significant myelosuppression.
- Acute blood loss (occult GI bleeding from a peptic ulcer) can cause anemia.
- Other causes of anemia (TB, iron-deficiency, etc.) are possible, but less likely to occur in the middle of treatment, especially if the patient is clinically improving.
- **Management strategy**:
    1. Stop the causative drug immediately for Grades 3 or 4; consider dose reduction for Grades 1 or 2.
    2. If iron-deficiency anemia is suspected to be contributing to the anemia where linezolid toxicity is involved, check iron stores and treat if iron-deficiency is diagnosed. Empiric treatment with iron can be done if testing for iron-deficiency is not possible. Note, oral iron may bind with the FQ and decrease the absorption of the FQ. Dose iron at least 3 hours apart from the FQ.
    3. Monitor full blood counts regularly.
    4. If erythropoietin is available, consider using for anemia Grades 3. (Most programs manage anemia secondary to linezolid toxicity without erythropoietin, with good antidotal outcomes).
    5. Hospitalize the patient and consider transfusion (or erythropoietin) if the myelosuppression is severe.
    6. Consider additional anti-TB drugs to reinforce the regimen if linezolid is being permanently stopped.

Erythropoietin (EPO) use in Myelosuppression

- Treatment with erythropoietin is not intended for patients who require immediate correction of anemia (Grade 4). In this case, blood transfusions should be considered. Whole blood count should be repeated weekly to assess the response to treatment. Blood pressure should be adequately controlled before initiation and monitored during therapy. Erythropoietin treatment should in any case be discontinued at hemoglobin levels over 12 g/dL. Erythropoietin is not effective if there is significant iron deficiency present.

Contraindications for EPO use

- Erythropoietin treatment should be administered with caution in the presence of:
  - Untreated, inadequately treated or poorly controlled hypertension
  - Epilepsy
  - Thrombocytosis
  - Chronic liver failure
  - Hyperkalemia

Presentation of EPO

- Epoetin alfa pre-filled syringes of 10,000 UI or 40,000 IU/ml to be stored in cold chain (2°C to 8°C).

Dosing of EPO

- Epoetin alfa: 150 IU/kg three times a week or 450 IU/kg once a week, subcutaneously or intravenously.

3. Prolonged QT interval

Possible anti-TB drug causes: Cfz, Bdq, Mfx, Dlm, Lfx

Possible other causes: Many other drugs can cause QT prolongation. For example: erythromycin, clarithromycin, quinidine, ketoconazole, fluconazole, and antipsychotics – all have some risk including haloperidol, chlorpromazine, and risperidone. Many anti-nausea drugs (ondansetron/granisetron, domperidone), methadone, and some antiretrovirals, in addition to genetic causes such as long QT syndrome and hypothyroidism can also cause QT prolongation.

- Check an ECG if the patient has clinical symptoms (tachycardia, syncope, palpitations, or weakness or dizziness) of cardiotoxicity. Check the QT interval and rule out an arrhythmia.
- Please refer to the aDSM SOPs for details on measuring corrected QT intervals and ECG procedures.
- The QTc will be calculated using the Fridericia's formula which corrects for the heart rate and has been shown to be more accurate at slower or faster heart rates than other correction formulas:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Where:

- QTcF = the corrected QT interval
- QT = the time between the start of the QRS complex and the end of the T wave
- RR = the time between the start of one QRS complex and the start of the next QRS complex

Checking and repleting serum electrolytes:

- Serum potassium (K+), ionized calcium (ionized Ca++), and magnesium (Mg++) should be obtained in the event a prolonged QT interval is detected. In the event that ionized calcium and magnesium is not able to be checked, give empiric magnesium whenever hypokalemia (low potassium) is found.
- Abnormal electrolytes in all oral STRs are most commonly due to vomiting or diarrhea, as the injectable is not used. The vomiting or diarrhea should be assessed and treated.
- Whenever a low potassium is found to be Grade 3 or 4, it should trigger urgent management with replacement and frequent repeat potassium testing (often daily or multiple times a day) to document if potassium is moving in the correct direction.

Clinical management strategy for Prolonged QT interval:

1. Stop all QT prolonging drugs immediately. ART is usually not stopped unless the patient is severely unstable.
2. Hospitalize and consider continuous electrocardiac monitoring for Grade 3. Hospitalization should occur in a facility capable in the management of Torsades de Pointes arrhythmia.
3. Check electrolytes and manage as described above.
4. Check TSH and treat any hypothyroidism found.
5. Once stable (QTCF interval below 450 and normal electrolytes), critical QT prolonging anti-TB drugs can be added back:
    - If the patient is on any non-TB drugs that are prolong the QT interval, consider suspending them.
    - If the patient is on moxifloxacin, consider using levofloxacin instead.
    - If the patient is on clofazimine, consider suspending it permanently if not critical to the regimen.
    - If the patient is on bedaquiline and it is considered critical to the regimen, consider adding the drug back to the patient's regimen while suspending all other QT prolonging drugs (with the exception of stopping ART, which should not normally be suspended in the management of QT prolongation).
    - If the patient is on delamanid and it is considered critical to the regimen, consider adding the drug back to the patient's regimen while suspending all other QT prolonging drugs (with the exception of stopping ART, which should not normally be suspended in the management of QT prolongation).

4. Optic nerve disorder (optic neuritis)

Possible anti-TB drug causes: Lzd, E, Eto/Pto, rifabutin, H, S

Possible other causes: ddI

- Optic neuritis is inflammation of the optic nerve eventually resulting in permanent vision loss. The first sign of optic neuritis is usually the loss of red-green color distinction. This is best tested using the Ishihara test (The procedures and interpretations for Ishihara test is described in aDSM implementation SOPs). Other symptoms include central scotomas.
- Linezolid is by far the most common cause of optic neuritis amongst all of the TB drugs. In a clinical trial of linezolid, 18% of patients eventually developed optic neuritis, mostly after four months of treatment.

- Patients with diabetes are at increased risk for optic neuritis. They should be managed with tight glucose control as a means of prevention. Patients with advanced kidney disease are also at increased risk for optic neuritis.
- Visual acuity may be difficult to formally assess in young children and age-appropriate visual screening tests should be used. Visual acuity can also be assessed with object tracking, especially using bright objects or toys. Symptoms of diminished visual acuity in children may include bumping into walls or objects, tripping, and inability to grasp or find objects.
- **Clinical management strategy**:
    1. Do not restart the suspected causative drug (linezolid or ethambutol).
    2. Refer patient to an ophthalmologist for immediate evaluation and management.
    3. Optic neuritis generally improves following cessation of offending drug, if it can be stopped early enough.
    4. Consider additional anti-TB drugs to reinforce the regimen.

5. Elevated liver enzymes (hepatotoxicity)

- **Possible anti-TB drug causes**: Z, H,R, Cfz, PAS, Eto/Pto, Bdq, FQ, Amx/Clv
- **Possible other causes**: viral hepatitis (A, B, C), NVP, many other drugs, alcohol
- Hepatitis is characterized by nausea, vomiting, jaundice, scleral icterus, tea-colored urine, pale stool, and diminished appetite in the setting of elevated liver function tests.
- Mild elevation of liver enzymes(especially at baseline)may be related to TB rather than an adverse effect of treatment.
- Generally, hepatotoxicity due to medications resolves upon discontinuation of suspected drug.
- In HIV co-infection, cotrimoxazole can be a cause of hepatotoxicity.
- NVP hepatotoxicity usually occurs shortly after exposure, accompanied by flu-like symptoms with or without rash. It can also happen late as an isolated hepatitis without constitutional symptoms. Patients who experience NVP hepatotoxicity should not be re-challenged.
- Chronic alcoholism is a major cause of hepatotoxicity in patient with RR-/MDR-TB. If alcohol is considered to be contributing to the hepatotoxicity, treatment for alcohol addiction may be need in order to help the patient abstain from alcohol.
- **Management strategy:**
    1. If elevated liver enzymes ≥3 times the upper limit of normal in the presence of symptoms or ≥5 times the upper limit of normal in the absence of symptoms and/or a total bilirubin >2 are found, anti-TB medications should be stopped. Other causes of liver disease should be excluded (biliary disease, pancreatitis, gastritis, infectious hepatitis), but often drug-induced hepatitis from one of the anti-TB drugs is likely.
    2. Treatment with drugs which are hepatotoxic should be held **until liver enzymes return to less than twice the upper limit of normal** at which time they can be re-introduced with careful follow up of liver enzymes for 5–7 days. In most patients (90%), there is no repeated rise in liver enzymes. For the 10% who have repeated hepatotoxicity, a predominant hepatitis picture is associated with INH and a predominant obstructive picture, especially with a raised bilirubin, is associated with Rifampicin.

3. Anti-TB drugs should be reintroduced in serial fashion by adding a new medicine every three to four days. The least hepatotoxic drugs should be added first, while monitoring liver function tests after each new exposure.
4. Consider suspending the most likely offending drug permanently if it is not essential to the regimen. This is often the case for pyrazinamide if it is less likely to be effective by clinical history. Consider additional anti-TB drugs to reinforce the regimen.
5. Using an injectable drug (Streptomycin or Amikacin) and ethambutol can protect against drug resistance when re-introducing a single drug.

6. Hypokalemia

- **Possible anti-TB drug causes:** Cm, Km, Am, S
- **Possible ART causes**: TDF (rare)
- **Other causes**: Vomiting, diarrhea
- Hypokalemia and hypomagnesemia are often asymptomatic.
    - Moderate cases may present with fatigue, myalgia, cramps, paresthesia, lower extremity weakness, behavior or mood changes, somnolence, and confusion.
    - Severe disturbances can lead to tetany, paralysis, and life-threatening cardiac arrhythmias.
- Hypokalemia and hypomagnesemia are common in patients receiving MDR-TB treatment.
- Common causes in MDR-TB patients are:
    - Vomiting and diarrhea
    - Renal tubular toxicity from the injectable (probably more common in capreomycin than the aminoglycosides). None of the commonly used drugs in the all-oral STR cause electrolyte wasting or renal tubular toxicity
- Formulations of oral potassium chloride vary by manufacturer and country. Slow-release versions are common in resource-limited settings. The amount of potassium is often different than the tablet size. For example, one 200-mg tablet of Slow-K contains 8 mEq of potassium.
    - Oral potassium and magnesium should be administered either two hours before or four to six hours after fluoroquinolones as they can interfere with fluoroquinolone absorption.
    - Oral potassium can cause nausea and vomiting. Oral magnesium can cause diarrhea.
- Dietary intake of potassium should be encouraged. Bananas, oranges, tomatoes are good sources of supplementation.
- **Management strategy:**
    1. Monitor serum potassium, magnesium, and calcium frequently in patients with vomiting/diarrhea and patients receiving injectables.
    2. Check for signs of dehydration in patients with vomiting and diarrhea. Start oral or intravenous rehydration therapy immediately until volume status is normal.
    3. Replete potassium and magnesium.
        - Hypokalemia may be refractory if concurrent hypomagnesemia is not also corrected.
        - If unable to check serum magnesium, give empiric oral replacement therapy in all cases of hypokalemia with magnesium gluconate 1000 mg twice daily.

- In all cases of detected serum electrolyte disturbances (Grades 1-4) obtain an electrocardiogram as soon as possible and then weekly until potassium and other electrolytes return to normal.
- Drugs that prolong the QT interval should be discontinued in patients with evidence of QT interval prolongation in the presence of Grade 2 or above hypokalemia.

Table 43 Potassium Replacement Therapy

Potassium level (mmol/L)	Dosing	Monitoring frequency
> 3.4	None	Monthly
3.3 -3.4	40 mmol PO in 2-3 divided doses daily	Monthly
2.9 -3.2	60-80 mmol PO in 3 divided doses daily	Weekly
2.7- 2.8	60 mmol PO every eight hours	One to two days
2.5 -2.6	80 mmol PO every eight hours	Daily
<2.5	10 mmol/hour IV and 80 mmol 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 mmol (3 ampoules) in 1L of NaCl 0.9% infused over 4 hours. Do not exceed an infusion rate of 10 mmol/hour (250 mL/hour). Potassium chloride 10% (100mg/ml) ampoules = 1g per ampoule = 13.4 mmol. Potassium chloride controlled release tablets of 600mg = 8mmol/tablet.		

Table 44 Magnesium Replacement Therapy

Magnesium level (mmol/L)	Total Daily Dose	Monitoring frequency
> 0.70 or more	None	Monthly
0.60-0.70	1,000 mg – 1,200 mg	Monthly
0.45-0.59	2,000 mg	One to seven days
< 0.45	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 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).		

7. Hypothyroidism

- **Possible anti-TB drug causes**: Eto/Pto, PAS
- **Possible ART causes**: d4T
- None of the drugs commonly used in the all-oral STR are associated with thyroid toxicity; however, patient may have a history of receiving TB drugs that are thyroid toxic.
- Ethionamide (or prothionamide) and PAS have a direct toxic effect on the thyroid that interferes with thyroid hormone synthesis. The exact incidence of hypothyroidism is unknown, but it is probably more common than traditionally thought.
- Patients may develop symptoms as soon as a few weeks after exposure to offending medications.

- Symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, as well as depression and inability to concentrate. Thyromegaly and delayed deep tendon reflexes may be encountered on exam.
- In primary hypothyroidism, the diagnosis is confirmed by a serum level of TSH greater than 10.0 mU/L, indicating suppression of the thyroid hormone production by the thyroid gland. No other thyroid tests (e.g., free T4, T3) are necessary for diagnosis or treatment monitoring.
- In HIV coinfected patients there is some evidence that subclinical hypothyroidism may be associated with some ARVs, particularly stavudine (d4T).
- Hypothyroidism can result in QT interval prolongation. Check an ECG whenever hypothyroidism is found and if QT interval prolongation or an arrhythmia is found refer for hospitalization and appropriate management.
- **Management strategy:**
- In patients with hypothyroidism, most adults will require 100 to 150 mcg of levothyroxine daily.
    - Young healthy adults can be started on 75 to 100 mcg daily.
    - Older patients should begin treatment with 50 mcg daily.
    - Patients with significant cardiovascular disease should start at 25 mcg daily.
- Children clear thyroxine faster than adults, so daily replacement doses may be higher.
    - Children (4-15 years): 4 mcg/kg/day (maximum dose is 200 mcg).
    - Infants (1-3 years): 10-15 mcg/kg/day (maximum dose is 200 mcg).
- Monitor TSH every 1 to 2 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.
- Hypothyroidism is reversible upon discontinuation of ethionamide/prothionamide or PAS. As a result, thyroid hormone replacement may be stopped several months after completion of MDRTB treatment.

Table 45: Clinical Management of Adverse Events of Interest during DR-TB Treatment according to severity grading

1. Peripheral Neuropathy				
Criteria and Actions Required	Severity Grade			
	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Life-threatening
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 sensory neuropathy score 7- 10 on any side.	Incapacitating; or not responsive to narcotic analgesia
Actions	Stop Cs/Trd, highdose 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/Trd or high dose H are not essential to the regimen, consider suspending these drugs.	Stop Cs/Trd, highdose H, and Lzd. If symptoms improve, and if the drugs are essential to the regimen, consider restarting Cs/Trd or high-dose H. Do not re-introduce Lzd. Provide symptomatic relief as described below.	Same as Grade 2.	Same as Grade 2.
2. Myelosuppression				
Anemia	Hgb 10.5 - 9.5 g/dL	Hgb 9.4 - 8.0 g/dL	Hgb 7.9 - 6.5 g/dL	Hgb < 6.5 g/dL
Platelets decreased	99,999 - 75,000 /mm^3	74,999 - 50,000 /mm^3	49,999 - 20,000 /mm^3	< 20,000 /mm^3
White blood cells decreased	<LLN- 3000/mm^3	<3000 – 2000 /mm^3	<2000 -1000/mm^3	<1000/mm^3
Absolute neutrophil count low	1,500 –1,000/mm3	999 - 750/mm3	749 - 500/mm3	<500/mm^3
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). For Grade 2 neutropenia, stop Lzd immediately.	Stop Lzd immediately. For Grade 3 anemia, consider erythropoietin (if available). Restart Lzd 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.
3. 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 de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia
Action	Monitor more closely; at least weekly ECG until QTcF has returned to less than grade 1.	Monitor more closely; at least weekly ECG until	Stop the suspected causative drug(s).	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.

	Replete electrolytes as necessary.	QTcF has returned to less than grade 1. Replete electrolytes as necessary.	Hospitalize and replete electrolytes as necessary.	
4. Optic nerve disorder				
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 in the affected eye: 20/200 [6/60] or worse
Action	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.
5. Hepatotoxicity (elevated liver enzymes)				
ALT (SGPT)	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
AST(SGOT)	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Action	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Stop all drugs, including anti-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.	Stop all drugs, including anti-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.
6. Hypokalemia and Hypomagnesemia				
Hypokalemia				
	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Grade 4: Life-threatening
Hypokalemia	3.4 - 3.0 mmol/L	2.9 - 2.5 mmol/L	2.4 - 2.0 mmol/L or Intensive replacement therapy or hospitalization required	< 2.0 mmol/L or abnormal potassium with paresis, ileus or life-threatening arrhythmia
Action	Start oral potassium replacement therapy. Check serum magnesium and replace if necessary.	Start aggressive oral Potassium replacement therapy. Replace magnesium as necessary.	Start IV potassium Replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary.	Start IV potassium Replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary.
Hypomagnesemia				
Hypomagnesemia	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 IV Magnesium replacement therapy in addition to oral. Replace other electrolytes as necessary.	Start IV Magnesium replacement therapy in addition to oral. Replace other electrolytes as necessary.
7. Hypothyroidism				
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 consequences; 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.

12. 4 Pharmacovigilance /Drug safety monitoring

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse events in patients being treated with drugs.

The safety, efficacy /performance and quality of medicines shall be assured throughout their life cycle starting from manufacturing until they are used by patients. The national medicine regulatory agencies are legally mandated to undertake major regulatory functions including market authorization, quality control lab testing, regulatory inspection (Good manufacturing practice and supply chain inspection), pharmacovigilance, market surveillance and control, and clinical trial monitoring to ensure the safety, efficacy, quality, and rational use of the medicines and medical devices.

The Ethiopian Food and Drug Control Authority (EFDA), a national regulatory agency, is mandated as per the proclamation 1112/2019, to ensure the safety, quality and efficacy of medicines and medicine devices by undertaking the major regulatory functions including market authorization, quality testing/, regulatory inspection (Good manufacturing practice and supply chain inspection), pharmacovigilance, market surveillance and control and clinical trial monitoring. No medicine and medical devices, obtained either from locally manufacturers or foreign source, can be marketed and made available for use in the country without market authorization or permission from EFDA. EFDA is authorizing marketing or availability for use of medicine and medical devices in the country after ensuring the safety, efficacy, and quality of medicines and medical devices through dossier evaluation, Good Manufacturing Practice Inspection, and Laboratory Quality testing, as well as issuing pre-import approval and port clearance permit. EFDA is also undertaking and coordinating post-market or use surveillance: including undertaking regulatory inspection, marketing surveillance and control, and pharmacovigilance to ensure safety, efficacy and quality of medicine and medical device after are made available for use in the country.

The National Pharmacovigilance (PV) system

The Ethiopian PV system was established in 2002 with a national PV center with subsequent establishment of sub-national/regional PV centers. It is guided by national PV directives, national PV guidelines and ADR reporting tools including the pre-paid yellow paper, electronic and MEDSAFETY ADE /ADR reporting tools. To support the coordination efforts, EFDA has established a national Pharmacovigilance advisory committee. The national PV center under EFDA has become the member of WHO UPSALLA drug monitoring center and is reporting ADR to the WHO drug monitoring center; undertake signal detection and risk – benefit management and had carried out regulator measures on such basis.

Active pharmacovigilance is considered one part of optimal management of adverse events in patients who are being treated for DR-TB. New TB drugs and regimens require active PV that follows practices that are part of good clinical care for individuals with DR-TB, including frequent and routine monitoring, assessment of symptoms, and actions taken to respond to any symptoms or abnormalities detected.

Scope of safety monitoring/data collection and definitions

Pharmacovigilance is in place to ensure timely detection and proper transmission of information relating to drug safety, especially adverse events.

Definition of common terms in Pharmacovigillance:
An adverse event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and that 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, whether or not related to this medicinal product. AE includes also adverse drug reaction (ADR), Medication Error (ME), or Product Quality Defect (PQD).
Adverse drug Reaction: A response to a drug which is noxious and unintended which occurs at doses normally used for prophylaxis, diagnosis, treatment and physiological modification.

An unexpected ADR –Any reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or is unexpected from characteristics of the medicine.
Passive surveillance-is a system in which regulatory authorities and pharmaceutical companies wait for healthcare professionals, patients, or consumers to make the effort to contact the authority or company to spontaneously report an encountered adverse drug event. It is also called voluntary reporting.

Active surveillance- systems or situations in which adverse events are purposely sought in the post marketing setting by a health authority's request to all physicians to report an adverse drug event of a particular drug or class of drugs in the form of prompted reporting or stimulated reporting or observational studies to more closely follow, identify and investigate on a potential or weak signal.
Medication error is defined as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use.
Product quality defect- is quality problem of products with suspected contamination, questionable stability, defective components, poor packaging and labeling and therapeutic failure.
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.

Roles and responsibilities in Pharmacovigilance

The following section describes the roles and responsibilities for the stakeholders involved in activities to minimize the risk of medicine-related injuries or Pharmacovigilance.

1. Patients and Consumers-

Patients who suspect they have been affected by an adverse drug event should report to any health care professional including the one that had prescribed, dispensed or administered the drug that has caused the adverse drug event .This will then enable the health professional to report the medicine-related problems to the University hospital based regional Pharmacovigilance centers at regions or the Pharmacovigilance center at EFDA.

2. Healthcare professionals-

All healthcare professionals have a very important role to highlight problems occurring when a marketed medicinal product is used. They need to alert the EFDA about suspected adverse drug reactions, medication errors and product quality problems in order for the authority to take action in preventing or minimizing the occurrence of the medicine-related injury for other patients in the future.

The activities that healthcare professional need to perform when encountering an adverse drug event should include

A. Being vigilant and detecting adverse drug events-

Patients and healthcare professionals have the challenging task to monitor and be alert for possible medicine-related problems. It is important that clinicians are vigilant and perceptive towards any unexpected sign, symptom or complaint voiced by patients taking medicines, particularly in the early phases of treatment.

Distinguishing between the natural progression of a disease and an adverse effect by a medicine can be difficult. When an unexpected event, for which there is no obvious cause, occurs in a patient taking a medicine, the possibility that it is caused by the medicine or its use must always be considered.

Healthcare professionals should monitor for medication errors whilst prescribing, transcribing dispensing and administering medicines to patients.

Health professionals should make physical inspections of the medicinal product to be dispensed or administered. Pharmacy professionals have an important role in the work of detecting product quality defects. Color changes, separating components, powdering, crumbling, caking, molding, change of odor, incomplete pack, suspected contamination, poor packaging/poor labeling should be acknowledged.

B. Assessing the patient –

When a medicine-related problem is suspected, the clinician should carry out a thorough physical examination with appropriate laboratory tests and consider the patient's medical history, including history of a similar reaction or allergy; the existence of any potential risk factors, such as hepatic or kidney insufficiency; the existence of risk groups such as pediatric, elderly, pregnant and lactating patient.

C. Managing the encountered adverse event-

If an adverse drug reaction is suspected, the health care professional should treat the patient and consider to adjust the dose, replace the medicine or withdraw the medicine.

The patient should be informed about the suspicion of the adverse drug reaction and what actions are planned. Careful documentation of the adverse drug reaction in the patient's medical records should take place. Documenting and informing the patient is important to avoid future problems.

If a medicine has caused an allergy, the EFDA "Allergy card" is recommended to be used.

The purpose of the Allergy card is to prevent patients from being prescribed again the medicines for which they are allergic in the first encounter. Patients should then carry the card with them and present it to any health facility at upcoming visits.

If the event is believed to be caused by a medication error, action should be taken according to the hospital or healthcare facility routines in order to avoid similar problems in the future. Accordingly the adverse drug reaction, medication error or product quality defects encountered should be reported to EFDA immediately as described below.

D. Reporting and adverse drug event (How to report)

Suspected adverse drug events (adverse drug reactions, detected medication errors or product quality defects) should be reported to the Pharmacovigilance center at EFDA. Reporting can be done using any of the four available mechanisms described below:

1. Online reporting system accessed through http://www.fmhaca.gov.et/. Click on the ***Services*** tab of the website and then finally click on the ***e-reprting of ADR*** function to access the online reporting form.
2. The **yellow**, **prepaid report form** available at the facility (Annex 4)
3. The **Medsafety** mobile application that can be downloaded from Google play store for Android phones or and **the APP store for IOS users,** creating an account using an email address and then entering through the "new report" button and filling the information on the adverse drug event that is going to be reported.
4. **8482** (toll free line) or Telephone 01115523142(direct) or 0115524122(via operator)

Further, a monthly line listing excel sheet form is also used to report the monthly encountered adverse drug events. The excel sheet contains all the necessary data that is necessary to report an adverse event.

All adverse drug events ranging from minor reactions to disability or death should be reported. However there is a need to emphasize the reporting of suspected adverse drug reactions to new medicines, serious adverse drug reactions, unexpected reactions and drug interactions. If the event occurred in a university hospital Pharmacovigilance center it is very important to communicate with the adverse drug reaction focal person available to get the necessary support in the reporting process. These focal persons are also available in other health facilities and are designated by the facility to support Pharmacovigilance activities.

The reporter does not need to prove that there is a causal association between drug and adverse reaction. Therefore, uncertainty of the cause and effect relationship should not be a reason for not reporting. In addition as stated in the National Pharmacovigilance Guideline of Ethiopia, it should be understood that reporting an ADR will not lead to any blame on the reporters and will not be used for any legal action.

E. Timelines of reporting(when to report)

Any suspected adverse drug reaction, medication error or quality defect should be reported as soon as possible after all relevant information is compiled. Delay in reporting will make reports inaccurate and unreliable. Reporting while the patient is still in the health institution will give chance to the reporter to clear any ambiguity by re-questioning or examining the patient. When the reports have been received by EFDA, an acknowledgement letter will be sent to the reporter and follow-up questions might need to be answered.

Any follow-up information for an event that has already been reported can be sent on a new adverse drug event report form to EFDA. Clearly indicate that the report is a follow-up information related to an already reported event and indicate the report case number (available on the acknowledgement letter), so that this information can be matched with the original report. It is very important that follow-up reports are identified and linked to the original report to avoid duplications of reports in the Pharmacovigilance database.

3. Drug and Therapeutic Committee/DTC at healthcare facilities

The Drug and Therapeutic Committee is a technical working group established at health care facilities with representative members from each department with the aim of managing medication use problems. Using the information on medicine safety, the DTC should revise the facility specific medicine list and promote rational use of medicines.

The DTC should also implement programs to track adverse drug reactions, medication errors and product quality defects and use the information to improve healthcare. Programs could involve review of adverse drug events, medication errors or near misses, patient chart review, or physical inspection of products. It needs the involvement of all health professionals as a team to identify problems with medicines, setting standards and monitoring practice. The facility should also assign a focal person to coordinate all ADE monitoring activities in the facility and serve as a link between the facility safety monitoring activities and the national Pharmacovigilance centre.

4. Public health programmes

The monitoring of the safety of medicines of public health programmes like TB control program is crucial for the successful implementation of the programmes. Hence public health programmes should collaboratively work with EFDA starting from the inception of the specific programmes and throughout the implementation period by encouraging the users of the medicines and healthcare professionals to report any adverse drug events encountered through the use of the available reporting mechanisms of the national Pharmacovigilance system.

5. Decentralized Pharmacovigilance centers

Currently there are five decentralized Pharmacovigilance centers in five specialized referral hospitals throughout the country; Hawassa university hospital (Hawassa), Ayder university hospital(Mekele),Gonder university hospital(Gonder), Tikur Anbessa Comprehensive Specialized hospital(Addis Ababa University College of Health Sciences, Addis Ababa), Jimma university hospital (Jimma).These centers are empowered to provide training to healthcare providers in their catchment area to enable them report adverse drug events. Any adverse drug event report on medicines of health care programmes like TB could also be reported to these centers which will then analyze and send the report to EFDA.

6. Branch EFDA, and regional regulators

The role of the six EFDA branches that are available in the country at Jimma, Komblocha, Bahirdar, Hawassa, Diredawa and Mekelle and the regulators that are available at each of the eleven health bureaus in the monitoring of safety of medicines of public health programmes is significant. Most importantly, as they are closer to the health facilities, their role in inspection, investigation and sampling of medicines that have adverse events is vital.

PV Data management - What happens after a report is sent to the EFDA?

As the primary role and mandate of EFDA is to ensure that marketed medicines are safe and of quality, the experts at the Pharmacovigilance center perform the necessary data management activities after an adverse drug event report is received. These activities are-

1. Report entry

Pharmacovigilance experts at the center enter the incoming reports into the national Pharmacovigilance database which is ***vigiflow***. Each report is classified as an adverse drug reaction, medication error or a product quality problem. The recipient of the report will carefully review the report for the quality and completeness of the filled information obtained in the report form.

The center then provides an acknowledgment feedback to the reporter and might request information in case of missing pertinent data. Causality assessment is performed and the report is classified according to the WHO causality criteria. Causality assessment can also be performed at the regional Pharmacovigilance centers which are sending reports to the national center. The assessment can then be verified and finalized to be sent to Uppsala monitoring center of WHO.

The outcome of the report, together with any important or relevant information relating to the reaction will be communicated to the appropriate stakeholders.

2. Analyzing to detect signals.

The Pharmacovigilance experts at the EFDA review each incoming report (adverse drug reaction, medication error, product quality defect) individually to detect any medicine-related problems that need immediate action.

The authority works towards detecting new potentially causal drug and event associations, or a new aspect of a known association, i.e. a signal which could be-

1. Previously unknown adverse drug reactions
2. Increases in frequency of known adverse drug reactions
3. Risk groups, risk factors and possible mechanisms underlying adverse drug reactions.

A signal can initially be detected in a single incoming report. The literature, the WHO Signal document and the WHO Pharmaceutical Newsletter should be regularly screened to detect medicine-related problems relevant for the country. Each year, a summary of the reports received during the past year is produced and evaluated.

In addition, post marketing surveillance to detect product quality defects is performed by the EFDA. Samples of any product in the market are collected from various premises in a determined frequency per year. The samples are tested in the EFDA laboratory. Regulatory inspection is also carried out by regional responsible offices to detect product quality defects.

1. **Assessing for potential signals**

Each detected potential signal will undergo further evaluation. The WHO database, published literature and information from the market Authorization Holder are reviewed for similar cases. The National Pharmacovigilance safety Advisory Committee is provided summary information for evaluation. The committee recommends what action needs to be taken, i.e. if it is a signal that needs to be acted upon, it is not signal, or if further monitoring is needed.

2. **Taking regulatory measures**

Based on the result of the different evaluations carried out and if necessary using the quality control laboratory investigation results, and the recommendation obtained from the Pharmacovigilance advisory committee, regulatory measures will be taken on the specific medicine used in the public health programme so that appropriate actions are taken. The regulatory actions might range from warnings on the use of the specific medicine to the withdrawal or recall of the medicine and suspension from use by the programme.

Active Drug Safety Monitoring and Management (aDSM) in DR-TB Treatment

Adverse reactions are a significant cause of morbidity and mortality and can affect adherence to treatment schedules and increase the risk of resistance and relapse of the disease.

The treatment of ADRs imposes a largely unrecognized, but considerable, financial burden on health care due to the need for hospital care or other medical interventions.

Requirements for PV in public health:

The ultimate goal is for the success of the public health program through: rational and safe use of medicines by health professionals; assessment and communication of the risks and effectiveness of medicines used; and educating and informing patients.

Why pharmacovigilance for anti-TB medicines?

- TB patient on treatment is taking more than one anti-TB medicine simultaneously and regimens last from many months to 2 years or more. This increases the likelihood of ADRs, some of which are severe. Most patients on treatment for drug-resistant TB experience at least one side-effect. A recent study has shown that two thirds of such patients have had at least one medicine stopped temporarily or permanently as a result of ADRs. These events may damage public confidence in any national treatment program and affect patient adherence. Patients who stop taking antiTB medicines pose a risk to themselves and to others. The generation and transmission of drug resistance is a very real risk. The

contribution of ADRs to death, treatment interruptions and failure can therefore only be conjectured.

- Secondly, the widespread recognition by health workers that anti-TB medicines often cause ADRs is poorly reflected in the published information on the subject
- Thirdly, with the increasing use worldwide of more extensive regimens for drug-resistant TB, the added use of antiretrovirals (ARVs) in patients with HIV-associated TB, and the imminent advent of new classes of medicines to treat TB, the case for improved pharmacovigilance becomes even stronger.

Different approaches to pharmacovigilance for TB drugs

1. **Spontaneous (or voluntary) reporting**: No active measures are taken to look for adverse effects. Reporting of events responsible for patient safety is entirely dependent on the initiative and motivation of the health care professionals and sometimes the patients. This is the most widespread form of PV globally.
2. **Targeted reporting**: It focuses on adverse drug reactions in a well-defined group of patients on treatment. Health professionals in charge of the patients are sensitized to report specific safety concerns. This focused approach has the same objectives and uses the same flow of information as for spontaneous reporting. The reporting requires no screening to look for the particular syndromes.
3. **Active pharmacovigilance**: Measures are taken proactively to detect safety concerns. This 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.

Rationale for Active Pharmacovigilance

Its rationale is based on recent developments in MDR-TB treatment, particularly the approval for use of new medicines ahead of the completion of Phase 3 trials, increased use of repurposed drugs for XDR-TB treatment and the development of novel second-line anti-TB regimens. Such approaches need careful monitoring for drug-related harms, some of which may as yet not be described.

Active Drug Safety Monitoring and Management (aDSM)

Active Drug Safety Monitoring and management (aDSM) is defined as the active and systematic clinical and laboratory assessment of patients while on treatment. It applies to patients on treatment

with new anti-TB drugs; novel MDR-TB regimens; or XDR-TB regimens, in order to detect, manage and report suspected or confirmed drug toxicities.

The appropriate and timely management of all AEs and ADRs is an integral component of active pharmacovigilance and patient care.

Objectives of aDSM

The overall objectives of aDSM are to reduce risks from drug-related harms in patients on second-line treatment for drug-resistant TB and to generate standardized PV data to inform future policy updates on the use of such medicines

Specific objectives are:

- To ensure that patient safety is monitored alongside the effectiveness of the treatment
- To characterize known ADRs
- To ensure the earliest possible recognition of new ADRs, including interaction with other medicines, complementary and alternative medicines, foods and concomitant diseases
- To detect inefficacy, which might be due to: faulty administration; poor storage conditions; poor quality product; counterfeit product; or interactions.
- To measure risk (incidence), including comparative risk of different anti TB regimens or individual medicines.
- To identify risk factors for the important reactions so that appropriate risk management can be applied and the risk of harm minimized.
- To assess safety during pregnancy and lactation.
- To provide evidence for: effective risk prevention and management; safer use of anti-TB therapy; the benefits versus harm of different regimens or products; evidence-based regulatory action.
- To provide potential cohorts for further study of safety issues if required in the future.

Three essential activities in Active PV

1. Patients targeted for active PV should undergo active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs.
2. All AEs detected should be managed in a timely fashion in order to deliver the best possible patient care
3. Standardized data should be systematically collected and reported for any SAE detected

Reportable Events

- Serious Adverse Events (SAEs)
- Adverse events of interest (AEIs)
- Others: AEs leading to treatment discontinuation or change in drug dosage, AEs events judged as otherwise clinically significant, Pregnancy, Medication errors

AEs of clinical significance or special interest for Active Pharmacovigilance:

- All serious adverse events (SAEs)
- All adverse events of special interest (AEIs)
- AEs leading to treatment discontinuation or change in drug dosage
- AEs not listed above but judged as otherwise clinically significant by the clinician

Serious Adverse Events (SAEs): defined as any untoward medical occurrence that, at any dose:

1. Results in **death**,
2. 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
3. Requires **hospitalization** or prolongation of hospitalization,
4. Results in persistent or significant **disability/incapacity**,
5. Results in/Is a **congenital anomaly or a birth defect**,
6. 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. Suspected transmission of an infectious agent (e.g. pathogenic or non-pathogenic) via drug is always considered an SAE.

AEs of interest (AEI)*:* Defined as all AEs regardless of their seriousness, severity or causal relationship to the TB treatment, pertaining to the following medical conditions.

- Peripheral neuropathy
- Myelosuppression (anemia, thrombocytopenia, or neutropenia),
- Prolonged QT interval,
- Optic nerve disorder (optic neuritis),
- Hepatitis,
- Hearing impaired,
- Acute kidney injury,
- Hypokalemia, and
- Hypothyroidism.

Adverse events leading to treatment discontinuation or change in drug dosage: Defined as all AEs regardless of their seriousness, severity, or causal relationship to the DR TB treatment, leading to a discontinuation of DR TB treatment, including permanent and temporary treatment interruption, or changes in drug(s) dosage(s) or drug regimen, as decided by the clinician.

Adverse events judged as otherwise clinically significant: Defined as all AEs regardless of their seriousness, severity, or causal relationship to the MDR TB treatment, not pertaining to one of the above-mentioned category but considered of clinical significance by the treating physician.

Pregnancy: Must be avoided during MDR-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 the TIC for urgent decision if patients is on follow up at TIC or TFC and to ensure the patient receives standard of DR-TB treatment for pregnant women. All pregnancies 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.

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.).

Approach for aDSM:

- Immediate reporting of SAEs, pregnancies of female patients and medication errors (e.g. drug overdose),
- Regular collection of non-serious AEs of clinical significance including AEs of special interest, AEs leading to treatment changes/interruptions as decided by the treating physician, and AEs otherwise judged to be clinically significant by the treating physician
- Periodic reporting of compiled data on non-serious AEs to National PV center

How to Detect AEs:

- Systematic symptomatic screening, clinical examination, laboratory monitoring with referral for potential AEs during the scheduled and/or unscheduled visits.
- Systematic assessment of the evolution and outcome of the previously recorded AEs.

Recording, medical assessment and notification of adverse events

How to Report AEs: Upon detection of an SAE/pregnancy/ medication error the clinician should collect minimally the following information: 1) Patient Identifier information; 2) Suspected Drug Information; 3) At least one SAE/ Pregnancy/Medication error information; 4) Reporter identifier information. The recording and notification of adverse events occurs as follows:

- **Immediate reporting**(within 24 hours of awareness) of **Serious Adverse Events**, **drug-exposed pregnancies** and **medication errors** (with or without associated AEs/SAEs) to the EFDA using the online reporting system, or through the Medsafety mobile app or using the yellow form. Further reporting to global partners shall be made through NPV Center.
- **Routine reporting** 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 linelisting Form*.

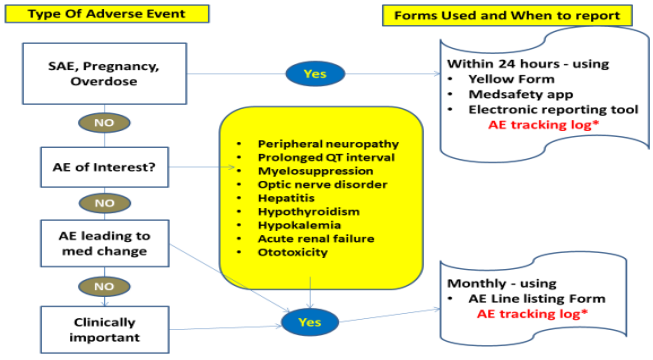


Fig 15: Reporting Timeline of AE/SAE/AEIs

Required Medical Assessment of SAEs/AEs: Two types of medical assessment are expected from the clinician at time of data collection**.**

1. **Evaluation of SAE severity**-based on standardized severity grading scale.

Evaluation of the causal relationship- between each SAE/AEI and each suspected drug. This evaluation should take into account all other possible causal factors (e.g. medical history, risk factors, past drug use, concomitant procedures, TB progression). Sources of Safety information for causality Assessment include: *Clinical trial data for the indication, Nonclinical data (in vitro, animals), Clinical Pharmacology studies, Clinical trial safety data for other indications, Post marketing experience, Medical literature, Safety profile of other drugs in the same class*.

Causality and severity assessments are not performed on medication errors or pregnancies. However, the medical consequences of such occurrences (e.g. miscarriage, liver failure) should be evaluated in terms of severity and causality.

Severity Grading: 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.

Table 46 General Definition of severity

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 possible	Extreme limitation in activity*, significant assistance required; significant medical intervention/therapy required, hospitalization or 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.

Causality Assessment: All AEs should additionally be evaluated to determine their **causal relationship with DR TB treatment** (including DR TB drugs and other drugs as appropriate), according to WHO-UMC Criteria indicated below.

Table 47: WHO-UMC Causality Criteria

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

13 TB/HIV AND OTHER COMORBIDITIES

13.1 TB/HIV Collaborative activities

The HIV/AIDS epidemic presents a major challenge to the control of TB in Ethiopia. The dual epidemic has a great deal of impact on the health sector. It increases TB and HIV burden, surges demand for care and worsens the situation of the already over- stretched health care delivery system in the country. The expanded scope of the strategy for tuberculosis control in Ethiopia comprises interventions against tuberculosis and HIV. Therefore, the National Tuberculosis and HIV Prevention and Control programs must strengthen the health system's ability to respond to the healthcare needs of TB/HIV patients' in the country.

Knowing the dual burden and shared deleterious consequences of the two diseases, the programs must not only collaborate to provide an integrated service for the co-infected patients, but also it must include the planning, monitoring and implementation of activities targeted for the co-infected patients. The collaborative aims to reduce the burden of TB/HIV diseases by:

- Strengthening the mechanisms for collaboration;
- Reducing the burden of TB among HIV-positives; and
- Reducing the burden of HIV among TB patients.

13.1.1 Nationally Recommended TB/HIV Collaborative Activities

A. Strengthen the Mechanisms for Joint TB/HIV Programming and services delivery:
- Strengthen the coordination mechanism for integrated TB/HIV services at all levels;
- Conduct surveillance to determine HIV burden among TB patients and TB burden among HIV patients;
- Carry out joint TB/HIV planning for integrated TB and HIV services delivery;
- Conduct monitoring and evaluation of collaborative TB/HIV activities.

B. **Reduce the burden of TB in PLHIV and initiate early antiretroviral therapy:**
- Intensify TB case finding and ensure quality TB treatment;
- Initiate TB prevention with earlier initiation of ART and TB preventive therapy;
- Ensure Tuberculosis infection control in healthcare and congregate settings.

C. **Decrease the burden of HIV among TB patients:**
- Provide HIV testing and counseling to presumptive and confirmed TB patients;
- Introduce HIV prevention interventions for presumptive and confirmed TB patients;
- Provide Cotrimoxazole preventive therapy for HIV positive TB patients;
- Ensure HIV/AIDS prevention, treatment and care for HIV positive TB patients;
- Provide antiretroviral therapy for HIV positives TB patients.

13.1.2 Management consideration for TB in HIV co-infected adults and adolescents

Early initiation of ART for patients with HIV-associated TB is critical in reducing morbidity and mortality. In the management of TB/HIV confection, treatment of tuberculosis always precedes ART initiation. ART is recommended for all HIV infected TB patients regardless of CD4 count or WHO clinical stage. CD4 cells count shall preferably be determined for all HIV infected TB patients. The preferred regimen for TB/HIV co-infected adult patients is TDF +3TC+EFV/DTG, regardless of pregnancy status.

Table 48: Management of TB/HIV Co-infected patients

TB develops before starting ART	TB developed while on ART
• Initiate ART for all TB patients, including those with drug-resistant TB, irrespective of the CD4 count. • Anti-tuberculosis treatment should be initiated first, followed by ART as soon as possible **within 2 weeks** of treatment. • Efavirenz should be used as the preferred drug in patients starting ART while on Anti-tuberculosis treatment • Use NVP as alternate but monitor liver function every month.	• Initiate anti-TB • Evaluate for HIV treatment failure • Continue ART with TB treatment with changes to the ART regimen: **If on first-line regimen** 1) In patients on DTG-containing ART, continue the same ART regimen but double the DTG dose and start TB treatment. In adults and adolescents, including pregnant/breast feeding women and children >20Kg body weight, the dose of DTG should be 50mg BID. For children less than <20Kg, the dose of DTG depends on the exact body weight of the child. **If on Second-line regimen:** 1) Adjust ART regimen as follows; Lopinavir / ritonavir 400/100mg every 12hours should change to lopinavir / ritonavir 800/200 mg every 12 hours, or LPV/r 400 mg/400 mg twice daily - This should be continued until 2 weeks after completion of TB treatment, when the dose can be reduced to the standard dose. 2) Monitor ALT monthly during TB treatment

Refer also to the latest edition National Guidelines for Comprehensive HIV Prevention, Care and Treatment for detailed TB/HIV co-management.

13.1.3 Management of TB/HIV Co-Infection in Children

Management of HIV and TB co-infection is complex and the clinical and public health consequences associated with the failure of treatment and other negative outcomes are serious. Treatment principles are similar in HIV-positive and HIV-negative children. TB treatment has priority over ART. Because they are expected to take multiple drugs for long period of time, ensuring adherence is a crucial factor for the success of both TB & HIV treatment. Monitoring for drug-drug interaction and toxicity is very critical for successful treatment completion.

BCG Vaccination for HIV-exposed Infants: BCG vaccination is contraindicated in HIV infected infants. Recent evidence shows that HIV infected infants who were routinely vaccinated with BCG at birth, when asymptomatic, and who later developed AIDS, are at high risk of developing disseminated BCG disease.

The implementation of selective BCG vaccination strategies may not be feasible in most TB high endemic settings including Ethiopia. However, BCG vaccination strategies in infants born to HIV-infected women need strategies to reduce the risk of vertical HIV transmission and disseminated BCG disease in infants. Current national recommendation for BCG immunization of infants continues until all programs for implementing selective deferral of HIV exposed infants are in place.

13.1.4 Management consideration of drug resistant TB in PLHIV:

The treatment of drug-resistant TB in patients with HIV is very similar to that in patients without HIV infection. Additional management considerations include:

- Patients at high-risk for R/MDR-TB should be started on an empiric treatment with second-line anti-TB drugs regimen, even before laboratory confirmation of MDR-TB.
- Antiretroviral therapy is recommended for all patients with HIV and drug resistant-TB requiring second-line anti-TB drugs, irrespective of CD4 cell- count, as early as possible (within the first 8 weeks) following initiation of anti- TB treatment.
- While there are few drug–drug interactions with second-line TB drugs and ART regimens, the problem of overlapping drug toxicities is an ever-present concern.
- A common first-line ART regimen used in DR-TB treatment is AZT + 3TC +EFV. TDF is generally avoided because of the possibility of overlapping renal toxicity with the injectable. If TDF is used, additional monitoring of renal function and electrolytes is indicated.
- Many of the medications used to treat drug-resistant TB and HIV have overlapping, or in some cases additive, toxicities.
- Treatment should be monitored closely and with direct supervision, considering the increased pills burden, and increased risk of overlapping toxicities.
- Integrated delivery of drug-resistant TB and HIV services are recommended.
- Use of Dlm may be preferred to Bdq due less drug-drug interactions.

Further drug-drug interactions of anti-TB medicines and ARVs is provided in the latest ART guidelines and please refer for additional guidance.

13.1.5 Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS has emerged as an important complication of ART. IRIS is relatively common in mild to moderate forms in patients with TB/ DR-TB started on ART. This syndrome can present as a paradoxical worsening of the patient's clinical status, often due to a previously subclinical and 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 generally presents within three months of the initiation of ART and is more common with a low CD4 cell count (<50 cells/mm3).

It is important to note that IRIS is a diagnosis of exclusion. 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.

The management of IRIS is complex and depends on the clinical status of the patient and the site and extent of involvement. Treatment modalities include non-steroidal anti-inflammatory drugs (NSAIDs) in mild disease, and corticosteroids in moderate to severe disease. Most patients can be treated without interruption of ART.

13.2 Tuberculosis and Malnutrition

The association between TB and undernutrition has long been known. TB makes undernutrition worse and undernutrition weakens immunity, thereby increasing the likelihood that latent TB will develop into active disease. Malnutrition increases the risk of developing TB by 3-fold, which could predispose large population at risk to progress to TB in high TB burden setting like Ethiopia. The 2016 Ethiopian DHS show that 38% of surveyed under 5 children are stunted, while 10% were are wasted. National wide rapid nutritional assessment in 2015 reported that two out of three registered TB patients had low BMI below 18.5 Kg/m2. Hence, all TB care providers should integrate the recommended nutritional assessment and care intervention packages for all TB patients registered to care and treatment service.

13.2.1 Nutritional care and support for Tuberculosis patients

Nutrition assessment, counseling, and support (NACS) is an approach that aims to improve the nutritional status of individuals by integrating simple assessment of nutritional status, providing counseling on proper nutrition for TB and providing nutritional support for patients found to have malnutrition.

13.2.2 Nutritional Assessment

Nutritional indices that are used to assess and classify for malnutrition include:-

- Body Mass Index (BMI)-For Adult
- BMI-for-age-For children and adolescents 5-18 Years
- WFH or MUAC- for children under 5
- Mid-Upper Arm Circumference (MUAC) - Pregnant and lactating women and for others BMI cannot be taken.

Assessment of a TB patient on treatment should be done:

- At initial assessment and preparation of TB treatment
- At end of intensive phase of TB treatment, and
- Up on documenting unintentional loss of weight during TB treatment.

13.2.3 Classification of TB patients by their nutritional status

After measuring the parameters, the patient should be classified for nutritional status using the various recommended references. Table 49 below is classification for adult patients using Body mass index.

Table 49: Malnutrition classification by Body Mass Index (BMI)-For Adult

BMI	Classification
<16	Severe Malnutrition
≥ 16.0 and <17.0	Moderate Malnutrition
≥ 17.0 and <18.5	Mild Malnutrition
≥ 18.5 and < 25.0	Normal

Source: WHO.1999. Management of Severe Malnutrition: A manual for physicians and other senior health workers. Geneva. WHO

13.2.4 Nutritional Support

Nutritional care plan and management of malnourished patients with TB has three care plans depending on the degree of malnutrition and the age of the patient, see table 50.

Table 50: Nutritional Care Plan and Management of Malnourished Patients with TB

CARE PLAN	Degree of Malnutrition	Intervention
A	Severe acute malnutrition (SAM)	Ready to Use Therapeutic Foods (RUTF) or Plumpy nut*
B	Moderate acute malnutrition (MAM)	Ready to Use Supplementary Foods (RUSF) or Plumpy sup#
C	Mild or no acute malnutrition	Nutritional counseling on essential elements
*Plumpy nut is an energy dense fortified therapeutic food designed for the treatment of SAM. #Plumy sup is an energy dense fortified supplementary food designed for treatment of MAM.		
Duration of Intervention: If a TB patient has SAM, RUTF is given for 3 months (or less if patient comes out of SAM before completion of 3 months). Treatment is then continued with RUSF for 3 months. If a TB/HIV co-infected or MDR-TB patient has MAM at initial time of assessment, RUSF is given for 3 months.		

Nutritional support is recommended for:

- Severe Acute Malnutrition (SAM) in a patient with active TB.
- Moderate Acute Malnutrition (MAM) in patient with:
  - TB/ HIV co-infections
  - MDR TB, and
  - Pregnant and lactating women with active TB.

Supplementary foods are generally recommended for MDR TB patients to accelerate recovery and weight gain knowing the fact that majority had previous unsuccessful treatment history and higher prevalence of malnutrition. For details of the management of malnutrition, refer to the latest version of national nutritional guidelines.

13.2.5 Essential elements for Nutritional counselling for patient with TB

Every TB patient should regularly receive the following essential advice and support in order to provide good nutrition for patient with Tuberculosis, see box 2.

Box 2: Essential elements for Nutritional Counseling of all Patients with Active TB:

1. Have nutritional status checked (especially weight) upon scheduled visits to clinic
2. Eat more and a variety of food stuffs
3. Maintain a high level of hygiene and sanitation
4. Drink plenty of clean and safe (boiled or treated) water
5. Maintain a healthy lifestyle and practice infection control at home
6. Get tested for HIV
7. Take your medicines properly and on time under DOT
8. Seek early treatment for adverse drug reactions
9. Follow instructions for taking your TB medicine in relation to food and other drugs

13.3 TB and Diabetes mellitus (DM)

DM increases the risk of primary infection with TB and is associated with delayed sputum conversion. It may also play a role in the development of DR-TB.

The management principles of TB/DR-TB in patients with diabetes remain similar to nondiabetic patients. However, this may need reconsideration in view of the increased treatment failure rates seen in patients with uncontrolled diabetes. Aggressive treatment is recommended for patients with uncontrolled diabetes since these patients have increased rates of relapse and recurrence. Very close monitoring of the patient is required to optimize glycemic control. Priority should be placed on early detection of both diseases through active screening, monitoring of adherence to medications for both diseases, and integration of TB and DM management strategies that would facilitate the provision of more comprehensive services that TB patients with DM require.

Considerations in management of Tuberculosis in Patients with Diabetes Mellitus:

- Optimal management of DM-associated TB begins with early TB case detection.
- Despite the increased risk of TB among those with poorly controlled diabetes and the benefit of TB preventive therapy, there is no current global policy to provide TPT in people diagnosed with DM. Standard course of TB treatment is recommended in patients with Diabetes mellitus who develop TB.
- In poorly responding TB patients, whenever possible, it is advised to screen for high glucose levels either fasting/random blood glucose or hemoglobin A1C of TB patients. This includes TB patients who remained sputum smear positive after the end of second or fifth month, and those who relapsed with TB. If high level detected, repeat testing should be done to confirm DM status and decide on the need of oral diabetic medications or insulin.
- In patient with Diabetic nephropathy, necessary precautions should be made in management of TB with consultation of expert physician.

13.4 TB and Chronic Obstructive Pulmonary Disorders (COPD)

COPDs are frequent co-morbid conditions in patients with TB. Patients with COPD have a three-fold increased risk of developing active TB compared to the general population, mainly due to an excess risk of pulmonary TB. Moreover, TB patients with COPD have a two-fold increased risk of death within first year after TB-diagnosis. A diagnosis of COPD doesn't alter the clinical presentation of pulmonary TB. Pulmonary TB also can be a risk factor for COPD development, particularly in long standing disease and if the extent of parenchymal involvement is extensive. Pulmonary TB can lead to remodeling of the lung architecture and this can be manifested as extensive fibrosis, Cavitation, traction bronchiectasis, broncho-stenosis or parenchymal lung destruction leading to long term medical problem as TB sequale.

Considerations for Addressing TB and COPDs:

- Awareness creation and risk reduction intervention on Tobacco smoking and biomass exposure
- Early identification and effective TB treatment reduce risk of COPD as TB sequale
- Targeted interventions to reduce the burden of TB among patients with COPD
- Intensified TB case finding in clinics where patients with COPD attend long term care
- TB screening among patients with COPD receiving long term corticosteroid therapy
- Infection prevention in settings where patients with COPD live or work
- Evidence generations and research

13.5 TB in Elderly patients

With the rapid pace of population ageing, TB in the elderly has increasingly become a public health challenge. The TB mortality rate among the elderly is six times higher than that of the younger population groups. Despite the evidences that showed the increasing burden of TB and the associated poor treatment outcome and mortality in the vulnerable elderly, there is scarcity of information on understanding the shifting TB epidemiology. Underlying acute or chronic diseases, malnutrition, and the biological changes with aging, can the attenuate immune responses to infecting agents putting the at high risk for reactivation of latent TB as well as susceptible to new TB infection. The institutionalized elderly are particularly vulnerable to TB.

TB diagnosis can be difficult and consequently overlooked. Elderly often face difficulty in reporting their complaints, and encounter multiple barriers that prevent them from early seeking of medical attentions. Clinical features of TB in older age may be atypical, non-specific, and may presents with constitutional complaints (fever, appetite loss and weight loss) and nonspecific respiratory symptoms (dry cough, dyspnea and chest pain).These presentations are difficult to measure, due to the frequent coexistence with other respiratory, cardiovascular or systemic diseases of similar clinical profiles. Therefore, high index of suspicion is critical for early TB diagnosis.

Table 51: Summary Clinical Manifestations of TB in Elderly

Type of TB	Manifestations
Primary TB	Respiratory and systemic symptoms; cough, excessive sputum production, frank hemoptysis, fever, anorexia, weight loss, night sweats, and fatigue; are less common in the elderly
Miliary TB	Acute onset of fever, weight loss, hepatosplenomegaly, and, occasionally, fever of undetermined origin. Elderly patients are more likely to present with the nonreactive form: numerous small caseous lesions with large numbers of replicating bacilli, sparse neutrophil in- filtrate, and no granulomatous reaction.
Tuberculous Meningitis	Headache, fever, weakness, and confusion. Clinical features in the elderly are similar to those in younger persons. In addition, elderly patients may present with unexplained dementia or obtundation.
Tuberculous Arthritis	Large weight-bearing joints such as the hips can be involved. In the elderly, other peripheral joints, such as the knees, wrists, ankles, and metatarsophalangeal joints, may be involved aswell

TB treatment in the elderly is challenging due to an increased incidence of adverse drug reactions and associated chronic diseases. Standard TB treatment is recommended in management of TB in elderly with no extension of treatment duration. Dose adjustment of TB drugs often required especially for drugs excreted by renal mechanism. Strict Monitoring for adverse reactions and drug-drug interactions is also part of the care plan. Recommended interventions to address TB in elderly: increased awareness, better medical and social support, early case-finding through systematic screening particularly in elderly institutions, adequate follow-up treatment with close monitoring and evaluation, as well as targeted programmatic management.

14. TB PATIENT-CENTERED CARE AND ADHERENCE SUPPORT

14.1 Integrated patient-centered care and support

Patient-centered approach to treatment, care and support of TB patients, drug-susceptible TB and drug-resistant TB, is fundamental to promote adherence, improve quality of life and relieve suffering of patients' and their family members not only from the untoward immediate medical, pyscho-social, nutritional and economic consequences but also from long-term sequale of the disease by developing flexible packages of interventions, in addition to the supervision of the medical therapy. The primary aim of these intervention packages is to meet the needs, values, preferences and rights of the patients/patient groups to inform the access and delivery of services while maintaining mutual respect between the patients and the provider.

14.2 Supervision of treatment

The national TB program utilizes the innovative community based TB care approach as a main strategy to decentralize essential TB service to be accessed at community level by TB/DR-TB patients and their families.

14.2.1 Directly Observed Treatment

Directly observed treatment (DOT) refers to when TB patient takes its medications under the direct supervision of a treatment supporter (any person observing that a TB patient takes the right medication, in the right doses, for sufficient period of time). Supervision of treatment may take place at a hospital, a health center or health post, the patient's workplace, resident institution or home as per the agreement reached during adherence preparation.

14.2.2 TB Treatment Supporters (TTS)

The National TBL Control program recommends the following to serve as a TB Treatment Supporter for supervised TB treatment: health care worker, Health extension worker or a trained TB treatment supporter from the community including household members.

TB Treatment Supporter (TTS) is a person identified and accepted by the patient, willing to supervise treatment on daily basis, consents to maintain confidentiality and trained to directly observe the optimal administration anti TB treatment outside the health facility. The designated treatment supporter could be a Health extension worker, family member, Neighbour, workmates, or community figures. The designated TTS should be trained by the TB focal on how to daily supervise treatment administration and record information on the TTS card. The TTS shall also assist in identifying and communicating any adherence barrier; as well as retrieval of TB patients who interrupt treatment.

14.3 Recommended combined treatment adherence support interventions

A package of treatment adherence interventions, in addition to treatment supervision, is recommended to be offered to all TB/DR-TB patients on treatment whenever feasible and resource allows. Patient care and adherence support packages should be tailored to the needs of individual patient/group of patients putting into consideration the applicability in the local context without overstretching the provider/ service delivery. Recommended adherence interventions for patients being treated for TB/DR-TB and their providers include the following:

14.3.1 Patient and care provider's education

Every TB/DR-TB patient, along with their family and designated treatment supporter, must receive verbal and written educations by trained TB focal person starting from time of diagnosis and preparation to treatment till the completion of treatment and release from care.

Patient education must focus on acquisition of comprehensive knowledge and skills by the patient on prevention of further transmission, importanceof contact investigation, optimization of adherence to treatment and care. The Zonal/WoredaTB program manager is expected to periodically assist TB care providers, including TB laboratory personnel in building their competency on effective communication skills in order to comprehensively assess and understand potential barriers including TB related stigma and arrange individual level care plan in participatory manner. TB care providers are advised to use educational counseling tools prepared by the TB program. Use of TB patients' charter is helpful to ensure client satisfaction which later optimizes adherence and treatment outcome.

14.3.2 Psycho-Social support

TB care providers, health extension workers, adherence supporters and family members should work together to be caring, respectful and compassionate in provision of continuous emotional support not only to optimize adherence but also to prevent and address TB related stigma, depression and/or anxiety problems. Provision of targeted psycho-social support also helps to maximize health equity.

14.3.3 Former TB patients support

Former TB patients should be encouraged to take part in provision of continuous adherence and emotional support to patients on treatment through arranged platforms. They should also be engaged in adherence support, TB stigma reduction, promotion of contact tracing, TBpreventive therapy, advocacy and other community level social mobilization activities with thehelp of Health care workers.

14.3.4 Nutritional Support

Nutritional support package aims to enable TB/DR-TB patients to overcome hardships that might force them to be poorly adherent and treatment interrupters. Currently the national TB program has nutritional and socio-economic support packages to be provided to the eligible DR-TB patients as integral part of the comprehensive treatment services.

Additional guidance on the details of the standardized package and implementation of the service to reach all eligible TB patients will be provided on separate SOP.

14.3.5 Economic support

Economic support to the needy via locally available economic strengthening initiatives should start at enrollment. This should continue when he/she feels better and is ready to resume productive life, hence catastrophic costs impacted t by the disease is averted

14.4 Palliative care for TB and DR-TB patients

Palliative care refers to all measures taken to relieve the suffering of persons affected by a life-threatening condition. Although the priority in TB is to ensure timely diagnosis and access to life-saving treatment, patients left with limited/no effective treatment options, are at high risk of suffering due to the disease, the toxicity of treatment and the sequelae of both.

Components of palliative care include:

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

In the context of M/XDR TB, palliative care should be provided as follows: Pain and symptom management, adverse drug reactions assessment and management, management of complications of M/XDR TB like lung fibrosis, corpulmonale, bronchiectasis, pneumothorax, Psychosocial and economic support, and End of life care.

Hence, palliative care is needed in the course of the illness as part of the continuum of care in the management of M/XDR TB patients from diagnosis to end of treatment or death. It should not be limited to the care provided as end of life care.

14.5 Terminal Illness and End of life care

Unfortunately, in patients with extensive lung disease, highly resistant strain, and a non-response to a course of second-line anti-TB drugs, the only realistic option is palliative care by addressing all the four dimensions of the patient's needs (physical, psychological, social and spiritual). Terminally ill patients, where circumstances permit, may be discharged for care by family members, with the consent of the family. Conditions, under which the patient may be discharged, include:

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

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

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

- Pain control and symptom relief. The three Step WHO analgesic ladders should be utilized in the management of pain. Pain assessment should be done every visit. Paracetamol, tramadol or codeine with paracetamol, gives relief from moderate pain. For Severe pain stronger analgesics, including morphine, should be used to keep the patient pain free. Refer to the Ethiopian pain management guideline.
- Relief of respiratory insufficiency. Oxygen can be used to alleviate shortness of breath. Morphine also provides significant relief from respiratory distress.

- Nutritional support. Small and frequent meals are often best for a person at the end of life. Nausea and vomiting or any other conditions that interfere with nutritional support should be treated.
- Continuation of ancillary medicines. All necessary ancillary medications should be continued as needed. Codeine and morphine help control cough, as well as pain. Bronchospasm symptoms can be controlled with a meter-dosed inhaler with a spacer or mask. Depression and anxiety, if present, should be addressed. Anti- emetics may still be needed. Treat fever if the patient is uncomfortable.
- Regular medical visits. When therapy stops, regular visits by the treating physician and support team should not be discontinued. This is particularly important if palliative care is provided at home.
- Preventive measures. Oral care, prevention of bedsores, bathing, and prevention of muscle contractures are indicated in all patients.
- Infection control measures. Infection control measures should be continued at home, including both environmental controls and personal protection.
- Respect patient's beliefs and values at the end of life.

15. TB INFECTION PREVENTION AND CONTROL MEASURES

Basics of TB Infection Control

TB infection prevention and control (TB IPC) is a combination of measures designed to 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 IPC requires and complements the implementation of core interventions in TB control, HIV control and strengthening of health systems.

Rationale

TB infection prevention and 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.

Set of TB IPC activities

The set of national and regional level managerial activities is given & described in box12 below. At this level, activities 1–6 are all managerial. They provide policy makers at national and sub-national level with a comprehensive framework that can support and facilitate the implementation, operation and maintenance of TB infection prevention and control in all levels of health-care facilities, on-health care setting with a high-risk of Mycobacterium tuberculosis.

Set of Activities for National and sub-national TB Infection prevention and Control

1. Identify and strengthen a coordinating body for TB infection control, and develop a comprehensive budgeted plan that includes human resource requirements for implementation of TB infection prevention and control at all levels.
2. Ensure that health facility design, construction, renovation and use are appropriate.
3. Conduct surveillance of TB disease among health workers, and conduct assessment at all levels of the health system and in congregate settings.
4. Address TB infection control advocacy, communication and social mobilization (ACSM), including engagement of civil society.
5. Monitor and evaluate the set of TB infection control measures.
6. Enable and conduct operational research.

Guiding Principles

- Effective IPC measures are a critical part of the quality of health service delivery to achieve people-centred, integrated universal health coverage.
- The IPC guidelines are based on a public health approach to implement evidence-based interventions for IPC, including transmission-based precautions, and the recommendations given here should be considered as the minimum IPC standard.
- Implementing these guidelines requires an understanding of the interdependence of the three-level hierarchy of IPC, giving prominence to the implementation of administrative controls as the basis for reducing the risk of transmission of M. tuberculosis.
- The implementation of these recommendations needs to be accompanied by efforts to promote and protect the human rights of all patients, their communities and care providers.

Reducing Transmission of TB in Healthcare Facilities

This section describes the various elements that can be combined to achieve TB infection control at facility level. The recommendations of TB infection prevention and control measures that apply at facility level are listed in box 3 below. Implementation of the national and regional managerial activities described above facilitate the implementation of measures described in this section and should therefore be implemented as a set.

Box 3: Tuberculosis infection prevention and control recommendations (Summary)

Administrative controls:

1. Triage of people with TB signs and symptoms, or with TB disease, is recommended to reduce M. tuberculosis transmission to health workers (including community health workers), persons attending health care facilities or other persons in settings with a high risk of transmission.
2. Respiratory separation / isolation of people with presumed or demonstrated infectious TB is recommended to reduce M. tuberculosis transmission to health workers or other persons attending health care facilities.
3. Prompt initiation of effective TB treatment of people with TB disease is recommended to reduce M. tuberculosis transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission.
4. Respiratory hygiene (including cough etiquette) in people with presumed or confirmed TB is recommended to reduce M. tuberculosis transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission.

Environmental controls:

5. Upper-room germicidal ultraviolet (GUV) systems are recommended to reduce M. tuberculosis transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission.
6. Ventilation systems (including natural, mixed-mode, mechanical ventilation and recirculated air through high-efficiency particulate air [HEPA] filters) are recommended to reduce M. tuberculosis transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission.

Respiratory protection:

7. Particulate respirators, within the framework of a respiratory protection programme, are recommended to reduce M. tuberculosis transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission.

Hierarchy of infection prevention and control

TB prevention and control consists of a combination of measures designed to minimize the risk of M. tuberculosis transmission within populations. A three-level hierarchy of controls comprising administrative controls, environmental controls and respiratory protection has been shown to reduce and prevent the risk of transmission and exposure to M. tuberculosis.

1. Administrative Controls

A set of administrative controls is the first and most important component of any IPC strategy. These key measures comprise specific interventions aimed at reducing exposure and therefore reducing transmission of M. tuberculosis. They include triage and patient separation systems (i.e. management of patient flows to promptly identify and separate presumptive TB cases), prompt initiation of effective treatment and respiratory hygiene.

2. Environmental Controls

To reduce the risk of transmission of M. tuberculosis, air can be made less infectious through the use of three principles: dilution, filtration and disinfection. Environmental controls are aimed at reducing the concentration of infectious droplet nuclei in the air. This is achieved by using special ventilation systems to maximize airflow rates or filtration, or by using germicidal ultraviolet (GUV) systems to disinfect the air. Ventilation systems can also be used to control the direction of airflow to reduce the spread of infection; for example, through the use of exhaust fans to generate negative pressure gradients. Environmental controls are used in combination with other IPC measures to help prevent the spread of M. tuberculosis.

3. Respiratory protection Controls

Respiratory protection controls are designed to further reduce the risk of exposure to M. tuberculosis (and other airborne pathogens) for health workers in special areas and circumstances. The recommendations given here are aimed at strengthening these controls, and preventing the inadequate implementation of respiratory protection programmes that may lead to a false sense of security and therefore increase the risk to health care staff.

Infection Control for Congregate Settings

Congregate setting is a mix of institutional (non-health care) settings where people reside in close proximity to each other. Congregate settings range from correctional facilities (prisons and jails), to homeless shelters, refugee camps, army barracks, hospices, dormitories and nursing homes.

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.

Administrative Controls: To decrease TB transmission in congregate settings, cough etiquette and respiratory hygiene should be implemented. This should be done with early identification, followed by separation and proper treatment of infectious cases. In particular, all inmates of long-term stay facilities and inhabitants of other congregate settings should be screened for TB before entry into the facility. All staff must be given appropriate information and be encouraged accordingly to undergo periodic TB screening and diagnostic investigation if they have signs and symptoms suggestive of the

disease. People suspected of having TB should be diagnosed as quickly as possible. They should always be separated and/or isolated in an adequately ventilated area, until sputum smear conversion. Directly observed therapy (DOT) while a patient is on treatment is also recommended. In short-term stay congregate settings, such as jails and shelters, a referral system for proper case management of cases should be established. In congregate settings, patients living with HIV and other forms of immunosuppression have to be separated from those with suspected or confirmed infectious TB. All staff and persons residing in the setting should be given information and be encouraged to undergo HIV testing and counseling. If diagnosed with HIV, they should be offered a package of prevention and care that includes regular screening for active TB.

In congregate settings with patients having, or suspected of having, drug-resistant TB, such patients should be separated from other patients (including other TB patients), and referral for proper treatment should be established.

Environmental Controls: Buildings in congregate settings should comply with national norms and regulations for ventilation in public buildings as well as specific norms and regulations for prisons.

Respiratory protection Controls: When a person residing in a long-term stay congregate setting is suspected or diagnosed as having TB and is physically separated, the same recommendations on infection control apply as they do for health-care facilities. In short-term stay congregate settings, appropriate referral should be organized.

Reducing Transmission of TB in Households

Remarks or considerations on specific interventions are made where applicable (e.g. respiratory hygiene, ventilation systems and respiratory protection).

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. Whether the patient subsequently remains at home or moves to a sanatorium appears to have little impact on household transmission, provided the patient is treated effectively. 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). Further, 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 immune-suppressed individuals; and Spend as little time as possible in congregate or crowded settings such as churches, markets and public transport.

16. CLINICAL AND PROGRAMMATIC MANAGEMENT OF LEPROSY

16.1 Epidemiology of Leprosy in Ethiopia

Ethiopia is among the 23 countries reporting over 1000 cases of leprosy annually. In 2019, Ethiopia reported a total of 3426 leprosy cases. Among the total registered cases 2957 (86.3%) were new and 368 (10.7%) were registered as relapse. Among the new cases 67.5% was MB 15.1% children and 13.9% with grade 2disability. During the same period, the treatment completion rate was 87% and 99% for MB and PB, respectively.

16.2 National Leprosy Elimination Strategy

Ethiopia adopted the global strategy to eliminate leprosy. The main principle of leprosy control is based on timely detection of new cases and provision of effective chemotherapy with multi drug therapy. The emphasis will remain on providing patient care that is equitably distributed, affordable and easily accessible.

The main elements of the strategy are:

- Strengthen patient and community awareness on leprosy
- Improve access to leprosy services in the high burden areas through establishment/strengthening health facilities capable of comprehensive leprosy care;
- Active case finding for targeted high-risk and vulnerable groups in hifgh endemic areas (as an outreach program)
- Promote early case detection with focus on contact management
- Ensure political commitment and adequate resources for leprosy control Promote coalition building among persons affected by leprosy

Please refer to the National TBL NSP 2021-2025/6 for details on targets and strategic interventions to eliminate leprosy in Ethiopia.

16.3 Basics of Leprosy

Leprosy is a chronic infectious disease caused by Mycobacterium leprae, an acid-fast bacillus. The disease mainly affects skin, peripheral nerves, mucosa of the upper respiratory tract and the eyes. It affects persons in all age groups and both sexes. The age group mainly affected is between 15 and 45 years. Factors related to poverty increase the risk of developing the disease.

Mode of Transmission: Leprosy is transmitted through **air borne spread of droplets from the nasal mucosa and mouth,** containing the bacilli expelled by untreated leprosy patients and inhaled by healthy persons. Persons living in the same household and in close contact with an infectious person have the greatest risk to get infected and develop the disease.

Natural Evolution: Under normal circumstances, only a very small proportion (less than 5%) of all individuals who are infected by the leprosy bacilli will develop the disease during their lifetime. In the majority of people, the immunological defense kills the bacilli. The disease slowly progressed with an average incubation period of 3 to 5 years, but it may vary from 6 months to more than 20 years. If not treated, leprosy can cause severe disability, mainly as a result of peripheral nerve damage.

Association of Leprosy with HIV: few data suggest that immune-mediated reactions that complicate leprosy occur at a higher frequency in co-infected patients. Leprosy has also been reported as immune reconstitution disease in HIV-positive populations commencing highly active antiretroviral treatment.

16.4 Leprosy Case Finding Strategies

There are two methods of leprosy case detection, active and voluntary. The voluntary self-reporting strategy is main strategy recommended by the national program whereas the place of Active case-finding is limited to the special characteristics of the affected population.

The major objectives of Leprosy case finding are:

- To identify infectious leprosy cases serving as sources of infection in the community.
- To treat infectious cases rapidly and interrupt the chain of transmission.
- To prevent the occurrence of irreversible nerve damage and disability by promotion of early diagnosis and cure

Self-reporting or voluntary case finding: is the main Leprosy case-finding strategy used to detect of active leprosy cases by examination of self-referred patients attending health facilities. All healthcare personnel should identify suspects by asking for symptoms of leprosy (e.g. skin changes) among persons who voluntarily visit medical services at OPD.

Active case finding: includes the use of small scale campaigns in restricted special situations and suspected or known leprosy pocket areas. It should be a one-time activity with the aim of establishing sustainable services.

Contact Investigation and management for leprosy: Household contacts and other close contacts are at an increased risk of Leprosy infection and hence disease. Hence, promotion of contact tracing may contribute to early identification of leprosy cases, thus decreasing its severity and reducing transmission to others.

When a new case is detected, household and other close contacts of the patient should be examined for evidence of leprosy. If asymptomatic, they should be educated on early signs of the disease, the significance, and be advised to return if any suspected skin lesions or motor or sensory changes occur.

Activities for Leprosy contact investigations:

- Upon diagnosing a new Leprosy case, initiate contact tracing for household members and close contacts.
- Arrange to bring all contacts to health facility; or send a Health worker to examine contacts at home. Evaluate all leprosy contacts for symptoms and signs of leprosy
- Identify those with signs and symptoms compatible with leprosy. Diagnose contacts with the cardinal sign of leprosy as a case of leprosy and initiate MDT.
- Educate asymptomatic contacts about the purpose of a contact screening, early signs of the disease, risk of transmission and importance of conducting early medical evaluation and treatment. Consider chemoprophylaxis if eligible.
- Advice contacts to return if they notice any suspected skin lesions, motor or sensory changes
- Record all the information (full name, age, sex, address…) about the contacts on a register
- Repeat leprosy screening for contacts at least every year for five consecutive years.

Efforts to increase case detection are focused on facilitating self-referral by people who develop leprosy. This is done by increasing awareness of the early signs and symptoms of leprosy among the general public and by promoting to remove various barriers which could prevent people with possible leprosy reporting for examination.

In addition, public education will promote the breakdown of barriers such as stigma, discrimination and fear associated with leprosy.

At Community level, HEWs, trained community representatives including association members of leprosy affected populations should create awareness about early signs and symptoms of leprosy, and provide patient support to facilitate self-reporting of suspected cases to the nearby health facility to receive appropriate evaluation and management.

16.5 Identification and evaluation of patient to diagnose Leprosy

Health workers need to have the necessary skills to examine a patient for possible leprosy disease especially in areas where cases of leprosy are known to present.

16.5. 1 Identification of a Leprosy Suspect

Leprosy should be considered in an individual who presents with:

- Pale or reddish patches (skin patch with discoloration) on the skin;
- Painless swelling or lumps in the face and earlobes;
- Loss of or decreased sensation on the skin;
- Numbness or tingling of the hands and/or the feet;
- Weakness of eyelids, hands or feet;
- Painful and/or tender nerves;
- Burning sensation in the skin; or
- Painless wounds or burns on the hands or feet.

Pale or reddish discoloration of the skin is the most common & early symptom of Leprosy.

16.5.2 Patient evaluation to diagnose a Leprosy Case

Over 95% of leprosy cases can be diagnosed on clinical grounds. Laboratory investigation is indicated only in doubtful cases for confirmation and sometimes for patient classification. Evaluate the patient as follows:

A. Clinical History

The following information should be obtained from the individual suspected of leprosy:

- General information: socio-demographic information of the patient.
- Characterize the presentations: History of onset, duration of symptoms, painless wounds/burns; burning sensation; weakness in picking or holding objects or closing eyelids; unusual sensation in hands and feet (numbness, tingling); and presence of itching sensation
- History of previous leprosy treatment.
- History of prolonged contact with a leprosy patient in the household or other confined spaces

B. Physical Examination

Physical examination should be focused to skin, nerves and eyes:

Examination of the Skin: Examination for skin lesion must always be carried out with adequate light (preferably natural light) and sufficient privacy for the patient to feel at ease.

- Inform client about purpose of the examination,
- Request the client to remove all garments,
- Examine systematically from head to toes, including the front and back sides.
- Check for presence of skin lesions (patches or nodules),
- Check for loss of sensation over the skin lesions (patches) using a "wisp of cotton wool" ,and
- Count the number of skin lesions, if any

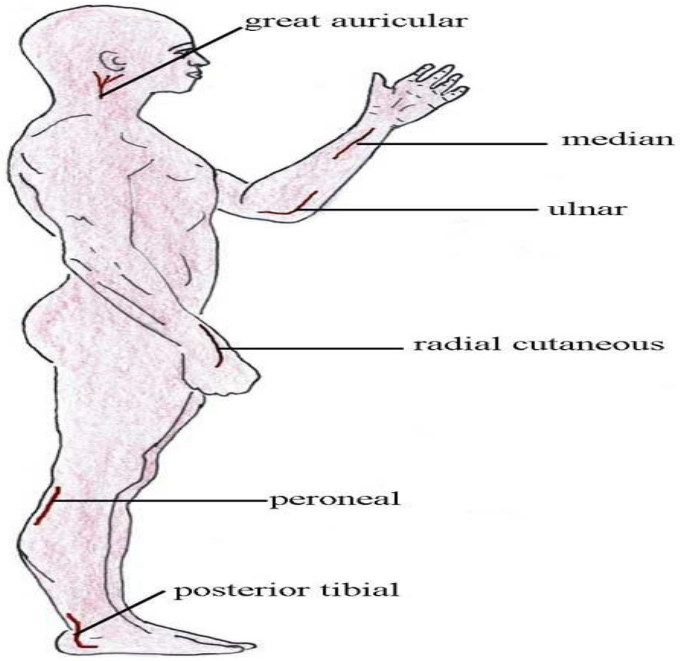
Skin sensation Testing: Any skin lesions should be checked for sensory loss using a "wisp of cotton wool" as follows:

- Explaining to the patient the purpose of the test and what is expected from him.
- Rolling the end of a wisp of cotton wool into a fine point. Touch the skin with the fine point of the cotton wool until it bends.
- Touching the skin with the fine point of the cotton wool until it bends with the patient's eyes opened and instructing the patient to point to the location where they feel the wisp of the cotton. Continue until the patient has demonstrated understanding of the test.
- Repeating the step with the patient's eyes closed, first on the normal skin and then on the skin patch, touching the normal skin now and then
- Watching that the patient's eyes are closed when the test is carried out.

Definite loss of sensation in the skin patch is indicative of leprosy.

Note that if a patient points accurately to areas of normal skin, but sometimes points away from where the skin in a patch is tested. This is called mis-reference and shows diminished sensation in the patch. If this is consistent during repeated testing of a patch, it is a cardinal sign justifying a diagnosis of leprosy.

Examination of the Nerves: Leprosy may affect most peripheral nerves including greater auricular, ulnar, median, radial cutaneous, peroneal and posterior tibial nerve (See below in the diagram). The ulnar and peroneal nerves are the ones that are most commonly enlarged and can be felt quite easily.

Nerve Palpation: Palpation of the nerves aims to check for cord enlargement and/or tenderness: ▪ Palpate the nerves starting from the head and going down to the feet. Compare the right and left sides. ▪ When palpating a nerve, always use the pulp of two or three fingers to roll over the affected nerves.	

A definite enlargement of one or more peripheral nerves is indicative of leprosy.

C) Examination of Skin Smears

Bacteriological examination of a skin smear is recommended only for doubtful cases to confirm the diagnosis and/ or classification of leprosy. WHO recommend that Skin smear can be taken at least from three sites: forehead, ear lobe and from skin lesion. Only one slide, with smears taken from two sites must be collected and examined. One positive-smear result is enough for diagnosis of leprosy. The finding of a negative-smear examination result doesn't rule out leprosy.

When encountering difficulty in reaching diagnosis of Leprosy, Do one of the following:

- Consider the possibility of another skin disease and treat appropriately.
- Refer the patient to an experienced health workers or a dermatologist for re-evaluation.
- If referral is not possible, Re-evaluate the patient after three- months.

16.6 Case definition and classification in Leprosy

A case of leprosy is a person with one of the cardinal signs of leprosy requiring chemotherapy.

The cardinal signs of leprosy are:

1. *Definite loss of sensation in a pale (hypo-pigmented) or reddish skin lesion.*
2. *Thickened or enlarged peripheral nerve with or without tenderness.*
3. *The presence of acid-fast bacilli in a slit skin smear.*

Criteria: Presence of one or more of the three cardinal signs of leprosy is confirmatory to the diagnosis of Leprosy.

Note that a leprosy patient who has completed a full course of chemotherapy should no longer be regarded as a case of leprosy, even when sequelae of leprosy such as skin lesions, disability and/or disfiguration occur or remain.

Classification of a case of Leprosy: leprosy patients are classified according to the WHO classification based on the number of leprosy skin lesions and nerve involvement. The classification also helps on choosing the treatment regimen and predicts the future risk of complication:

1. **Paucibacillary (PB) Leprosy**
   - One to five leprosy skin lesions.
   - Only one nerve trunk enlarged
2. **Multibacillary (MB) Leprosy**
   - Six or more skin lesions.
   - Less than six skin lesions, which have a positive slit skin smear result.
   - If there is involvement (enlargement) of more than one nerve

Besides, leprosy cases that are doubtful to be classified should be taken as a Multi-bacillary case of leprosy and be treated accordingly. Patients with pure neural leprosy should also be classified and treated as a MB case.

Pure Neural Leprosy*: are patients who do not have any skin lesion, but have clearly thickened nerves with or without signs of nerve damage.*

16.7 Examination of the peripheral nerves, eyes, hands and feet

After diagnosis of leprosy is made, the health workers need to examine the peripheral nerves, eyes, hands and feet as these are the most commonly affected organs by leprosy.

11.7.1 Nerve Function Testing

The following nerve functions tests must be carried out:

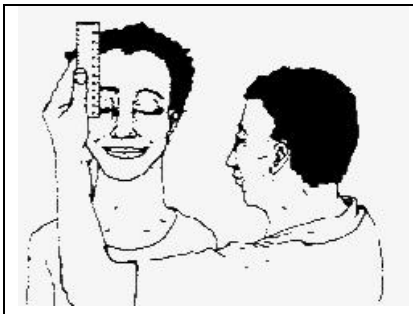
- Voluntary Muscle Testing (VMT)
- Sensory Testing (ST)
- Autonomic nerve function test for dryness of palms and soles

i) Voluntary Muscle Testing (VMT): VMT is done to check Muscle strength of eye, hands and feet. The strength should be graded as **Strong (S), Weak (W) or Paralyzed (P).**

The muscle strength of eyes, hands and feet is tested as follows:

Voluntary muscle testing (VMT) of the eyes: eye closure

- Ask the patient to close his eyes lightly as in sleep.
- Observe whether or not the closure on both eyes is complete. Inability to fully close the eye is called lagophthalmos (paralysis "labeled as P" of the eyelid muscles).
- If there is lagophthalmos, measure lid gap in mm as shown in the diagram below



Lid Gap Measuring Procedures

1. Explain the procedure to the patient.
2. Ask the patient to close his/her eyes lightly, as in sleep.
3. Measure and record any gap in mm as illustrated on the right side.
4. If closure is normal, record: "0 mm."

- If the patient is able to fully close his/her eyes, then ask the patient to close his eyes firmly, gently try to open the eyelids using the pulp of your thumbs to check for strength.
- Grade the eye muscle strength as weak (W) if the eyelids open easily; or strong (S) if it is difficult to open the lids.

Voluntary Muscle testing (VMT) of the hands and feet:

Check for range of movement on the fifth finger:

- ASK patient to abduct 5th finger (move finger away from the rest). If patient cannot move the finger, record as paralysis (P), an indication of ULNAR nerve damage
- If movement is normal, test for resistance by PRESSING gently over the proximal phalanx of the 5th finger using your index finger as shown in the diagram below, holding the other 3 fingers steady and ask the patient to maintain the position and RESIST the pressure of the examiner's index finger as strongly as possible.
- Press gradually more firmly and judge whether resistance is strong (S) or weak (W).

COMPARE the right hand with the left hand always.

Check for range of movement of both thumbs:

- ASK the patient to first flex the thumb over the palm (touch the root of 5th finger) and later point the thumb to his/her nose while you hold the remaining 4 fingers. If patient cannot move the thumb, record as paralysis (P), an indication of MEDIAN nerve damage.
- If movement is normal, test for resistance by PRESSSING gently over the proximal phalanx of the thumb using your (examiner') index finger as shown in the diagram below, holding the other 4 fingers steady and the ask the patient to maintain the position and RESIST the pressure of the examiner's index finger as strongly as possible.
- Press gradually more firmly and judge whether resistance is strong (S) or weak (W).

COMPARE the right hand with the left hand always.

Check for the range of movement of the wrist:

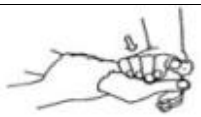
- **ASK** the patient to make a fist then extend the wrist. If patient cannot extend the wrist, record as paralysis (P), an indication of RADIAL nerve damage called WRIST DROP.
- If movement is normal, **test for resistance by PRESSING** gently over the dorsum of the hand as shown in the diagram below, whilst you (examiner) hold the wrist with your other hand. And ask the patient to maintain the position and resist the pressure as strongly as possible.
- Gradually, press more firmly and judge whether resistance is strong (S) or weak(W).

COMPARE the right hand with the left hand always.

Check the movement of the feet

- **ASK** patient to dorsi-flex his foot (move up his foot at the ankle). If patient cannot dorsi-flex the foot, record as paralysis (P), an indication of PERONEAL nerve damage called FOOT DROP.
- If movement is normal, **test for resistance by PRESSING** gently over the dorsum of the foot as shown in the diagram below, whilst you (examiner) hold the leg with your other hand. And ask the patient to maintain the position and resist the pressure as strongly as possible.
- Gradually, press more firmly and judge whether resistance is strong (S) or weak (W).

COMPARE the right foot with the left foot always.

a. Is movement full?	**b. Is resistance full?**
Little finger in: test of ulnar nerve function  *Hold these 3 fingers straight*	 *Patient tries to hold a card between ring- and little fingers. Assessor pulls card gently.*
Straight Thumb up: test of median nerve function  Patient moves thumb base fully *out and across*	 Assessor resists at side of thumb *(not at front or back)*
Wrist up: test of radial nerve function 	
Foot up: test of peroneal nerve function 	

ii) Sensory Testing (ST): Sensory testing is done to check the presence of sensation in the eyes, hands and feet. The sensation of eyes, hands and feet is tested as follows:

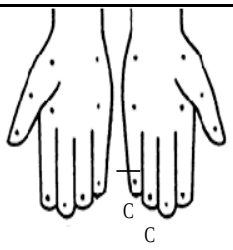
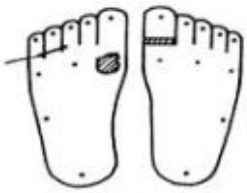
Sensation of the eyes (cornea):

- ASK patient to blink his/her eyes.
- Observe the patient's spontaneous blinking while talking to him/her. If there is a blink, corneal sensation is normal. If there is no blink, the eye is at risk.

Sensation of palms and soles:

ST on palms and soles should be done with a ball point pen. The tests are done on ten standard points. The tests can also be done by using 2gm monofilament for the hand and 10gm monofilament for the feet.

Hand and Foot Mapping, Including Sensation Test (ST)

1. Explain the test to the patient. Rehearse it with the patient. Then test. The eyes of the patient should be covered.	2. Compare sensation of the little finger with that of the thumb and sensation of one hand with the other to see if there is difference. Compare findings with those shown on any earlier records.
3. Support the patient's hand or foot so that fingers/toes are well supported to prevent joint movement during the test.	4. Record: (√) If the patient feels, If not, (**X**)
	5. Mark any wounds ( ), open cracks ( ) clawing of digits (c) and bone loss or absorption (**X**) on the Patient Record Card or VMT/ST Form.
6. Dent the patient's skin by 1-2 mm at dot sites using a ball-point pen -- asking the patient to point to the exact site whenever he/she feels. The stimuli should be irregular in timing and placing.	
7. Look for any CHANGE. Make sure that the change is real and not due to inaccuracies in testing.	

16.7.2 Examination of the Eye

Check for Visual Acuity:

Vision of both eyes of the patient should be tested according to the demonstration below and should be recorded on the Patient Record Card.

• Test vision with good light falling on the assessor. • Ask the patient to cover one eye, then count the number of fingers that the assessor holds up. • Test at 6 meters. If the patient cannot see at 6 meters, re-test at 3 meters. • Record the findings	

Look for other eye problems/complications:

Look for injury of cornea and loss of vision due to incomplete blink and/or eye closure.

16.7.3 Examination of Hands and Feet

Patients should also be examined for the following complications, which result from nerve damage:

- Skin cracks on palms and soles with sensation loss
- Wounds on palms and soles with sensation loss
- Clawed fingers and toes
- Foot drop
- Wrist drop
- Shortening and scarring in fingers and toes with sensation loss

16.8 Disability Grading in Leprosy

Disability is a broad term covering any impairment, activity limitation or participation restriction affecting a person.

Every new case of leprosy must be assigned a "Disability Grade", which depicts the condition of the patient at diagnosis. The grade is on a scale of 0, 1 or 2. Each eye, each hand and each foot is given its own grade, so the patient actually has six grades, but the highest grade given is used as the Disability Grade for that patient.

Table 52 Disabilities grading criteria for Leprosy	
Eyes	**Description**
Grade 0	No disability found. This means there is no eye problem due to leprosy and no loss of vision.
Grade 1	The eyes are not given a grade of 1.
Grade 2	Visible damage or disability is noted. This includes the inability to close the eye fully (lagophthalmos) or obvious redness of the eye (typically caused by a corneal ulcer or uveitis). Visual impairment or blindness (vision less than 6/60 or inability to count fingers at 6 meters) due to leprosy should be graded as grade 2.
Hands and Feet	
Grade 0	No disability found. This means there is no loss of sensation or visible deformity or damage.
Grade 1	There is loss of sensation in the palm of the hand or sole of the foot, but no visible deformity or damage.
Grade 2	There is visible damage or disability due to leprosy. This includes weakness or paralysis of muscles on the hands and feet, wounds and ulcers as well as visible deformities such as a foot drop or a claw hand or absorption of fingers.
Interpretation: *The highest grade in one of the six sites (eyes, hands or feet) is the overall disability grade for that patient.*	

16.9 Case Definition and Treatment of Leprosy

11.9.1 Case definitions &management of Leprosy

Leprosy patients who need treatment with MDT are grouped either as “New Cases” or “Other Cases” and recorded on Leprosy register in order to facilitate the patient registration, reporting and cohort outcome analysis:

Table 53: Case definitions in Leprosy

Case Definition			Management
New case		A patient with MB or PB leprosy who has never had treatment for leprosy before	Treat according to the clinical assessment (and/or laboratory diagnosis).
Other cases ***(includes Relapse, Return after loss to follow up, Transfer in, and others.)***	**Relapse after MDT**	A patient declared "treatment completed" after a course of MDT, but who reports back to the HF and found to have active leprosy.	Treat according to the new clinical assessment (and/or laboratory diagnosis) independent of the previous category of treatment.
	Return after loss to follow up	An MB or PB who returns for treatment after having missed more than 3 months' doses of MDT (both cumulative and consecutive).	**Treat MB** according to the **new** clinical assessment (and/or laboratory diagnosis) independently from the previous treatment category.
	Transfer in	A patient received from another HF to continue treatment.	Treat according to the **previous** classification assessed in the original health facility.
	Other	Any leprosy patient requiring chemotherapy and who does not fit any of the above mentioned categories, including patients who relapse after treatment with dapsone mono-therapy in the past.	Treat according to the clinical assessment (and/or laboratory diagnosis).

16.9.2 Treatment of Leprosy

The objective of the treatment is to:

- Cure leprosy by rapidly eliminating the bacilli;
- Prevent the emergence of drug resistance;
- Prevent relapse; and
- Prevent disability.

Multi-drug Therapy (MDT) is a combination of drugs that is very safe and effective in treating leprosy to prevent the emergence of drug resistance; under no circumstance should leprosy be treated by a single drug. MDT is provided free of charge to all who need it. All drugs are all taken by mouth. The drugs are supplied in special and convenient blister packs for both MB and PB cases. Each blister pack contains supplies for 4 weeks (28 days). The MDT blister pack contains Rifampicin, Clofazimine and Dapsone.

The best way to prevent the spread of leprosy is to treat all patients with MDT. Patients are considered no longer infectious after taking the first dose of MDT. There are virtually no relapses or recurrences of the disease after completion of treatment with MDT.

A **3-drug regimen of rifampicin, dapsone and clofazimine for all leprosy patients, with a duration of treatment of 6 months for PB leprosy and 12 months for MB leprosy is recommended**. This represents a change from the previous standard treatment for PB leprosy, which is rifampicin and dapsone for 6 months, due to some evidence indicating better clinical outcomes with a 3-drug, 6month regimen over a 2-drug, 6-month regimen. A potential advantage of using the same three drugs for PB and MB leprosy is simplification of treatment (i.e. the same blister pack could be used for treating both types of leprosy) and reduced impact of misclassification of MB leprosy as PB leprosy, since all patients will receive a 3-drug regimen. For MB leprosy, the current standard treatment is a 3-drug regimen for 12 months. Evidence on the potential benefits and harms of a shorter (6-month) 3-drug regimen was limited and inconclusive, with a potential increase in the risk of relapse. Therefore, the WHO GDG determined that there was not enough evidence of equivalent outcomes to support a recommendation to shorten the treatment duration for MB leprosy.

Management of Drug resistance in Leprosy

For rifampicin-resistant leprosy, treatment with at least two second-line drugs (clarithromycin, minocycline or a quinolone) plus clofazimine daily for 6 months, followed by clofazimine plus one of these drugs for an additional 18 months. When ofloxacin resistance is also present, a fluoroquinolone should not be used as part of second-line treatment. The regimen of choice in such cases shall consist of 6 months of clarithromycin, minocycline and clofazimine followed by clarithromycin or minocycline plus clofazimine for an additional 18 months.

Resistance has been reported from several countries, although the number of patients is small. Evidence on the potential benefits and harms of alternative regimens for drug-resistant leprosy was not available. Therefore, recommendations for second-line regimens are based on expert opinion and the known activity of alternative drugs, including the likelihood of cross-resistance.

Drugs Used in MDT:

Rifampicin(R): are supplied as 150mg and 300mg tables to be administered once a month. No toxic effects have been reported. Rifampicin may cause slight discoloration (reddish) of the urine and this should be explained to the patient before starting MDT.

Clofazimine (Clz): are supplied as 50mg and 100mg tablets to be administered orally. The drug is well tolerated and virtually non-toxic in the dosage used for MDT. The drug may cause brownish discoloration and dryness of the skin. However, this disappears within few months after stopping treatment. This should be explained to those patients who have started the treatment.

Dapsone (DDS): is supplied as 50mg and 100mg tables to be administered daily. It is very safe in the dose range used in MDT and side effects are rare. The main side effect is allergic reaction, causing itchy skin rashes and exfoliative dermatitis. In rare cases daposone may cause severe reaction which is called dapsone hypersensitivity syndrome. Patients known to be allergic to any of the sulpha-drugs should not be given Dapsone. It can also cause Haemolytic anemia.

MDT Regimens

The MDT Regimens consist of Rifampicin, Dapsone and Clofazimine to be prescribed to all MB leprosy cases for 12 months and to all PB cases for 6 months.

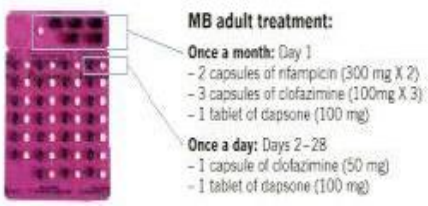
Table 54 MDT Regimen

Age group	Drug	Dosage and frequency	Duration (Months)	
			MB	PB
Adult	Rifampicin Clofazimine Dapsone	600 mg once a month 300 mg once a month and 50 mg daily 100 mg daily	**12**	**6**
Children (10–14 years)	Rifampicin Clofazimine Dapsone	450 mg once a month 150 mg once a month, 50 mg on alternate days 50 mg daily	**12**	**6**
Children < 10 years of old or <40 kg	Rifampicin Clofazimine Dapsone	10 mg/kg once month 100 mg once a month, 50 mg twice weekly Dapsone 2 mg/kg daily	**12**	**6**

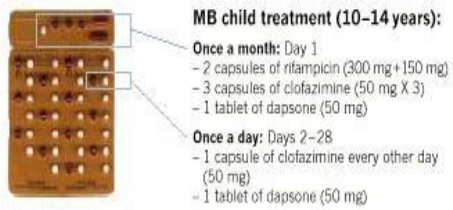
MDT drugs are provided in blister calendar packs each containing a four weeks (one month) supply, except for children below 10 years. The appropriate dose for children under 10 years of age can be decided on the basis of body weight. [Rifampicin: 10 mg per kilogram body weight (mg/kg); Clofazimine: 1 mg/kg daily and 6 mg/kg monthly; Dapsone: 2 mg/kg daily. The standard child blister pack may be broken up so that the appropriate dose is given to children under ten years of age. Clofazimine administration can be spaced out as required.

Fig 16: MDT Blister Packs

MDT blister packs for adults



MDT Blister Packs for Children



Administration of MDT and Phases of Chemotherapy:

Phases of Leprosy Treatment: MDT regimens consist two phases:

1. **Supervised**: drugs are administered under the direct observation by the health worker on fixed clinic days at four weekly intervals.
2. **Unsupervised**: drugs are self-administered daily by the patient.

The health worker instruct the patient and make understand which drugs to be taken on daily basis and which drugs to be taken once a month. The patient should also be appointed to the health facility on every 28th days to administer the once-a-month directly observed dose.

The drugs are to be taken orally and should be taken in a single dose on an empty stomach or two hours after a meal.

Duration of MDT

PB: the duration of treatment for PB patient is 6 months. The monthly supervised dose is Rifampcin Clofazimine & Dapsone (R, Clz & DDS) and is taken at the start of treatment (day 1) and every 28th day of the month for 6 consecutive months. The daily self-administered dose is with Clofazimine and Dapsone and is taken every day for 6 months. The full course of treatment must be completed within 9 months after initiation of treatment.

MB: the duration of treatment for MB patient is 12 months. The monthly, supervised dose is with Rifampcin, Clofazemine & Dapsone (R, Clz & DDS) and is taken at the start of treatment (day 1) and then every 28th day of the month for 12 consecutive months. The daily, self-administered dose is with Clofazemine and Dapsone and is taken every day for 12 months. The full course of treatment must be completed within 15 months.

16.10 Treatment in Special Conditions

Pregnancy and Breast-feeding

The standard MDT regimens are safe, both for the mother, the foetus and the neonate. It therefore can be administered during pregnancy and breast-feeding.

Patients Co-infected with HIV

Patients infected with HIV usually respond equally well to leprosy treatment as those without HIV infection.

Patients Co-infected with TB

Patients suffering from both TB and leprosy require standard TB treatment in addition to the standard MDT. Hence, skip the monthly dose of the Rifampicin in the leprosy MDT regimen. Once the TB treatment is completed, the patients should continue their MDT.

16.11 Monitoring of Treatment and Follow-up

MDT should be given on fixed clinic days. Patients who cannot attend on the fixed day appointment at the clinic, he/she should be allowed to collect drugs on the following days or by trained family member.

During the monthly scheduled visit, the Health workers should do the following:

- Educate the patient about the importance of taking medications regularly, the major side effects of the drugs, and signs and symptoms of reactions/neuritis.
- Patient should be instructed to report immediately if they encounter/notice any problem/complication while on treatment.
- Conduct nerve function tests (VMT and ST of the eyes, hands and feet) to detect nerve function damage early to prevent the occurrence of disability.

REMEMBER to examine the eyes, hands and feet (including VMT-ST) at any time if the patient complains loss of sensation and/or change in muscle strength or problem with vision. This should be done regularly every month as long as the patient is on MDT and just before Release From Treatment (RFT).

Nerve function assessment at the end of treatment should be compared with that of the start of treatment. This includes comparing disability grades and VMT-ST status at the start and completion of treatment. The assessment should be scored as improved (I), same (S) or deteriorated (D) and be recorded in the patient record card and unit leprosy register.

11.12 Treatment Outcome

Multibacillary (MB) cases should complete a total of 12 month doses of MDT within a maximum period of 15 months.

- After completion of the 12 month doses of MDT, the patient should be released from treatment (RFT) and recorded as treatment completed.
- If a patient misses some treatment, the number of doses missed should be added on at the end to compensate for the missed doses. If the patient fails to complete their treatment within 15 months after initiation in total, should be recorded as default.
- If a MB patient recorded as defaulter reports back to the clinic, a second course of MDT should be started, after the importance of regular treatment is discussed with the patient.
- Patients who restarted treatment must be entered into a new treatment cohort, which is currently open for intake. They should be re registered as “return after default” with a new registration number. The previous number should be recorded in the column ‘remarks’ to indicate such patients have been included in two different cohorts.
- If a patient fails to complete the second course of MDT, she/he should not be given a third chance. Such patients must be recorded as default immediately after they have missed the 4th month doses of MDT. They should be told to report immediately if they notice signs of active disease once again.

Pauci-bacillary (PB) cases should complete 6 month doses of MDT within a maximum of 9 months period.

- After completion of the 6 month doses of MDT, the patient should be recorded as treatment completed and released from treatment (RFT).
- Patients who have missed more than 3 month doses of MDT in total should be recorded as default/Lost to follow-up. If they return to the clinic again, they should not be given a second course of MDT unless they are found to have signs of active disease.

Definitions of Treatment Outcome:

Treatment completed: A patient who has completed a full course of MDT within the prescribed period (six months doses in nine months for PB, and twelve months doses in 15 months for MB). **Died:** A patient who dies of any cause during the course of MDT **Lost to follow up:** A patient who has failed to collect more than three (consecutive or cumulative) four-weekly (monthly) doses of MDT. **Transfer out:** A patient who has started treatment and has been transferred to another health institution and for whom the treatment outcome is not known at the time of evaluation of the results of treatment.

16.13 Retrieval of Absentees

If a patient has neither attended the fixed clinic day nor frequented during the two weeks thereafter, he/she has to be considered as an absentee and should be retrieved. Consequently the following measures are suggested:

- Inquire from fellow patients as to why the patient has failed to collect his/her drugs and ask them to contact and advise the absentee.
- Notify the contact person, recorded in the register, through available means and request his/her assistance to encourage the patient to return for treatment.
- Communicate with health extension workers to assist in retrieving the patient.
- Visit the home of the patient if possible.

11.14 Treatment for Patients Living in Inaccessible Areas

Some patients who live in geographically inaccessible areas or whose lifestyle (e.g. pastoralists) does not permit regular visits to health facilities or who cannot attend clinics at certain times (e.g. rainy season) should be given a sufficient supply of MDT blisters to make for their period of absence. In exceptional cases it is acceptable to give a full course supply of MDT blisters to these patients. However, the involvement of health extension workers in monitoring of drug intake should always be ensured. Such patients should strongly be advised to report to the nearest health facility if they develop any problem or complication.

11.15 Referral of Leprosy Patients for Special Care

The patient requires referral to an experienced physician or hospital, if s/he has:

- Severe reaction with no response to steroid treatment (: two weeks for PB patients and four weeks for MB patients, respectively) - Recurrent/chronic reaction - Red and/or painful eye - Diabetes mellitus	- Not improved with current treatment - Developed a reaction for the second time - Deep ulcer(s); and - Permanent paralysis that is fitting for reconstructive surgery.

When a patient is referred, attach the copies of the sensation maps and strength records showing recent changes with the patient's referral form.

16.16 Follow-up and Care after Release from Treatment (RFT)

Most patients will have no further problems after release from treatment. However, after being congratulated for completing treatment, they need to be made aware of possible complications:

- The skin patches caused by the leprosy will not disappear immediately.
- Loss of sensation, muscle weakness and other nerve damage may also persist.
- Leprosy reaction can still develop after MDT and these reactions can be effectively treated. If any unusual symptoms occur, the person should come back immediately for examination and treatment.
- Recurrence of the disease (relapse) is rare, but if they suspect the disease has returned, they should come for further examination.
- Return to the health facility in **6** months' time for a routine follow-up review. Patients should be reviewed every 6 months for 5 years after release from treatment to identify any late reaction or nerve function damage.
- Visit or report to the nearby health facility whenever they have complaints.
- For patients who are resistant to rifampicin two of the following drugs are recommended clarithromycin ,minocycline or ofloxacilin plus clofazamine daily for 6 months followed by clofazamine clarithromycine of minocycline plus clofazamine for an additional 18 months

Care to leprosy patients include:

- Management of neuritis
- Provision of protective foot wears
- Provision of Vaseline ointment
- Basic medications such as analgesics, antibiotics, eye ointments have to be provided.

These are provided to the patients free of charge if and only if they are made available by the control programme. When this is not the case, patients should be encouraged to buy by themselves. All these care activities should be recorded in the RFT register and some of them (like neuritis treatment and provision of protective foot wears) should be reported quarterly.

16.17 Complications of Leprosy and Their Management

Complications of leprosy may occur or may have already occurred at the time of treatment. These include:

- adverse drug reaction
- leprosy reaction
- complications of advanced disease, and
- Psychosocial problems.

16.17.1 Management of Adverse Effects of drugs used in MDT

Drugs used in MDT are generally well tolerated with very minimal occurrence of serious adverse effects.

Educate the patient on common side effects:

- To anticipate some minor side effects that are of no harm and temporary
- To report to the HCW if they notice any unusual feelings or sickness

Management approach to adverse drug reaction:

- If the patient develops minor adverse effect => Conservative management
- If the patient develops major adverse effect => Refer to higher center for appropriate management

Table 55: Adverse effects of MDT drugs

Side Effects		Responsible Drug (s)	Action
Minor	Itching and skin rash	Rifampicin	Reassurance
	Loss of appetite, nausea and abdominal pain	Rifampicin	Give drugs with food
	Orange/red urine, faeces, saliva and sputum	Rifampicin	Reassurance (harmless and will disappear after cessation of MDT)
	Brown discoloration of skin lesions and pigmentation of the conjunctiva	Clofazimine	Reassurance (harmless and will disappear after cessation of MDT)
	Dryness of the skin and ichthiosis (thick, rough and scaly skin)	Clofazimine	Apply Vaseline ointment
	Insomnia (sleeping difficulties and disturbances)	Dapsone	Give the drug in the morning
	Anaemia	Dapsone	Give iron and folic acid
Major	Jaundice (Yellowish discoloration of the sclera, skin and mucous membranes)	Rifampicin Dapsone	Stop treatment and refer
	Skin rashes, severe itching and urticaria (pale red, raised itchy bumps)	Dapsone & Rifampicin	Stop treatment and refer

16.17.2 Leprosy Reactions

Leprosy reaction is an abnormally increased immunological response to the bacilli, presenting as acute inflammatory episodes. Our immune systems always fight against the leprosy bacilli even again those dead bacilli which need few years to clear totally from human body.

- It is the sudden appearance of symptoms and signs of inflammation on the skin, eyes and peripheral nerves.
- Clinically manifest with acute onset of redness, swelling and sometimes tenderness of the existing skin lesions or with appearance of even new skin lesions. There may be swelling, pain and tenderness of nerves, often accompanied by loss of function.
- It can occur before, during and after release of the patient from treatment.
- It often results in the long-term problems related to leprosy (deformity and disability) by damaging the nerve damage.
- Therefore, early detection and adequate management of reactions is very important.

There are two types of leprosy reactions:

i. **Type 1 reaction: also called Reversal Reaction**

ii. **Type 2 reaction: also called Erythema Nodosum Leprosum (ENL)**

Both types are further divided into mild or severe reactions.

Mild reaction is one that appears only on the skin (as long as it does not occur over a major nerve or in the face). It may manifest with mild fever and slight swelling (oedema) of the limbs. It can be managed with rest and analgesics.

Severe reactions affect the nerves or eyes and require corticosteroids treatment.

i. Type I Reaction

Both PB & MB patients can develop this type of reaction. Consider Type I reaction in patients with the following signs and symptoms:

- Pain over the lesion
- The lesion becomes more red, warm, swollen and tender
- Edema of the face, hands and feet
- Deterioration in the nerve function

Management of Mild Reversal Reaction:

Diagnosis: when a leprosy patient has swelling and redness of the skin lesions appearing areas other than the face and overlying nerve trunk.

If there are any signs of neuritis such as nerve pain or tenderness or loss of nerve function, the reaction is no longer mild, and should be managed as a severe reaction.

TREAT: patient should be treated with analgesics acetyl-salicylic acid (Aspirin 600 mg up to 6 times a day [adult dosage].

Examine the patient after one week. If the signs persist, continue the same treatment for another week after ruling out any new nerve damage. If nerve damage observed, manage the patient as severe reaction.

Management of Severe Reversal Reaction:

Diagnosis: when a leprosy patient develops one or more of the following signs:

- Pain or tenderness on palpation in one or more nerves, with or without loss of nerve function.
- Change in voluntary must testing (including eye closure) of less than six months duration. The change can be from strong to weak, weak to paralysis, or strong to paralysis.
- Change in Sensory test of less than six months duration. A change is considered to be significant when any hand or foot has increased loss of sensation at two or more points.
- A raised, red swollen patch overlying a nerve trunk or around an eye.
- Red, raised and ulcerating skin lesions.
- Edema of hands or feet.
- A mild reaction persisting for a period longer than 6 weeks.

TREAT: Administer prednisolone treatment unless the patient requires referral for impatient management at referral hospital. And if the patient has evidence of nerve involvement, advise to rest the affected limb.

ii. Type II Reaction (Erythema Nodosum Leprosum: ENL)

ENL occurs in MB patients only. It usually appears quickly and may disappear within 1-2 weeks. Erythematous (red) and tender (painful) sub-cutaneous nodules are usually present and are more commonly seen on the face and/or the external surface of the limb.in severe cases the skin lesion may ulcerate.

Management of Severe ENL: Signs and Treatment

Diagnosis: Suspect/confirm Type II reaction if a patient has one or more of the following:

- Appearance of Erythematous sub-cutaneous nodular lesions with ulceration
- Tenderness on palpation or spontaneous pain in (a) nerve trunk(s)
- Loss of muscle strength and/or loss of sensation in eyes, hands or feet for < 6 months
- Painful eyes, with redness around the limbus cornea, increased lacrimation, fixed narrowing (constriction) of the pupil and diminishing vision (irido cyclitis)
- Painful testicular swelling (orchitis)
- Painful swollen fingers (dactylitis)
- General condition: fever and malaise

Patients may experience several episodes of ENL, one after the other (recurrent ENL). MB patients may develop a reversal reaction and an ENL reaction simultaneously. All patients with ENL should **immediately** be referred (to a hospital where experienced health workers are available) with their clinical records to hospital for treatment. Patients with ENL reaction should always be admitted as this may be a life threatening condition.

N.B.: All ENL (Type II) reactions are severe

Table 56: Ambulatory treatment of severe reversal reaction with Prednisolone

Duration of Treatment		**Daily Dose**
MB	**PB**	**(do not exceed 1 mg per kg body wt)**
4 weeks	2 weeks	40 mg
4 weeks	2 weeks	30 mg
4 weeks	2 weeks	20 mg
4 weeks	2 weeks	15 mg
4 weeks	2 weeks	10 mg
4 weeks	2 weeks	5 mg
Total: 24 weeks	**Total: 12 weeks**	**STOP**

Follow up patients on prednisolone treatment (for reaction) every 2 weeks.

- Assess the patient condition and do VMT and ST at each visit.
- Refer any patient in whom nerve function deteriorates during the standard course or who does not show improvement after 4 weeks on prednisolone treatment to hospital where higher dosages of prednisolone can be given.
- Refer a patient who has responded positively to a previous full course of prednisolone, but the reaction re-occurs or the nerve function deteriorates.

Criteria for referral to a hospital during reaction:	
▪ ENL reaction ▪ Deep ulcer(s) ▪ Red and/or painful eye ▪ Pregnancy ▪ Younger than 12 years of age ▪ Severe peptic ulcer disease	▪ Diabetes ▪ General illness with fever ▪ Patient who improved during previous courses, but develops a reaction for 3rd time ▪ Severe depression or psychosis ▪ Suspected relapse

Management of Severe Reactions in Hospitals:

For hospitalized patients the initial dose of prednisolone will be as high as 80mg in a daily single morning dose. The dose can be tapered by 10mg every 1-2 weeks depending on the severity and response to treatment until a level of 40mg is reached. Then normal tapering off should recommence as indicated in the table above. If at any dosage, the clinical signs of reaction fail to improve after 5-7 days or if nerve damage increases, the prednisolone dosage should be doubled for about 2 weeks. Then reduce stepwise at intervals of 2-4 weeks or so till it returns to the previous level; normal tapering off should then recommence.

16.17.3 Relapse in Leprosy

Relapse is defined as the re-occurrence of the disease at any time after the completion of a full course of treatment with MDT.

Relapse is defined as the multiplication of M.Leprae suspected by an increase of bacillary index (BI) by 2 units at any single site as compared to the base line with evidence of new active skin lesion. Or biopsy should be done from new active skin lesion and M.Leprae should be identified on the histology.

- If a full course of treatment has been administered properly, relapse is generally rare.
- Most relapses occur long after the treatment was given, sometimes more than 10 years later.
- Relapse cases can be treated effectively with the same MDT regimen as there is minimal risk of acquired drug resistance in leprosy.

Use the table below to differentiate PB relapses from reversal reactions.

Table 57: Differentiating relapse and reactions

Criteria	Relapse	Reaction
Development of signs	Slow	Sudden
Duration after treatment completion	> 3 years	< 3 years
Site	New patches	Over old patches
Tenderness/ pain	No (unless also in reaction)	Nerves usually, skin sometimes
Damage	No (unless also in reaction)	Sudden and rapid
General condition	Not affected (unless also in reaction)	Often fever, joint pain etc.
"therapeutic trial" using steroids	No clinical improvement	Rapid clinical improvement

MB relapses should be investigated by using skin smears, histopathology and, where possible, for drug sensitivity using recently standardized molecular tests. Hence, such cases should be referred to higher level immediately.

Management approach to patient with relapse:

At peripheral level: Suspected relapses should be referred for further investigation and management decision to a referral center.

At Referral level: **Suspected PB relapse**: PB relapse is diagnosed by the appearance of a definite new skin lesion and/or a positive skin smear. However, the diagnosis of a PB relapse can never be absolutely certain. A skin smear should be carried out, if at all possible, to ensure that an MB case is not being misclassified as PB. The evidence for either a relapse or a reaction must be weighed and a decision made. A case PB relapse is treated with six-month course of PB-MDT.

MB relapse is diagnosed by the appearance of definite new skin lesions and/or an increase in the bacterial index (BI) of two or more units at any single site compared to BI taken from the same site at the previous examination. Care should be taken not miss patients suffering from leprosy reactions. MB relapses are generally treated with 12 months' of MB-MDT.

- DO careful examination of the skin and asses the nerve function in order to identify any signs of a recent reaction.
- Arrange for a skin smear test to be done; an MB relapse is associated with an increase in the bacillary load. Obviously, if no previous smear has been done, it is impossible to identify an increase. In this case, the presence of solid staining bacilli in the smear provides support to the diagnosis of a relapse.
- If the diagnosis id uncertain after these investigations:
    - A trial of steroids may be considered and if it is a reaction, clinical signs would begin to settle in 10-14 days while remain unchanged in cases of relapse.

16.17.4 Complications in Leprosy

Advanced disease of leprosy may results in eye problems leading to blindness because of damage to the cornea, or due to damage to the internal structures of the eye. The health worker must refer to an eye specialist any patient who reports decreased vision or has a red or painful eye.

Patients may already have sunken nose, loss of eyebrows and the so-called 'leonine' face, which used to be characteristics of untreated MB leprosy; these are cosmetic problems and visible disfigurements that lead to severe stigma and discrimination. Plastic surgery is needed to correct these lesions.

Patients with suspected complication should be referred to the nearest hospital for appropriate management.

16.18 Prevention of Disability (POD) in Leprosy

Most disability and deformity result directly or indirectly from loss of function of peripheral nerves supplying the eyes, hands and/or feet.

Disability and deformity can be prevented by timely detection and prompt treatment of neuritis. Poor treatment of leprosy can cause permanent disability and deformity, which aggravates hopelessness, and stigma and fear against those affected.

The following procedures best prevent disability:

- Early diagnosis of leprosy and prompt treatment.
- Recognize nerve function impairment at the time of diagnosis and start treatment with steroids for recent development (less than 6 months).
- Recognize and promptly treat new signs and symptoms of leprosy reactions with nerve involvement during treatment.
- Educate patients to recognize early signs of nerve function impairment and report this immediately.
- Train patients on self-care for patients at risk of developing disabilities.

Interventions for Preventing Disability

Patients as well as health workers should learn how to manage specific leprosy-related problems and disabilities. There are three categories under which useful interventions can be practiced to prevent (further) disability in leprosy. These are:

1. Home-based self-care
2. Simple interventions organized at the local clinic
3. Referral for complex interventions that require specialty care

A) Home-based Self-care to Prevent Disability:

Health workers should educate leprosy patients about self-care while they are on treatment and upon release from treatment to help them prevent disability.

The most effective self-care training is:

- Specific to the patient (targets disabilities they have/are at risk of)
- Practical (the patients actually do the self-care with the health worker)
- Achievable by the patient (promotes simple and affordable methods)
- Repeated (what has been taught is reviewed each time the patient visits to make sure that they have understood and are practicing it).
- Empowering(the patient believes "I can do it" in terms of self-care and prevention of further impairments)

Self-care for the Eyes

<table>
<tr><th>If there is:</th><th>Motor weakness: can't close eyes fully
(lagophthalmos)</th><th>Sensory impairment
(corneal anesthesia)</th></tr>
<tr><td rowspan="2">The patient must be advised to:</td><td>• Exercise (close the eyes strongly) if the muscles are weak, or
• Do 'passive blink' often if eyelid muscles are completely paralyzed
• Cover the eyes with a clean cloth when sleeping;</td><td>Do "Think-blink" exercises (consciously blink eyes frequently)</td></tr>
<tr><td colspan="2">1. Protect eyes during the day, e.g., use spectacles, hat, scarf;
2. Inspect the eyes daily using mirror and check for foreign bodies or redness;
3. Clean eyes daily with clean water; and
4. Apply lubricating eye drops or one drop of castor oil in the morning and evening.</td></tr>
</table>

Self-care for the Hands

When patients have problems on the hands, advise them to do the following at home:

- Inspect the hands daily for signs of injury.
- Soak the insensitive hand in water for about 30 minutes every day to maintain skin elasticity and prevent dryness of the skin.
- Use a rough stone to smoothen the callus, and then apply oil or petroleum jelly when the skin is still wet to prevent it from drying out.
- Use a clean cloth to cover any open wound.
- Avoid handling hot materials with bare hand.
- If there is weakness of the muscle in the hand, passive stretching and active exercises should be done to prevent muscle tightening and ensure some strengthening.

Self-care for the Feet

When the patient has problems on the feet, advise for the following to be done at home:

- Inspect the feet daily for signs of injury.
- Soak and then apply oil to the feet. As for the hands, use a rough stone to rub away the callus.
- Walk as little as possible slowly. Rest frequently.
- If ulcers are present, rest is essential.
- Use a clean cloth to cover open wounds.
- If there is a foot-drop, do passive stretching to prevent a contracture of the Achilles tendon.

B) Simple Interventions Organized at the Local Clinic:

When the patient has eye problems:

- Provide to the patient saline drops for use at home if the eyes are very dry.
- Treat conjunctivitis with antibiotics and an eye pad.
- Refer more serious eye problems to an eye clinic or ophthalmologist.

When the patient has problems on the hand:

- Provide available cooking gloves if the patient has insensitive hands.
- Refer more serious hand problems to the referral centers for physical rehabilitation

Interventions on the Feet: Provision of Protective Footwear

Any kind of footwear will protect the feet as long as it has:

- Hard sole (so thorns, glass and the like on the road can't penetrate);
- Soft insole (to spread force and prevent blisters);
- Back-strap or heel cup (so footwear can't fall off); and
- Flexible, adjustable, good fit (e.g. made of leather or cloth, with laces, buckles, or Velcro).

If no deformity is present, provide proper protective footwear (canvas shoes, embedded with MCR) or market shoes. Patients can collect canvas shoes, embedded with micro cellular rubber (MCR), and other orthopedic appliances from MDT providing health facilities and nearby orthopedic workshops respectively. If significant foot deformity is present, use special orthopedic appliances made in orthopedic workshops.

Refer more serious problems to the referral centers for physical rehabilitation.

Closed plastic shoes are not suitable as they exacerbate sweating, blisters, and infection of the skin as well as underlying tissues.

C) Arrange referral for specialty for the following conditions:

- Any acute eye problem
- lagophthalmos
- Thick callus and chronic ulcers
- weakness or a contracture/claw-hand
- invasive infection (the hand is hot, red and swollen)
- Foot-drop

16.17 Prevention of Leprosy

Chemo prophylaxis:

Single dose rifampicin (SDR) as preventive treatment for adult and child (2 years of age and above) contacts of leprosy patients, after excluding leprosy and TB disease and in the absence of other contraindications. The COLEP2 randomized controlled trial found SDR in leprosy contacts associated with a 57% reduction in the risk of leprosy after 2 years and 30% after 5–6 years.

BCG: BCG vaccination has a documented and substantial effect in preventing leprosy and is therefore considered as an important tool for leprosy prevention.

17. COMMUNITY BASED TB CARE, ENGAGING ALL CARE PROVIDERS, AND THE TBL ACSM

17.1 Community Based TB prevention and Care (CBTC)

Community Based TB Care is a working partnership between the health sector and the community in the prevention and care activities of TB. Communities' involvement in TBL control aims at empowering the community to produce its own health through Health extension program package services.

Objectives of CBTC

- Increase community awareness on TB transmission, prevention and treatment
- Improve TB case notification through early identification presumptive TB cases
- Ensure access to patient-centered TB care services
- Ensure patient adherence support and tracing of absentees/interrupters

Components of CBTC

- Community awareness creation and social mobilization on TBL
- Identification and referral of individuals who are presumptive TB case
- TB and Leprosy contact tracing at household and community level
- Community based DOT and treatment follow-up
- Retrieve TB treatment absentees, interrupters and lost to follow up tracing
- Promotion of TB Infection control at community and household level

17.1.2 Implementation of Community based TB Care

CBTC implementation is a collective responsibility of all stakeholders including political and health managers, health care workers, Health extension workers and the com- munity at large. The CBTC package is among the sixteen health extension packages being implemented at health post level and community.

Role of Health Centers in CBTC: TB focal from the catchment health centre provides TBL related technical, programmatic and administrative support for the five networked health posts. Health posts get monthly re-supply of TBL anti-TB drugs, recording and reporting tools. Besides, catchment health centers are responsible in capacity building of HEWs and monitoring of the implementation of CBTC activities.

Role of Health Posts in CBTC: Health extension workers implement all the CBTC packages as per the national implementation guidelines and receives support from the catchment health centers and Woreda Health office. *For details, Please refer to the updated version of National CBTC implementation guideline.*

17.1.3 Community Engagement and Empowerment Strategy

Health Development Army (HDA): HDA is a social mobilization community level structure whereby six households form a one-to-five network for the purpose of identification of bottlenecks to the implementation of the HEP packages, designing solutions for the identified gaps and learning from their experiences in HEP implementation.

HDA and TB Prevention and Control

The prevention and control of TB is one of the 16 HEP packages being implemented by the HDA. The HDA will be vital in:

- Improving community's awareness on TB prevention and control
- Fostering early identification and referral of TB suspects
- Active TB contacts tracing and referral
- Improving Community based DOT and adherence to treatment
- Minimizing TB treatment interruption and in fostering defaulters tracing
- Enhancing TB Infection control measures at community and household level

17.2 ACSM Support for TBL Control Program

17.2.1 Principles of ACSM

Advocacy, communication and social mobilization (ACSM) is a concept that embraces the three key communication strategies used to influence policy changes and sustain commitments. The goal is to improve knowledge of the target audiences on TB control policies, programmes and services with an intended result of bringing positive behavioural changes, and ensuring the engagement of the society in the fight to Stop TB epidemic.

Advocacy is intended to secure the support of key constituencies in relevant local, national and international policy discussions and is expected to prompt greater accountability from governmental and international actors. It is a process to create change in policies, laws and practices.

Communication (Behaviour Change/program communication) is concerned with informing the public and people with TB and to empower them to express their needs and take action. It also encourages providers to respect the expressed needs and perspectives of patients to make TB services more responsive to community needs. Behavior Change or Program Communication aims at increasing knowledge bring attitude change and promote practice among various groups of people. This is done by creating awareness about TB, improving interpersonal communication between patients and providers and empowering people to take actions.

Social mobilization is the process of bringing together all feasible and practical inter-sectoral allies to raise people's knowledge of and demand for good-quality TB care. It also assists to mobilize resources and services and strengthen community participation for sustainability. Social mobilization is important to create community will and commitment to participate in TB control and prevention within the context of the community. Communities, religious leaders, social networks etc. are among the targets.

Objectives

- Ensure the commitment of policy/ decision makers to mobilize resources for TBL prevention and control.
- Improve communities' healthcare seeking behavior on TBL and enhance TB case detection.
- Fight stigma and discrimination against TBL.

Strategies

The key TB controls challenges (commitment and resources, case finding & treatment adherence, stigma and discrimination and sustainability and self-reliance) are addressed through the following ACSM strategies:

- Empower and involve people affected by the diseases in the prevention and control activities.
- Strengthening evidence-based advocacy to ensure political commitment and resource mobilization.
- Promote use of standardized & harmonized guidelines and culture sensitive messages and materials.
- Educate different segments of the population to take action through mass media, school health programs, community groups, religious leaders, health extension workers and health education programs in HFs.
- Improve ACSM skills of program managers, service providers and promoters by implementing continuing professional development activities on TBL ACSM.
- Encourage formative researches to provide reliable data for ACSM materials development and monitoring and evaluation.

Key ACSM Activities

(1) Advocacy Activities:

- Develop TBL ACSM strategic framework, in line with HSTP and WHO End TB strategy,
- Strengthen a communication support coordinating forum for TBL control program,
- Ensure political commitment and support through sensitizing people in posi- tion of influence, media professionals' related promoters,
- Commemorate the world TB day integrating with annual TB research conference and carry out world Leprosy day.
- Involve public figures to support the ongoing TBL TB/HIV and MDR-TB control program,
- Enhance data generating efforts through M&E and operational researches etc…

(2) Behavior Change Communication Activities:

- Identify KAP gaps and develop target specific and program focused messag- es/materials, based on the gaps
- Carryout communication interventions for different segments and high risk population groups,
- Revitalize ACSM capacity building trainings for program managers, officers and service providers including HEWs etc…

(3) Social Mobilization Activities:

- Coordinate/Facilitate community based communication interventions through implementing HEP & HAD strategies,
- Organize community events (festivals, testimonials, community drama, etc…) in all urban and rural Kebeles,

17.3 Engaging all care providers in TB

17.3.1 Introduction

Engaging all relevant healthcare providers in TB care and control through public-private mix approaches is an essential component of the National TB control strategy. Public-Private Mix for TB Care and Control (PPM-TB) represents a comprehensive approach for systematic involvement of all relevant healthcare providers in TB control activities. PPM-TB encompasses diverse collaborative strategies such as public-private (between public and the private-for-profit and private-for-non-profit sectors); public-public (between public and other public sector care providers such as general hospitals, prison or military health services as well as social security organizations); and private-private (between an NGO or a private hospital and the neighborhood private providers) collaboration. PPM-TB also implies engaging relevant care providers in prevention and management of TB/HIV co-infection and Drug Resistant-TB. At present, Ethiopia's PPM-TB model focuses on private-for-profit, private-not-for-profit (NGO) and workplace health providers. PPM model creates an opportunity to providers outside the public sector to build their capacity to contribute to the TB control efforts maintaining the national standards and guidelines.

RATIONALE

- Strong political commitment to encourage the contribution of private sector in health services delivery and the growing contribution of the private sectors in health sector.
- Enhanced quality of TB diagnosis, care and treatment
- The growing need to improved equity and access to services
- The need to standardize case management practices to reduce treatment errors and rational use of anti-TB drugs through formal engagement of the providers
- Increasing workload of public health facilities

17.3.2 Service Areas for Engaging Private Sectors in PPM DOTS

Private sectors and all other relevant providers outside of the realms of the National TB Program are encouraged to be engaged in the delivery of following services:

- Advocacy, communication and social mobilization
- Identification and referral of presumptive TB cases to nationally accredited diagnostic centre
- Participation in TB diagnostics and quality assurance services, Treatment delivery services including Community TB care services and delivering TB/HIV interventions, MDR-TB diagnostic and/or treatment services
- Mentoring, supportive supervisions, monitoring of performance and operational researches
- Sputum sample collection and transportation services to the designated diagnostic centre

Potential Private and governmental Care providers for engaging in PPM-TB in Ethiopia include:

1. **Private-for-profit**: Private hospitals, Clinics, centers, diagnostic labs, drug outlets
1. **Private-for-non-profit**: FBO clinics, NGO clinics, workplace clinics
2. **Other governmental organizations**: Uniformed service clinics, prison, factory

The delivery of one or combination of services can apply to one private facility after fulfilling the requirements, completion of preparatory procedures and signing memorandum of understanding (MOU) with the responsible governmental body. Detailed guidance on PPM-TB is provided in the latest edition of the National PPM-TB implementation guidelines and hence the NTP advises the users of this guideline to refer to it for details.

18. TB AND LEPROSY LOGISTICS SUPPLY MANAGEMENT SYSTEM

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 tuberculosis & leprosy has an adequate and uninterrupted supply of drugs, laboratory reagents, medical supplies and equipment.

18.1 TBL logistic supply management system arrangement

National TBL program in collaboration with the Ethiopian Pharmaceuticals Supply Agency (EPSA) are responsible to ensure uninterrupted and sufficient supply of TBL commodities in TB units through timely and appropriate selection, quantification, procurement, warehousing, and distribution and inventory management systems.

The drug management cycle for TBL Commodities:

Selection of TBL Supplies: Careful selection of TBL pharmaceuticals results in a high quality of care for patients, rational use of medicines and cost-effective use of health resources. Anti-TB medicines are selected based on disease prevalence, drug resistance patterns, and shall include the selection of medicines from quality-assured sources such as WHO Prequalification of Medicines Program (PQP), Stringent Drug Regulatory Authority (SRA)

Quantification and Procurement of TBL Commodities: The national TBL Control program, EPSA and other stakeholders conduct annual forecasting and quantification exercise to determine the country level need based on the updated information from program and logistic data. The quantification takes in to account: shelf life of the drugs, Length of intensive and continuous phase, lead time before procurement, Consumption report and annual enrollment plan.

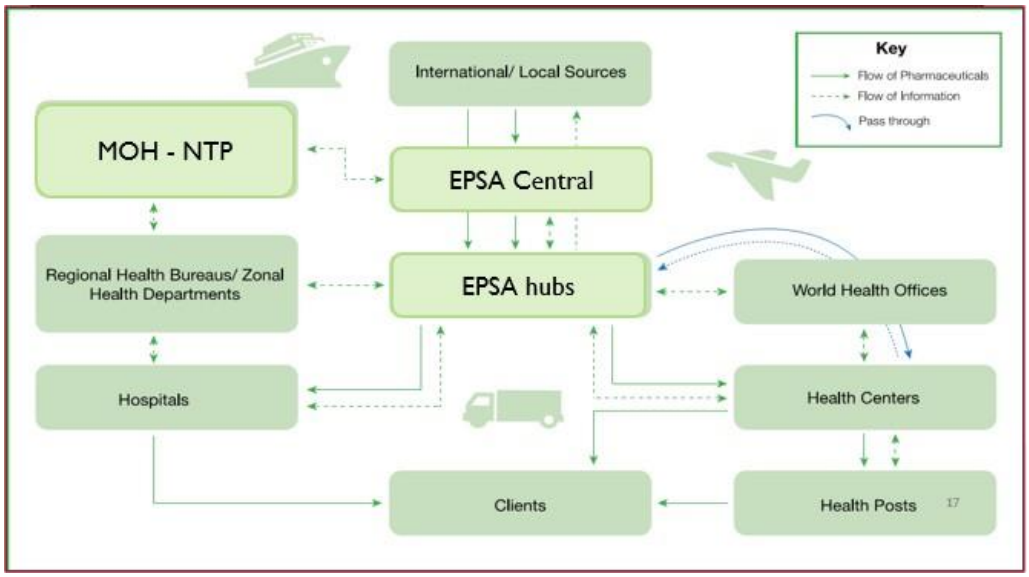
Effective management of procurement ensures the availability of selected drugs of assured standards of quality, in the right quantities, at the right time and at affordable prices. This is mainly managed by EPSA.

Distribution and storage of TBL drugs: EPSA handles timely clearance of custom and distribution of TBL medicines and related commodities to the respective health facilities. As per the national IPLS, Anti-TB commodities are stored at central warehouse, EPSA hubs and health facilities pharmacy stores. Health facilities, likewise, manage TBL medicines with rigorous recording and inventory management protocol as per national IPLS Manual, see figure 17 for the overall flow of commodities and information in the IPLS.

18.2 Distribution of First line Anti-TB drugs

The distribution of first line Anti-TB drugs follows the national IPLS. According to this the respective EPSA hubs re-supply hospitals and health centers every two months, while Health posts are re-supplied by the catchment health center monthly, based on their consumption report generated by the pharmacy unit of the center using logistics management information system (LMIS). TB clinics (including PPM sites) with no access to EPSA service are advised to receive their re-supply through the nearest Woreda/Town Health office.

Figure 17: Overall Flow of Commodities and Information in the IPLS



18.3 Distribution of Second line Anti-TB drugs

National supply and distribution management system used for second line Ant-TB drugs and related commodities is slightly different from IPLS as these products are imported for small number of patients and have short shelf-life predisposing the product for stock rupture and/or wastage.

18.3.1 Distribution to treatment initiating centers

The New Distribution System Design:

A new distribution system is designed to 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.

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.

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.

18.4 Distribution of Leprosy Commodities

Leprosy drugs are supplied in small volume and require strict distribution and stock inventory management system to avoid frequent stock rupture. While maintaining components of IPLS for anti-leprosy drugs distribution system, the following points need due emphasis and implement:

Distribution of anti-leprosy drugs should be based on the mapping study of leprosy disease burden. The mapping classified the areas into three different levels high, medium and low burden area.

- The distribution to high burden woreda will be done with high emphasis either directly through EPSA hub or through woreda level
- For medium leprosy burden woreda, EPSA hubs will do the supply based on the RRF request from facilities or woreda after cross checking the areas and the patient number based on the

mapping result and the quantity to refill might not to maintain the maximum rather the two month adjusted quantity to be supplied

- For low burden facilities; the request and refill will be made through the woreda i.e. some stock will be stored at woreda level.
- Facilities may not need to maintain stock of these drugs if there is no leprosy case in the health facility. Facilities should report to their respective Woreda promptly when they encounter the case and the Woreda requests EPSA.

18.5 Anti-TB commodities inventory management at facility level

The purpose of an inventory control system is to inform personnel when and how much of a commodity to order and to maintain an appropriate stock level to meet the needs of patients to prevents shortages, oversupply, and expiry of commodities.

18.6 Rational medicine use and adherence

In the context of TB treatment, a rational use of drugs is implemented with adherence to treatment protocol as per national TB treatment guideline. This will ensure the maximum benefit to the patients and to the health program at the same time. This has to be complemented with full adherence to a properly prescribed treatment. The drugs used in the first line treatment of TB are presented as fixed dose combination (FDC) considering the benefit of using FDCs over the individual formulations, see table 58.

Table 58: First line Anti-TB Drugs Formulations

Patient type	DRUGS	FORMULATION	STRENGTH(mg)	Preparation, route
Adult (Age 15 years and above)	HRZE	Tablet	75/150/400/275	FDC, oral
	HR	Tablet	75/150	FDC, oral
	RHE	Tablet	150/75/275	FDC, oral
	E	Tablet	400	Loose, oral
Pediatric Body- weight less than 25kg	RHZ	75/50/150	dispersible tab	FDC, oral
	RH	75/50	dispersible tab	FDC, oral
	E	100	dispersible tab	Loose, oral
	H	100	dispersible tab	Loose, oral

Distribution supply system for Anti-TB commodities supplied in small quantity: Some Anti-TB and leprosy commodities are supplied in small volume and require strict distribution and stock inventory management system to avoid frequent stock rupture. These commodities include Ethambutol, Streptomycin, pediatric formulations, SLDs and leprosy drugs.

To improve the efficient use and minimize the wastage, such commodities need to be distributed considering morbidity data in addition to the consumption report. In addition, the program recommends delegating a selected health facility/ woreda/Town Health office to receive such commodities from PFSA hubs and re-supply the remaining facilities on monthly basis using the re-

supply system for health posts. Recommendations for SLDs are presented on national PMDT guidelines.

Records and Reports used to manage Essential TB commodities

In the management of Essential TB commodities, the following standard LMIS recording and reporting forms are used:

Bin Card: is an individual stock keeping card that keeps information about a single lot of a product. The bin card should note quantities received or issued by the store, stock on hand of the specific product, as well as any losses and adjustments, etc. Note that all dispensing units, including TB clinics, are required to have regularly updated bin cards. Bin card is to be displayed at the bins (or shelf) where the lot is stored.

Internal Facility Reporting & Requesting Forms (IRRF): This form is used to re-supply the service outlets using the pharmaceuticals within the facility. Hence, the TB focal must fill the IRRF on agreed intervals to be re-supplied with the essential TB commodities from the institutional store.

Note that All TB commodities supplied from EPSA must be stored at the institutional store before supplies to TB clinic to dispense for clients.

Facility Combined Report And Requisition Form (RRF): this form is used by Hospitals and Health Centers to combine all supplies to be reported and ordered from PFSA hubs to get re-supply. This form is expected to be filled every 2 months by the health facilities and be sent to PFSA hubs and woreda Health office.

Consumption Records: is used to record the quantity of each item dispensed to a patient. Consumption records are completed by health personnel at the TB clinics whenever supplies are dispensed to patients.

Essential data items for LMIS

To ensure the presence of sufficient pharmaceuticals stock in health facilities and re-supply from PFSA hubs, The LMIS uses the following three variables on each pharmaceutical:

a) **Stock on hand:** The quantities of usable stock available at a particular point in time.
b) **Consumption Data:** The quantity of pharmaceuticals used during the reporting period.
c) **Losses/Adjustments:** Losses are the quantities of products removed from stock for any reason other than provision of services to patients or issuing to another facility (e.g. expiry, lost, theft, or damage) and are recorded as negative numbers.

Adjustments are quantities of a product received from any source other than EPSA mechanism, or issued to or received from other health facilities. An adjustment may also be a correction due to an error in mathematics. An adjustment could be a negative or positive number.

Note that reasons for losses/adjustments should be registered under the Remark column.

Different types of LMIS forms and their use

Logistics information is collected and reported monthly by Health Posts and every two monthly by Health Centers and Hospitals on logistics management information system (LMIS) forms.

- A combined order and report form is completed by Health Centres and Hospitals and sent to EPSA for order processing; the Health Centre order includes the commodity requirements of the Health Posts.
- A copy of the Health Centre report and order and a copy of each Health Post report are sent to the Woreda Health Office for management and supervision purposes; a copy of the Hospital report and order is sent to the Regional Health Bureau for management and supervision purposes.
- The Woreda Health Office aggregate logistics data from the Health Centers and send aggregated reports of logistics data to the Regional Health Bureau.

Note: Health Post data is already included in the Health Centre information and it is not added up in the aggregation again for it would be double counting of the Health Post data.

Anti-TB commodities inventory management at facility level

The purpose of an inventory control system is to inform personnel when and how much of a commodity to order and to maintain an appropriate stock level to meet the needs of patients to prevents shortages, oversupply, and expiry of commodities.

- At health centers/ hospital level, maximum of four months' stock, and minimum of two months' stock of Anti-TB medicines are recommended while two weeks are order points to request emergency re-supply.
- At health post level, maximum two months of stock and minimum one month of stock are recommended while one week of time is set to be order point to request emergency re-supply from catchment Health center.

The pharmacy unit at health center/hospitals re-supplies Anti-TB commodities to the "TB clinic" on every two weeks interval using IRRF. Note that the "TB unit" of the facility must add up the consumption at the clinic and catchment health posts to calculate IRRF and get re-supply from the pharmacy store.

18.7 TB Patient Kits System in Ethiopia

The national TB control program has implemented the use of "TB patient kits" for the treatment of Adult TB patients considering its additional benefits: contributing to efficient procurement, simplifying drug quantification, promoting rational drug use, promoting the patient-centered care, and facilitating drug management.

A TB patient kit is a pre-packed container that contains the full course of Anti-TB drugs needed to treat a single patient. The kit helps limit confusion and wastage, and makes it easier to monitor the regularity of treatment; avoiding stock-outs and maintains a patient confidence in the health system. TB patient kit consists of Intensive Phase of 56 daily doses (2 months) and Continuation Phase of 122 daily doses (4 months).

TB patient kit for New TB patients

Treatment consists of Intensive Phase of 56 daily doses (2 months) and Continuation Phase of 112 daily doses (4 months).

A kit for New TB patients contains two separate boxes:

- One for the Intensive Phase: 4 drug fixed-dose combination tablets (FDC-4) (RHZE 150/75/400/275 mg).
- One for the Continuation Phase: 2 drug fixed-dose combination tablets (FDC-2) (RH 150/75 mg)

NB on blister pack contains 28 tables packed in blister sheets of 4 rows of 7 tablets.

Note on TB patient kits:

- TB patient kit is only for adults and adolescents
- A kit is pre-prepared only for weight band range of 40-54kg
- Patients weighing either below 40kg or exceeding 54kg kit needs to be adjusted before initiation of treatment
- If patient interrupt treatment before completion of full course, readjust the kit to be used by another patient.
- Note that one blister pack contains FDC 28 tabs
- Always level the patients details on the outer cover of the patient kit

18.7.1 Dose Adjustment for using patient kits

Dosage according to the patient's weight is essential in tuberculosis control. Patient kit contains all the drugs (see table 59), needed for the most common weight band of patients 40-54 kg. Kits are easily adjustable by health workers (see table 60) at the start of the treatment by removing or adding blister sheets to accommodate other standard weight bands. One blister pack contains 28 tables of FDC.

Table 59: Pre-packed TB Kit for New TB Patient

Drugs Name	Daily FDC tablets per day (A)	Duration of treatment in Months (B)	Total tabs required per phase (C=A x B)	Number of tablets in one Blister pack (D)	Total of Blister packs required for a kit (=C/D)
RHZE 150/75/400/275mg	3	2	168	28	6
RH 150/75 mg	3	4	336	28	12

Table 60: Adjustments to the kit based of patient weight band for New TB Patient

Patient weight	**RHZE FDC blisters needed in Intensive Phase**	**Adjustment (from the pre-packed)**	**RH blisters needed for continuation phase**	**Adjustment (from the pre-packed)**
20-29	3	Remove 3 blister	6	Remove 6 blister
30-39	4	Remove 2 blister	8	Remove 4 blister
40-54	6	None	12	None
≥55	8	Add 2 blister	16	Add 4 blister

18.7.2 USE TB kit system at Health post level

Once patients are initiated TB treatment with TB kit, their kit may be transferred to the delegated health post by the health extension worker. Unlike the blister pack, there is no need for monthly refill for the HEW as the full course of treatment for each patient can be transferred at once. The Health worker/pharmacy personnel must supervise the inventory management and practice of DOT at health post level during supervisory visits.

19 PROGRAMMATIC MANAGEMENT OF TUBERCULOSIS

19.1 TBL program management levels and coordination mechanisms

Structure of the National TB and Leprosy Control Program

National Level: The National TB and Leprosy Control Program under the Diseases Prevention and Control Directorate (DPCD) of the Ministry of Health with similar structure at RHBs and TBL focal persons down to woreda health offices. At national level, it is led by TBL case team coordinator who works with officers delegated to lead major thematic areas of TBL activities and Technical advisors of the program. Furthermore, the program closely works with various agencies of the ministry which include:-

- Ethiopian Pharmaceutical Supply Agency (EPSA) for the supply chain management,
- Ethiopian Food and Drug Authority (EFDA) for the regulatory aspect of Tuberculosis, and
- Ethiopian Public Health Institute (EPHI) for the laboratory aspects of TB and leprosy.
- The Armauer Hansen Research Institute (AHRI) for TBL related research coordination.

Besides, TB/HIV TWGs has been established to support programmatic implementation of TBL program both at national and regional level. In addition, at national level sub technical working groups has been established to support the thematic areas under the TBL program.

Regional Health Bureau level: TBL and TB/HIV program is managed by TB/HIV case team under Health Promotion and Disease Prevention core-processes.

Zonal/Subcity Level, there are focal points responsible for coordination and management of TB/HIV Prevention and control activities in their respective health offices.

Woreda level, in addition to TB/HIV prevention and control activities in their respective health offices, the office is responsible for District level management in public and private facilities with TB TB services and CTBC at health post level.

19.2 TB services at Health Facility Level

Health Posts: Health posts are the level where community based TB care (CBTC) services are implemented by the health extension workers as part of the sixteen Health extension package where by the HEW pay critical role on TBL case finding, treatment support and retrieve treatment interrupters, and promotion of preventive activities.

Health Centers: Health Centers carryout all activities as health posts, and provide microscopy services for sputum smear examination, short course chemotherapy (SCC) for TB and MDT and prevention of disability (POD) for leprosy, diagnose and treat reactions and other complications, carry out TB/HIV collaborative activities. Health centers provide support to health post staffs on CBTC, keeping program record and generate timely programmatic reports. Selected health centers may also serve as treatment follow up centers (TFCs) for DR-TB services.

The main responsibility of TFCs are:-

- Manage all patients referred/transferred from DR-TB treatment initiation center
- Involve in case finding process of DR-TB including contact screening.

Hospitals: Hospitals carry out all the activities listed under health centers, provide referral services for diagnosis and inpatient treatment for seriously ill patients. Selected hospitals also provide/ initiate treatment for DR-TB patients, serving as Treatment Inititiation Centers (TICs). The main responsibilities of TIC are:-

- Designate space for inpatient and outpatient DR-TB treatment service
- Handle all patient preparation and initiation of treatment with SLDs
- Admit difficult cases and those with serious complications
- Schedule and handle patient monitoring tests during and post treatment.
- Involve in case finding process of DR-TB including contact screening.

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

Team composition: Clinicians from DR-TB center, Nurses, Pharmacist, Laboratory technologist, Chief clinical officer, Social workers, Local health office (Regional, Zonal &/or Woreda) TBL officers, and technical advisors.

NB: Both Hospitals and health centers have complementary roles in order for the program to function efficiently and deliver comprehensive DR-TB care.

19.3 DR-TB services in Ethiopia

19.3.1 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.

19.3.2 Minimum requirement for DRTB service provision

Table 61: Minimum requirements of centers for DRTB service provision

Criteria	Referral TIC	Ambulatory TIC	TFC
Service level	Hospitals serving as a comprehensive referral centers for management DR-TB and its complications.	Hospitals (or Health centers) that provide initiation and follow up services for stable and non-complicated DR-TB patients.	DOT clinics that provide treatment follow up and care.
Implementation	Regional level	Zonal level	Woreda level
DR-TB team	1 Internist &/or pediatrician 1 Medical doctor 1-2 HO or BSC nurses, 4-6 staff nurse +/- nurse counselor,	1 Medical doctor 1 HO or BSC nurse, 2 DOT nurses +/- nurse counselor, 1 lab personnel, 1 pharmacy personnel, +/-	1 HO/BSC nurse 1 TB DOTs 1 woreda TB focal person
	1 lab personnel, 1 pharmacy personnel, +/- Psychiatrist 1 social worker, 11 data clerk/HIT	1 Psychiatry nurse +/- 1 HIT +/-	
DR-TB out-patient services	1 exam rooms, 1 DOT clinic, 1 dispensary and sample processing area	1 exam room, 1 DOT clinic and sample collection area	TB DOTS clinic
DR-TB in patient service	Separate MDR TB ward (atleast10 beds); 2 isolation room	Short term admission area within the medical ward(at least 2 beds); +/- isolation room	NA
Designated Waiting area	Required	Required	Required
TB IC minimum packages	Required	Required	Required
DR-TB diagnostic service	• On-site Xpert MTB/RIF services • Link with culture and DST center	• On-site Xpert MTB/ RIF services • Link with culture and DST center	• Link with Xpert service or Culture & DST centers
Laboratory monitoring tests*	AFB, CBC, chemistry, electrolytes, hormone assay, radiology, EKG, audiometry	AFB, CBC, chemistry, electrolytes, radiology, +/-hormone assay	AFB

19.3.3 Service initiation steps for DR-TB

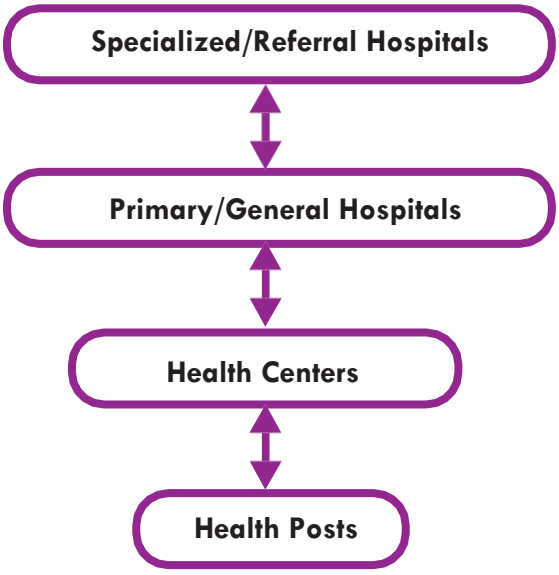
Stepwise approach for service initiation is recommended to be as follows:-

a. Engage hospital administration, Site assessment and preparation and Secure the minimum requirement/package including implementation of minimum TB IC packages
b. Supply furnishers and equipment(lockable cabinet, chair, tables, stationery, Desktop computer for data)
c. Establish linkage for sample transportation, Ensure provision of lab monitoring tests
d. Secure Patient support mechanisms and identify and prepare potential TFCs
e. Provide TB IC material, RR tools, guidelines, Protocols, Job aids
f. Supply essential Second line drugs, ancillary drugs and TB IC supplies
g. Training of health professionals and TB program managers, establish DR-TB panel team
h. Arrange sensitization forum for service initiation at treatment centers and initiate treatment
i. Develop mechanism for mentoring support and catchment area meeting

19.3.4 TB and DR-TB service referral and communication

Communication and referral system of health program is established in the three health tire system of the country, see figure 18. As part of the existing system, TBL and DR-TB services need to have strong referral communication and support mechanisms to improve quality of services.

Figure 18: Bilateral Referral and Communication of TBL, TB/HIV and DR-TB service



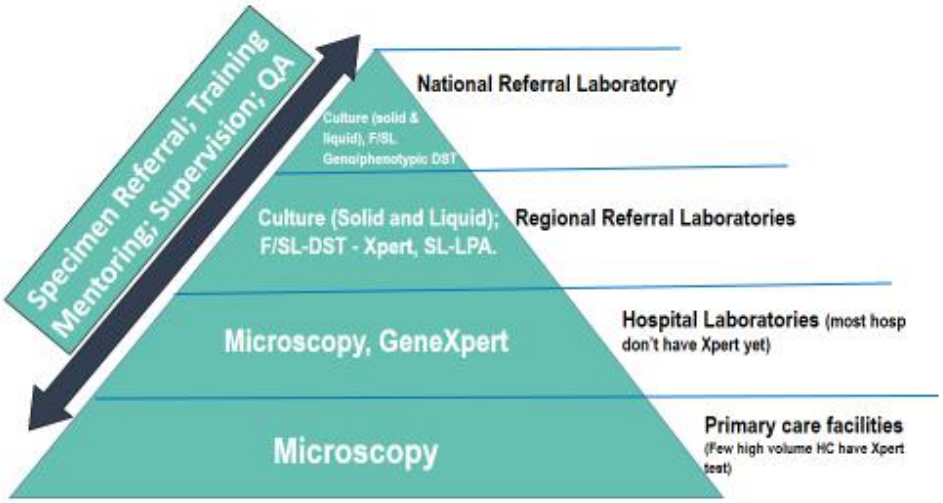
19.4 TB laboratory services organization, coordination and management

Organization of TBL diagnostic laboratory services are coordinated both with the clinical services and technically coordinated by the Ethiopian Public Health Institute (EPHI) in collaboration with Regional reference laboratories.

19.4.1 TB Laboratory Networking and national lab tier system

A laboratory service network is composed of laboratories at each level of the healthcare system committed to the proper diagnosis of diseases. There is a functional laboratory network with communication channels for TB laboratory diagnostic services, Quality Assurance, and exchange of information. Networking the diagnostic laboratory services according to their complexity and available resources is essential since facilities especially at the lower level cannot handle all the tests needed for the program. TB and DR-TB Laboratory services referral Linkage in Ethiopia are depicted figure 19.

Figure 19: TB and DR-TB Laboratory services and referral Linkage



The national TB control program in collaboration with EPHI has been scaling up the TB lab networking, specimen referral and result communication system using Postal services as a main courier system especially for TB culture and DST services to improve access to quality assured laboratory results.

In the implementation of referral based laboratory services, specimens are collected in health facility, transported via a suitable courier system to designated laboratory with testing service, and the result is returned back to the referring laboratory through appropriate route.

National TB Reference Laboratory (NTRL)

The NTRL at EPHI guides the TB laboratory service in the country by developing national level standards and implementation guidelines to ensure the provision of quality laboratory services. The NTRL also collaborate with global and national stakeholders to introduce new TB Laboratory initiatives.

Regional Reference Laboratory (RRL)

The regional laboratory coordinates regional TB laboratory program in collaboration with EPHI and RHBs. The RRL plays core functions in supporting the regional TB program through establishing and implementing quality assurance /EQA scheme, capacity building activities and in supporting and conducting the National TB surveil- lance surveys and in operational research activities.

Peripheral laboratory (Health Centers and Hospitals)

The primary role of peripheral laboratories is provision of quality assured TBL laboratory services in line with national algorithm.

19.4.2 Quality Assurance service for AFB sputum microscopy

Good quality laboratory services are the highest priority for TB Control Program. The main focus of QA program for sputum smear microscopy is to assure the reliability of the smear result. To optimize external quality assurance, decentralization of the supervision and monitoring of the laboratory network is essential. Hence, laboratories from selected hospitals are tasked to play the role of 'controlling' or re-checking laboratory in some of the regions.

19.4.3 EQA Centre arrangement for AFB microscopy

As per National AFB microscopy EQA guideline, AFB microcopy EQA service has been decentralized from limited Regional laboratories to eligible Hospital and sub-regional laboratories to achieve high level of QA service coverage and share the burden from the regional laboratories.

19.4.4 TB/HIV Integrated Sample Referral system

The TB/HIV integrated sample referral system in Ethiopia is a mechanism whereby specimens of different varieties are transported to testing center in an integrated manner with a fixed schedule. It facilitates transport of samples for diagnosis, treatment follow up and/or surveillance purposes. The system will improve access to quality diagnostic services to peripheral level by meeting the sample collection and transportation standards.

19.5 Programmatic Monitoring and Evaluation of TB, Leprosy and DR-TB

TBL and TB/HIV monitoring and evaluation is done at different levels of the health system where epidemiological and operational indicators are compiled, calculated and analyzed. Recording and reporting of TBL service helps to systematically monitor and evaluate progress of patient/s and treatment outcome as well as the overall program performance.

19.5.1 TBL and TB/HIV performance monitoring

Supportive Supervision: Supervision consists of observation, discussion, and supportive guidance provided on a regular basis. The overall aim of supervision is the promotion of continuous improvement in the program performance. Supervision should be conducted at all level in an integrated and in-depth TB Program-Specific supervisions manner based on supportive supervision guideline of FMOH. During supervision, data quality assurance should be performed on selected indicators. Before each visit the supervisor should review the assessment made during the last visit, corrective action taken and features that should demands special attention during the current visit. After each supervisory visit the supervisor (supervisory team) has to discuss strengths, weaknesses and problems identified, and recommendations with the heads of health bureaus, and TBL experts to

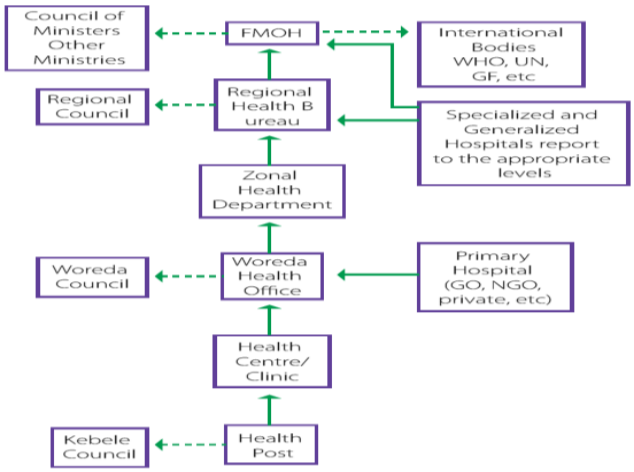
make the control program successful. At the end of each supervision visit, supervised institutions should be provided with copy of written supervision report and the supervisor (supervisory team) must help in resolving challenges originated at various levels of the health system.

Program performance review: it should be organized at various levels to review the program implementation status, achievements and challenges, and develop practical solutions for identified problems and challenges.

19.5.2 Data Reporting and Data Flow

The reporting of TB, DR-TB, Leprosy and TB/HIV collaborative activities is integrated into the national Districh Health Information System (DHIS) and all recording and reporting formats are standardized in line with DHIS 2 system throughout the country. Routine TB, DR-TB, TB/HIV and Leprosy DHIS2 data are reported on a quarterly basis with a plan to transition to a monthly reporting timeline. Facilities aggregate and review their data monthly and report to their respective facility and administrative office as per the reporting timeline. Further, there is a plan to shift the DR-TB reporting to a case-based electronic reporting system. The administrative office aggregates the data it receives, monitors its own performance and forward the report to the next level. DHIS2 Data flow from the facilities to the federal level is depicted in figure 20.

Figure 20: DHIS2 Data flow



19.6 TBL, DR-TB and TB/HIV Data Quality Assurance

Data Quality Check is one of the components of the M&E system. Once TBL, DR-TB and TB/HIV data are collected, the data needs to check for inaccuracies and obvious errors with DHIS2 unit using nationally recommended tool including Lot Quality Assur- ance Sampling (LQAS)

19.7 Description of recording and reporting forms in TBL

Drug susceptible TB register: Drug susceptible TB register is mainly useful to register detail information of patient's data including clinical management and treatment monitoring. The register is the main source of information to generate all programmatic reports on quarterly basis.

TB contact screening and LTBI treatment follow up register: The register is used to document information and follow TB screening status of clients with contact of pulmonary TB or DR TB cases.

It is also main source document to assess treatment adherence of eligible under five clients who are on LTBI treatment.

TB treatment supporter card: TB treatment supporter card is used for monitoring of daily directly observed treatment of TB patients and can be used by HEWs or HCWs or treatment supporters.

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

TB Microscopy Registration Book: TB Microscopy Registration Book is kept in laboratory of the health facilities. Patient's information and results of all specimens for AFB microscopy must always recorded in the TB Laboratory Register. The specific request form be used to record and report smear examination results

TB Xpert MTB/RIF Registration Book: The TB Xpert MTB/RIF Registration Book is used to document patient's information and result. All information indicating the registration group, HIV status and others be filled in from the request form.

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

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

Leprosy unit register: It is used to record information of leprosy cases. The information helps for patient monitoring, planning and for calculation of indicators. Instructions for completing the Register are printed in the inside covers of the register. The TB program managers at all level are responsible for ensuring that the register is properly completed and number of all cases put on MDT.

Leprosy VMT and ST card: This form is used to conduct disability assessment and grading at time of leprosy diag- nosis and on monitoring of treatment responses.

DHIS 2 Reporting forms: The reporting form of TB control program is integrated with DHIS2 reporting system. It consists of disaggregated data of both drug susceptible and drug resistance TB case notification, treatment outcome, and other important element to monitor and evalua- tion programmatic performance.

19.8 TB, TB/HIV, DR-TB and Leprosy Programmatic Indicators

The Programmatic indicators for tracking progress in TB, TB/HIV, DR-TB and Leprosy are revised along with the DHIS2 indicators revision of all health programs. The TBL indictaors revision considered the global recommendations, country commitments and the indicators need to track the revised TBL NSP implementation. Please refer to the latest *DHIS2 indicators definitions guide* for detailed guidance.

20. TB/ COVID-19 Joint Programming and Integration in Ethiopia

20.1 Background

COVID-19 pandemic continues to present a massive challenge to the continuity of essential health services including TB services. The pandemic has brought multifaceted impact on TB Programming at global and national levels including but not limited to the supply chain interruptions, TB services disruptions, impacting health care seeking, TB diagnosis, Treatment and care and reversal of the gains made so far in TB control. A recent global modelling study has revealed that stringent COVID-19 responses lasting months, would have a longer term impact on TB through their effect mainly on TB diagnosis and treatment. Global TB incidence and deaths in 2021 would increase to levels last seen in between 2013 and 2016 respectively – implying a setback of at least 5 to 8 years. To recover the gains made, it is important to have supplementary measures and resources to reduce the accumulated pool of undetected people with TB. Such measures shall include a ramped-up active case-finding, alongside intensive community engagement and contact tracing, and securing access to an uninterrupted supply of quality assured treatment and care.

The need for TB/COVID-19 integration:

- Essential to address both COVID-19 and TB if we are to guarantee an effective response to COVID-19 while ensuring that TB services are maintained.
- Many overlaps between TB and COVID-19 in disease presentation, transmission and control strategy, the integration of both programs could be key to making this happen.

Opportunities for effective TB/COVID-19 Programmatic Integration

There are several existent opportunities for that must be seized for an effective COVID-19/TB Programmatic integration.

- Both programs rely on similar strategies for effective control: early detection of an infectious case, infection prevention and contact tracing.
- Substantial overlaps in the core elements of COVID-19 response TB programmatic interventions:
    - Symptoms overlaps
    - Airborne IPC interventions
    - Screening and contact tracing needs
    - Diagnostic platforms
    - Sample referral system needs
    - Clinical care needs and approaches
    - Program supplies (e.g. N95 Masks, Diagnostics supplies)

20.2 Elements of COVID-19/TB Program Integration in Ethiopia

The TB/COVID-19 joint programming in Ethiopia considers the following three key elements of integrated care.

1. Programmatic Integration/Collaboration
2. Clinical Care/Clinical Services Integration
3. Community based TB-COVID Services

Elements of TB/COVID-19 Integration in Ethiopia:

1. **Programmatic Integration:** Effective COVID-19/TB Programmatic integration demands setting up a mechanism for integration. This requires the following programmatic actions
   a. Joint governance body at national and regional levels
   b. TB/COVID-19 Program Focal Points: National and Regional Levels
   c. Surveillance system to monitor the integrated care
   d. TB-COVID joint planning, monitoring, evaluation and Learning
2. **Clinical Care/Clinical Services Integration:**
   a. Integrate COVID response services in TB patients care points
      i. Integrated COVID-19 IPC and TB IC measures in health care settings- build on the existing HF TBIC plans and HF IPC Committee
      ii. Integrate COVID-19 Screening services with TB Screening services through an integrated screening algorithm at HF and community settings
      iii. Systematic COVID-19 Testing services for all Presumptive TB cases
      iv. COVID-19 Screening and testing services for all TB/DR-TB Patients with acute respiratory manifestation during the course of TB/DR-TB treatment
      v. COVID-19 Clinical management for TB/COVID-19 co-infected patients
      vi. Integrated HBIC with community based TB Care services
   b. Integrate essential TB services in the COVID-19 responses
      i. TB Screening and referral services at COVID-19 Pre-triage and Triage units/Cougher OPDs
      ii. Integrated TB Screening services with COVID-19 household contact investigations and HBIC follow up visits
      iii. TB Diagnostic Services for suspected COVID-19 patients and Symptomatic COVID-19 Patients – onsite and through integrated TB/COVID-19 sample referral
      iv. Ensuring continuity of TB/DR-TB Treatment and Clinical management of COVID-19/TB co-infected patients at COVID-19 isolation/treatment centers
3. **Community based TB-COVID Services Integration**.
   a. Integrated COVID cases contact tracing along with Community based TB case finding practices including house to house TB screening and TB contact tracing services
   b. Community based COVID-19 Screening/testing services for TB patients/TB affected households
   c. HBIC and Community based TB care services
   d. Community based sample referral services for TB testing among COVID-19 suspects/confirmed cases at home isolation
   e. Integrated community health education programs on TB/COVID-19

20.3 Programmatic Needs for TB/COVID Integrated Care

The following programmatic needs are required to be addressed for a seamless integrated delivery of TB/COVID-19 Care services.

1. **HRH Optimization:** Assignment of COVID-19/TB Integration Focal points and advisory team at national and regional level. This might require deployment of additional staffs within National and Regional TBL Team (at least one officer/advisor at national and RHBs).
2. **Logistics and supplies for integrated HBIC and community based TB care services**: IPC Supplies (PPE for home-based care and household screening), Integrated sample collection and referral services for TB testing and COVID-19 testing, logistics for scheduled home-visits

3. **Alignment of TB adherence support schedules with HBIC home-visit schedules** (twice during HBIC follow up period)
4. **PHC provider support tools for integrated HBIC and TB Care services** (integrated care algorithms and protocols)
5. **Budget support for close monitoring and supervisory visits** related to the implementation of the integrated HBIC and TB prevention and care services.

20.4 COVID-19 Screening/Testing and Isolation Protocols for TB/DR-TB patients

- All TB Patients currently on TB treatment must be screened for recent onset COVID-19 symptoms (recent or new onset fever, Cough, shortness of breath, headache, sore throat, loss of taste or smell), travel and contact history at all health facility visits.
- COVID-19 Screening for TB patients should be done at the designated screening area in the health facility plus at TB Clinics.
- All TB Patients with COVID-19 Symptoms or with contact history with COVID-19 Case/suspect or with travel history should be immediately isolated and sample for COVID-19 testing should be taken per the COVID-19 testing and isolation Protocol.
- Health Care Workers must observe all COVID-19 and airborne precautions while conducting the Screening of TB patients.
- If initial COVID -19 Screen is positive, direct patient to triage & testing area as per the latest COVID-19 guidelines.
- Secondary screening space should be separated from other patients. Providers should don full PPE and observe contact and droplet precautions. Follow protocols for specimen collection for laboratory testing.
- TB patients with no symptoms of COVID-19 but are at high risk due to contact or travel may be directed home with follow up and to self-quarantine pending test results.
- There should be separate isolation areas for persons under investigation (PUI) for COVID-19 who have not been confirmed to have COVID-19.
- When a patient comes to a facility with symptoms consistent with COVID-19 or known contact with COVID-19, it is important that IPC is adhered to.
- Asymptomatic PUI- known contact, but not displaying symptoms: Once tested asymptomatic suspect patients may return home with close follow up and instructed to self-quarantine pending test results.
- Symptomatic PUI: should be evaluated clinically for admission criteria per the COVID-19 guidelines and separated from asymptomatic suspects pending the test result.
- TB/DR-TB patients with confirmed COVID-19 test OR highly symptomatic PUI should be separated from other patients.
- TB/DR-TB patients with COVID-19 requiring in-patient care should be admitted in a well-ventilated separate isolation rooms with limited movement to avoid patient mix-ups while receiving treatment and care for COVID-19.
- Other COVID-19 Isolation facility IPC measures should be also applied strictly.

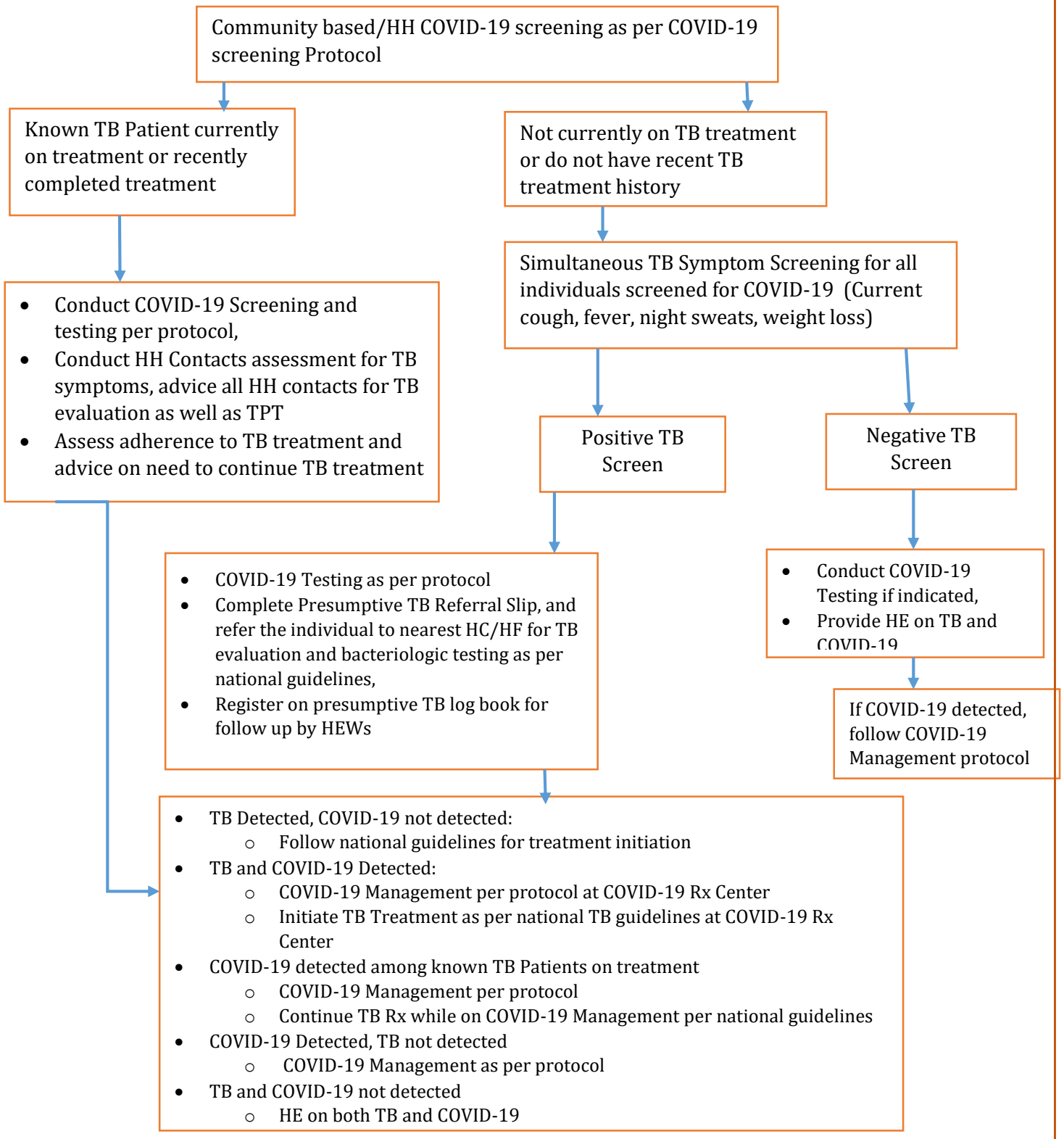
20.5 COVID-19 and TB Clinical management Protocols

- All COVID-19 Confirmed TB patients must continue taking their TB treatment per the national TB/DR-TB treatment guidelines while on COVID-19 treatment and care.
- The clinical management team should monitor for potential drug-drug interactions of anti-TB medicines and drugs used for COVID-19 management.
- Clinical monitoring tests should be done for TB/DR-TB patients as per the national guidelines. The COVID-19 Isolation facilities should have access to medical equipment such as radiology, ECG, Audiometry, Ishihara books, tunning forks.
- Lab monitoring tests such as Sputum smear, sputum culture, and Xpert/MTB RIF Tests could be delayed until COVID-19 treatment completion and patient becomes negative for COVID-19 to minimize potential transmission of the virus while handling such potentially infectious biological specimen. Such laboratory monitoring tests should continue immediately after completion of the COVID-19 care and patient is discharged from the isolation facility.
- Lab monitoring tests such as blood tests for hematology, organ function tests, and electrolytes could be done at COVID-19 isolation facility labs with the necessary precautions to be applied to minimize potential transmission of the virus while handling such potentially infectious biological specimen.
- Clinical and lab monitoring tests should focus primarily for possible adverse drug reactions detection and management as well as Clinical TB treatment response while on COVID-19 care.
- Management of adverse drug reactions while on TB/DR-TB treatment among COVID-19 patients should follow the national TB/DR-TB Treatment guidelines.
- Patients on Latent TB Infection Treatment should also continue taking their TB preventive Therapy (TPT) while on COVID-19 treatment and care per the national TPT recommendations.

20.6 TB/COVID-19 Integrated Screening and management algorithms in Ethiopia

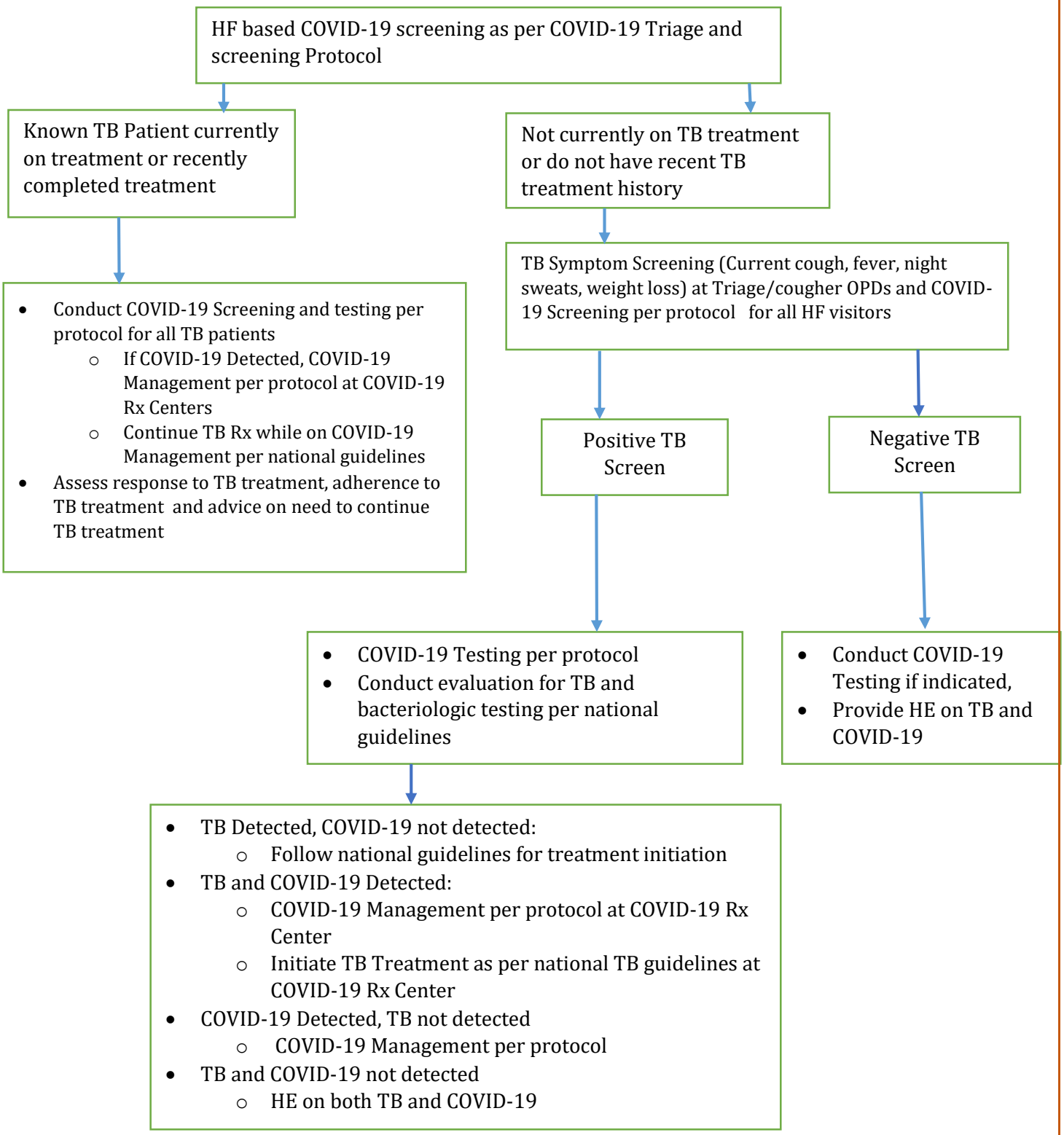
The following model algorithms for integrated TB/COVID-19 Screening and management at community and health facility level are recommended for implementation.

Figure 21: Algorithm for integrated TB/ COVID-19 Screening at community level in Ethiopia[1]



[1]*To be applied during all community based screening activities.*

Figure 22: Algorithm for integrated TB/ COVID-19 Screening & Management at health facilities (HFs) level in Ethiopia



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ANNEXES

Annex 1. Adjustment of Anti-TB Medication in Renal Insufficiency

Patients with calculated GFR below 60ml/min and especially with GFR below 30ml/min require renal dose adjustment of Anti-TB drugs as indicated below.

Drug	Frequency of administration	Recommended dose and frequency(GFR <30 ml/ min or hemodialysis)
Isoniazid	No change	300 mg once daily, or 900 mg 3X per week
Rifampicin	No change	600 mg once daily, or 600 mg 3x per week
Pyrazinamide	Yes	25–35 mg/kg per dose 3X per week
Ethambutol	Yes	15–25 mg/kg per dose three times perweek
Levofloxacin	Yes	750–1000 mg per dose three times per week
Moxifloxacin	No change	400 mg once daily
Cycloserine	Yes	250 mg once daily, or 500 mg/dose three times per week
Prothionamide or Ethionamide	No change	250–500 mg per dose daily
PAS	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	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 creati- nine clearance <10ml/min.
Source: Guidelines for the programmatic management of drug-resistant tuberculosis (WHO 2008).		

Annex 2: Common Clinical Presentations and Practical Considerations for EPTB

Common EPTBE Clinical presentations	Site of TB disease	Investigation
Symptoms: A painless enlarged mass, usually at the sides of the neck, may present discharge, Not responding to a course of Antibiotics. **Signs:** Asymmetrical, painless, non-tender lymph node enlargement for more than one month +/- discharging sinus. Commonly seen on the sides of the neck.	**TB** adenitis (commonly cervical)	Fine needle aspiration for culture, Xpert MTB/RIF Test and histology.
Symptoms: Chronic cough and shortness of breath, with plueritic chest pain. **Signs:** Dullness on percussion and reduced breath sounds +/-chest pain	**Pleural TB,** pericardial TB	CXR Pleural tap for Xpert and biochemical studies
Symptoms: Reduced playfulness, Head- ache, irritability/abnormal behaviour, vomiting (without diarrhoea), weight loss, reduced level of consciousness, +/- convul- sions. **Signs:** neck stiffness, lethargic, bulging fontanelle, cranial nerve palsies, +/- unconsciousness. Meningitis of acute or sub-acute onset, not responding to antibiotic.	**TB meningitis**	Lumbar puncture and obtain CSF for mWRDs, CXR
Non-specific, lethargic, presentation of Acute pneumonia with high fever, shortness of breath, respiratory distress	**Miliary TB**	CXR, Lumbar puncture obtain CSF to rule out TB Meningitis
Deformity of spine (especially of an acute onset) over thoraco-lumbar area,+/- lower limb weakness/paralysis	**Spinal TB**	X-ray of the vertebra, CXR to check for pulmonary sites
Symptoms and signs of heart failure, Distant heart sounds, difficulty to palpate Apical beat	**Pericardial TB**	CXR, Echocardiography, Pericardial tap
Unilateral Swelling of the end of long bones with limited movement, usually at knee or hip	**TB bone and joint**	X-ray bone and joint Joint tap

Annex 3: Surgery in the Treatment of Pulmonary TB Including DR-TB

Surgery must be considered as an integral treatment strategy in the care of patients with pulmonary tuberculosis. Therefore, health care providers at each level of care must consider surgery as a potential curative treatment modality and surgical consultation needs to be sought early in the course of the disease so that appropriate surgi- cal care can be provided. Delay in consultation may result in irreversible worsening of the disease.

Indications for surgery in patients with TB	
Emergency	• Significant life threatening hemoptysis • Tension spontaneous pneumothorax.
Urgent	• Recurrent hemoptysis that cannot be stopped by other treat- ment methods.
Elective	• Localized cavitary TB with positive sputum after four to six months of anti-TB chemotherapy; • M/XDR-TB characterized by failure of anti-TB chemotherapy; • Complications and sequelae of the TB disease: - Spontaneous pneumothorax/pyopneumothorax - Pleural empyema with or without bronchopleural fistula - Aspergilloma - Tuberculous constrictive pericarditis - post-TB broncho-stenosis - Chronic post-TB bronchiectasis - diagnostic challenge between tuberculoma and lung cancer

The presences of one or more of the following conditions are contraindications for surgery.

- Extensive bilateral cavitary lesion
- Impaired pulmonary function test (forced expiratory volume in one second less than 1.5 L in cases of lobectomy and less than 2.0 where pneumonec- tomy is planned;
- Body mass index up to 40–50% of the normal range;
- severe co-morbidity (complicated diabetes, severe heart disease, hepatic or renal impairment);
- Active bronchial TB.

Patient selection and timing of surgical intervention: In patients who meet the indication for surgery, the following pre-requisites must be fulfilled:

- The diseased lung segment must be localized to allow surgery
- The remaining lung tissue must reasonably be free of TB;
- The patient's surgical risk level is acceptable, with sufficient pulmonary reserve to tolerate the resection.

Proper patient selection and the timing of operations are crucial to avoid relapses, prevent complications and to provide a higher chance of cure. It must be emphasized that pre-and post-operative chemotherapy is vital to assure increased success of treatment.

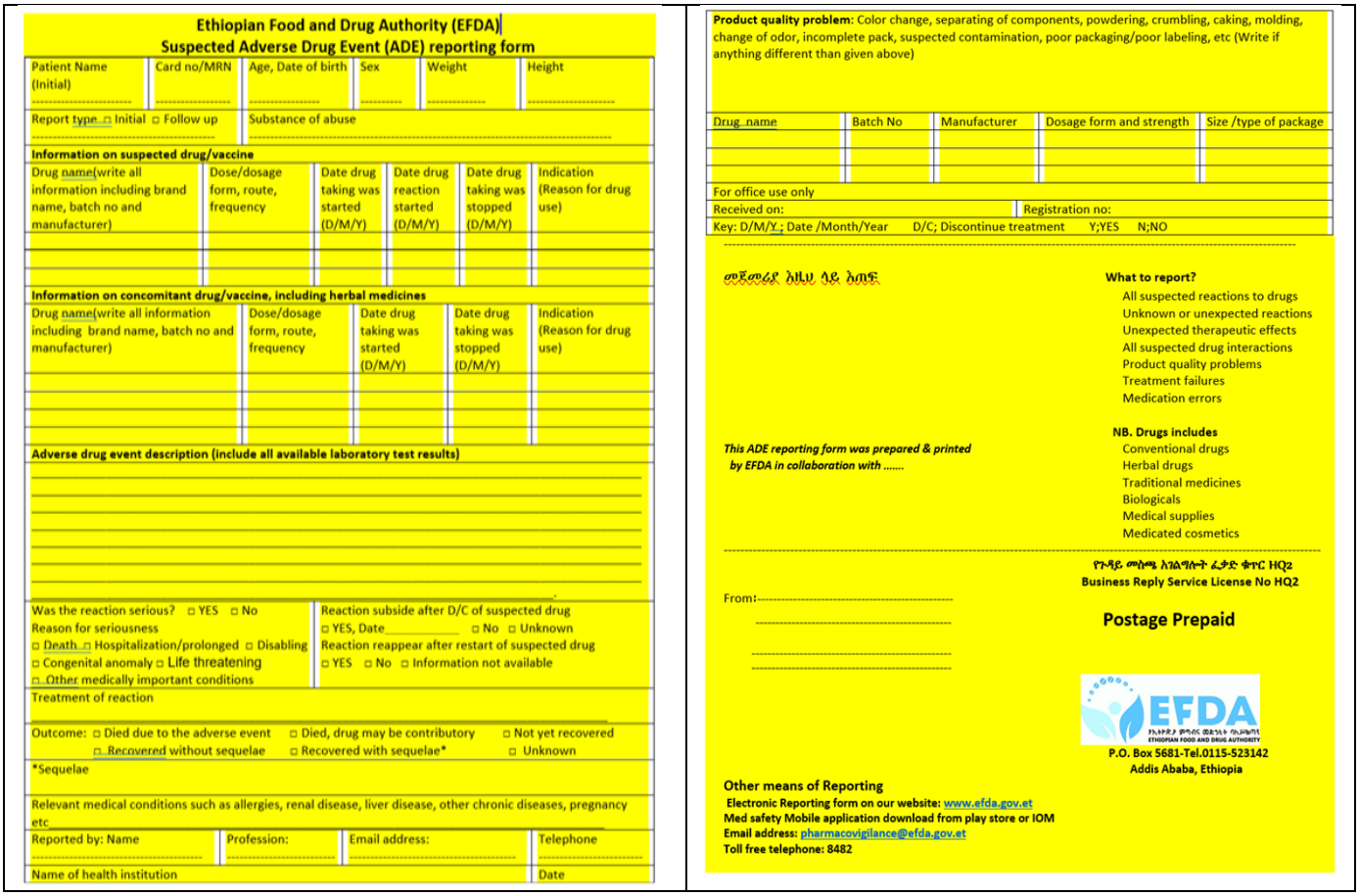
Anti-TB chemotherapy before surgery should be given at least for four months (and between four and six months) before surgery. In order to avoid serious and potentially fatal complications of TB surgery, it is recommended to perform the operation when the M. tuberculosis population is likely to be at its lowest level (preferably when the sputum and culture are negative).

The following preoperative workup must be carried out before surgery:

- A comprehensive and open discussion should be carried out with patients and their relatives about the nature of their TB and the necessity of surgical intervention, as well as the risks and benefits of surgery, and the short- and long-term prognosis with and without surgical intervention.
- Possible complications in terms of anaesthesia
- Consent for surgery must be obtained for all patients.
- The following preoperative investigations need to be carried out: full blood anal- ysis, biochemistry tests (liver and kidney, blood sugar, electrolytes, total proteins and albumin), HIV testing, sputum-smear microscopy, sputum-culture testing and DST, chest X-ray and CT scan, and bronchoscopy.
- The patient's cardiorespiratory reserve must be carefully evaluated based on pulmonary function testing and exercise tolerance tests, EKG and Echo.
- Nutritional assessment (body mass index) of the patient.
- Airways should be sanitized: respiratory exercises, postural drainage and routine aerosol inhalation, or nebulized bronchodilators and antibiotics used.
- Smoking cessation must be encouraged.

Postoperative chemotherapy is as indispensable as preoperative chemotherapy because after resection of the main lung lesion, scattered nodular lesions and tiny cavities may be left behind. It is, therefore, vital to ensure that all patients (in particular those with M/XDR-TB) remain on multidrug anti-TB regimens for a sufficiently long period to kill the bacilli present at the remaining lesions.

Annex 4: EFDA ADR Reporting form (Yellow Form)



Ethiopian Food and Drug Authority (EFDA)
Suspected Adverse Drug Event (ADE) reporting form

Patient Name (Initial)	Card no/MRN	Age, Date of birth	Sex	Weight	Height

Report type □ Initial □ Follow up — Substance of abuse

Information on suspected drug/vaccine

Drug name(write all information including brand name, batch no and manufacturer)	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)

Information on concomitant drug/vaccine, including herbal medicines

Drug name(write all information including brand name, batch no and manufacturer)	Dose/dosage form, route, frequency	Date drug taking was 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)

Was the reaction serious? □ YES □ No
Reason for seriousness
□ Death □ Hospitalization/prolonged □ Disabling
□ Congenital anomaly □ Life threatening
□ Other medically important conditions

Reaction subside after D/C of suspected drug
□ YES, Date_____ □ No □ Unknown
Reaction reappear 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 sequelae* □ Unknown

*Sequelae

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

Product quality problem: Color change, separating of components, powdering, crumbling, caking, molding, change of odor, incomplete pack, suspected contamination, poor packaging/poor labeling, etc (Write if anything different than given above)

Drug name	Batch No	Manufacturer	Dosage form and strength	Size /type of package

For office use only
Received on: — Registration no:
Key: D/M/Y.; Date /Month/Year D/C; Discontinue treatment Y;YES N;NO

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This ADE reporting form was prepared & printed by EFDA in collaboration with .....

What to report?
- All suspected reactions to drugs
- Unknown or unexpected reactions
- Unexpected therapeutic effects
- All suspected drug interactions
- Product quality problems
- Treatment failures
- Medication errors

NB. Drugs includes
- Conventional drugs
- Herbal drugs
- Traditional medicines
- Biologicals
- Medical supplies
- Medicated cosmetics

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MINISTRY OF HEALTH-ETHIOPIA
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