NATIONAL GUIDELINES FOR CLINICAL AND PROGRAMMATIC MANAGEMENT OF TB IN SIERRA LEONE

MINISTRY OF HEALTH
NATIONAL LEPROSY AND TUBERCULOSIS CONTROL PROGRAMME

MARCH 2024

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FOREWORD

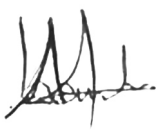
Sierra Leone has achieved significant progress in the fight against tuberculosis (TB) and was among the select few countries to meet the 2020 target of a 35% reduction in TB mortality. Nevertheless, TB continues to pose a substantial challenge to our nation, remaining one of the leading causes of morbidity and mortality. In 2023 alone, Sierra Leone reported 21,885 TB cases, accounting for 91 percent of estimated cases. This leaves approximately 2,000 infections undiagnosed, especially among our vulnerable children. The unchecked rise in missing cases of Drug Susceptible Tuberculosis (DST) management carries the ominous threat of Drug-Resistant (DR) TB, which could unravel the strides made by our national TB programme, and if not addressed effectively, may lead to extensively drug-resistant TB (XDR-TB).

Following a comprehensive mid-term epidemiological assessment in 2022, the revised TB guidelines have been meticulously designed to tackle a range of pressing issues, including:

- Community transmission
- TB Preventive Therapy
- Childhood TB surveillance
- Early, prompt, and accurate diagnosis
- Early initiation of treatment and adherence
- HIV /TB collaboration activities and
- Drug resistant tuberculosis

Our commitment to innovative approaches to enhance TB diagnosis and treatment is unwavering, with a strong emphasis on delivering quality care. Recognizing the global health security implications of TB treatment, these guidelines aim to integrate empirical data derived from clinical and laboratory testing into a comprehensive service delivery framework. To underscore our holistic approach, these recommendations have been designed to address the unique needs of adults, adolescents, and children affected by TB. We acknowledge the indispensable role that all healthcare professionals play in preventing transmission in our communities and recognize their crucial contribution to this endeavor.

I wholeheartedly hope that the diligent application of these guidelines will not only improve patient care but also aid the Ministry of Health in achieving its overarching objective of fostering better health for the people of Sierra Leone. Together, we remain steadfast in our commitment to curbing the impact of TB in our nation.



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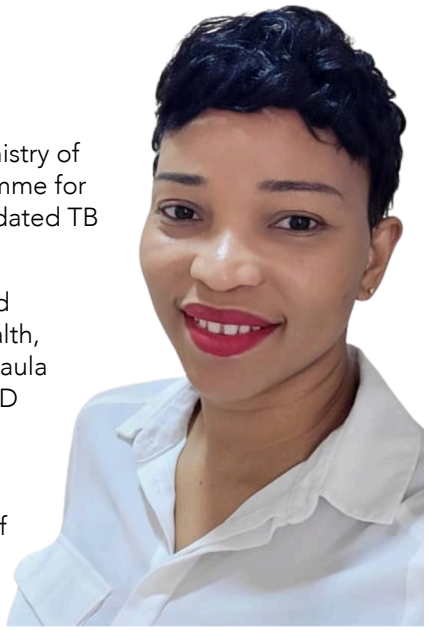

Dear Partners, Healthcare Professionals, and Supporters,

I am pleased to extend my heartfelt gratitude on behalf of the Ministry of Health and the National Leprosy and Tuberculosis Control Programme for your invaluable contributions to the development of the newly updated TB guidelines.

We would like to express our sincere appreciation to our esteemed partners, including the World Health Organization, Partners in Health, Medecins Sans Frontieres Holland (Dr. Kennedy Uadiale, Dr. Ana Paula Cavalheiro, Fathelrahman Ibrahim, Erick Vulu, Jobin Joseph), USAID and the German Leprosy Relief Association, for their unwavering commitment and technical assistance in crafting these guidelines. Your collaborative efforts have significantly enhanced our ability to provide evidence-based recommendations for the management of TB conditions.

A special acknowledgment goes to the dedicated healthcare professionals and practitioners who generously shared their extensive knowledge and precious time to shape these guidelines. Dr. Alhassan Lans Seisay, Dr. Kassa Hailu, Dr Philip Patrobas, Dr. Sulaiman Lakoh, Dr. Girum Bayissa, Dr. Jacob Mugisha, Dr. Michael Mazzi, Dr. Ayeshatu Mustapha, Dr. Alpha Sheriff, Dr. AbuBakarr Kallon, Dr. Suba M'bayo, Dr. Samuel Bailor, Scientist Zein Souma, Niguse Gade, Sr. Josephine A Koroma, Sr. Fatmata Lansana, Willie RME Barrie, Alhassan Conteh, Jonathan T. Bangalie, Rev. Paul Bangura, Mohamed Samura, Micheal C. Renner, and Ibrahim Sorie Turay – your expertise and dedication to improving patient care have been instrumental in this endeavor.

We must also recognize the invaluable support from healthcare institutions, academic centers, and professional organizations that provided the necessary resources, infrastructure, and collaborative environments for the development of these guidelines. Your commitment to advancing healthcare practices has been vital in ensuring the quality and relevance of these guidelines.

To all those mentioned above and countless others who have contributed, whether in visible or behind-the-scenes roles, we extend our sincere gratitude. Your unwavering support and dedication have transformed these treatment guidelines into a valuable resource for healthcare professionals, ultimately enhancing patient care and outcomes.

Thank you for your tireless efforts and commitment to the fight against tuberculosis. Together, we are making a profound difference in the lives of those affected by this disease.

Dr. Mariama Mahmoud

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ABBREVIATIONS

AFB	Acid Fast Bacilli
AMR	Anti-Microbial Resistance
ART	Anti-Retroviral Therapy
BCG	Bacille Calmette Guerin
CSF	Cerebrospinal fluid
CT	Computerized Tomography
CPT	Cotrimoxazole Preventive Therapy
CXR	Chest X-ray
DOTS	Directly Observed Treatment Shortcourse
DST	Drug Sensitivity Testing
DTS	District Tuberculosis Supervisor
ECG	Electro Cardiogram
EPTB	Extra Pulmonary Tuberculosis
EQA	External Quality Assurance
FAST	Find Actively Separate and Treat promptly
FDC	Fixed Dose Combination
FM	Fluorescent Microscopy
FLQ	Fluroquinolones
GOPD	General Out Patient Department
HCW	Health care Worker
HIV	Human Immunodeficiency Virus
HTS	HIV Testing Services
IGRA	Interferon Gamma Release Assay
IPC	Infection Prevention and Control
IPT	Isoniazid Preventive Therapy
LF-LAM	Lateral Flow Lipoarabinomannan
LPA	Line Probe Essay
LTBI	Latent Tuberculosis infection
MDR-TB	Multi Drug Resistant Tuberculosis
MRI	Magnetic Resonance Imaging
MTB	Mycobacterium Tuberculosis
MOTTs	Mycobacterium Other Than TB

NAAT	Nucleic Acid Amplification Test
NGO	Non-Governmental Organisation
NGS	Next Generation Sequencing
NLTCP	National Leprosy and Tuberculosis Control Programme
NTMs	Non-Tuberculous Mycobacteria
PMDT	Programmatic Management of Drug resistant Tuberculosis
PLHIV	People Living with HIV
PPM	Public Private Mix
PPP	Public Private Partnership
PTB	Pulmonary Tuberculosis
RIF	Rifampicin
RR	Rifampicin Resistance
SLD	Second Line Drugs
SOP	Standard Operating Procedure
TAT	Turn Around Time
TB	Tuberculosis
TB-LAMP	Loop Mediated Isothermal Amplification
TPT	Tuberculosis Preventive Treatment.
TST	Tuberculin Skin Test
WHO	World Health Organization
WRD	WHO approved rapid diagnostics
XDR-TB	Extensively Drug Resistant Tuberculosis
ZN	Ziehl – Neelsen

1. SUMMARY OF THE KEY UPDATES AND RECOMMENDATIONS

This national TB management guidelines presents the most updated current guidance on programmatic and clinical management of patients with Tuberculosis in line with the global recommendations of WHO End TB strategy.

In recent years, there has been several global updates and policy changes in TB/DR-TB prevention and care. Notably, the global recommendations for the use of rapid diagnostics for TB and RR-TB (Xpert Ultra, Trunat), increasing availability and evidences on the use of Artificial Intellegence (AI) Assisted Diagnostic technologies (AI assisted CXR), LF-LAM test, changes in recommendations on TPT, RR/MDR-TB treatment regimen changes (fully-oral LTR, fully oral Bdq-based RR/MDR-TB Shorter Regimen, BPaL Regimen for XDR-TB, novel fully oral STR under OR conditions) and others are remarkable.

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

The clinical sections, on the other hand, present the latest recommendations on TB 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 and DR-TB as well as monitoring of response during treatment. Key areas of focus in this document are summarized as follows:

Box 1: Key updates and recommendations

The national guidelines on management of TB, TB/HIV, DR-TB in Sierra Leone highlights the following key updates and recommendations:

1. Changes to the TB diagnostic algorithms with the use of molecular WHO-Approved rapid diagnostics (mWRDs) as an initial test for TB diagnosis and detection of rifampicin resistance has been made.
2. The following mWRDs are recommended for use in Sierra Leone:

- Xpert MTB/RIF Assay and Xpert MTB/RIF Ultra Assays
- Truenat MTB
- Line Probe Assays (FL-LPA, SL-LPA)
- Loop-mediated isothermal amplification (TB-LAMP);
- Lateral flow lipoarabinomannan assay (LF-LAM) test to assist in diagnosing TB in selected groups of HIV-infected presumed TB patients.

3. The use of the following biological specimens are recommended for mWRDs in patients being evaluated for TB:

- Sputum
- Nasogastric Aspirate
- Nasopharyngeal Aspirate
- Stool for TB and RR/TB detection among children
- Lymph node aspirate
- Cerebrospinal fluid (CSF) in a patient suspected of TB meningitis
- Synovial fluid for evaluation suspected osteo-articular TB
- Pleural and pericardial fluid in suspected TB pleurisy and TB Pericarditis
- Urine in suspected genitourinary tract TB or for use of LF-LAM in advanced PLHIV
- Blood to detect disseminated TB in patients with advanced immunosuppression (e.g, HIV)

4. Specific SOPs for sample collection, processing, and testing using each of the recommended biological specimen to be applied.
5. The use of Chest X-Ray (CXR) as a screening tool for TB in addition to the clinical (symptom-based) TB screening algorithm among high-TB risk populations. All patients with CXR abnormalities suggestive of TB should be evaluated for TB with bacteriologic test using the recommended mWRDs.
6. All patients with signs and symptoms suggestive of TB (positive TB Screen) or with CXR abnormalities suggestive of TB (including asymptomatic high-risk groups) shall be evaluated bacteriologically using the recommended mWRDs such as Xpert MTB/RIF Ultra or Truenat as an initial test where available.
7. The policy of Universal DST (.i.e. 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 as an initial test or as a baseline test prior to treatment initiation.
8. Treatment of DS-TB patients in adults remain unchanged, with the introduction of a shorter treatment regimen for non-severe TB in children.
9. The follow up algorithm for all bacteriologically confirmed PTB cases (both new and previously treated cases on FLDs) is updated. FL-LPA or Xpert XDR are 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.
10. 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. 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 to guide regimen design.

11. TB Preventive Therapy (TPT) is recommended for the following priority populations:

- Adolescents and adults living with HIV who are unlikely to have active TB based on symptom screening
- Children 12 months or older who are living with HIV and are unlikely to have active TB based on symptom screening
- Infants younger than 12 months who are living with HIV and who have been exposed to an index PTB case and are investigated for TB
- HIV negative children and adolescents (< 15 years of age) who have been exposed to an index pulmonary TB case after active TB is ruled out.
- The recommended TPT regimens are 3HR, 3HP, 1HP and 6H.

13. The TB Infection Prevention and Control section has been updated to reflect the latest guidelines on TB IPC.
14. Active drug safety monitoring and management (aDSM) is recommended for all patients on RR/MDR-TB regimens.
15. A unified reporting on the interim outcome and final outcomes of patients on RR/MDR-TB patients for both all-oral Bdq containing shorter regimen and longer RR/MDR-TB regimens is recommended. As such the 6-month interim outcomes will be reported for all patients enrolled to RR/MDR-TB patients during the same quarter of the previous year instead of 9 months later. This is aimed to minimize confusions. Similarly, the final outcome reports for all RR/MDR-TB patients will be reported after 24 months for both on shorter and longer RR/MDR-TB regimens.

2. INTRODUCTION TO TUBERCULOSIS AND NATIONAL STRATEGY

TB affects all individuals irrespective of age and sex. One-third of the world's population is estimated to be infected with Tuberculosis, leaving a high pool of vulnerability to develop active TB disease. Besides, it tends to be disproportionately concentrated among population groups that have either higher risk of exposure to infectious cases or an increased risk of progression to active TB if infected. TB usually affects the economically and culturally disadvantaged population where access to health services is often limited.

Despite the tremendous efforts and progress obtained towards the control of the Global TB epidemic since 1991, TB remains one of the single infectious agent that claims many lives each year. The large pool of missed TB cases, the strong association with HIV and the emergence of drug resistance to essential TB medicines puts TB among the serious threats that the world is facing today.

2.1 Global and National Burden of TB

Globally, Tuberculosis (TB) is the leading cause of death from an infectious disease. In 2022, an estimated 10.6 million people developed TB, and it claimed the lives of 1.3 million people, and an additional 167,000 deaths among PLHIV (WHO, 2023). The emergence of drug-resistant tuberculosis (DR-TB) poses a major challenge to ending the global TB epidemic. In 2021, the World Health Organization (WHO) estimated 3.3% of new and 17% of previously treated TB cases had Rifampicin Resistant/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).

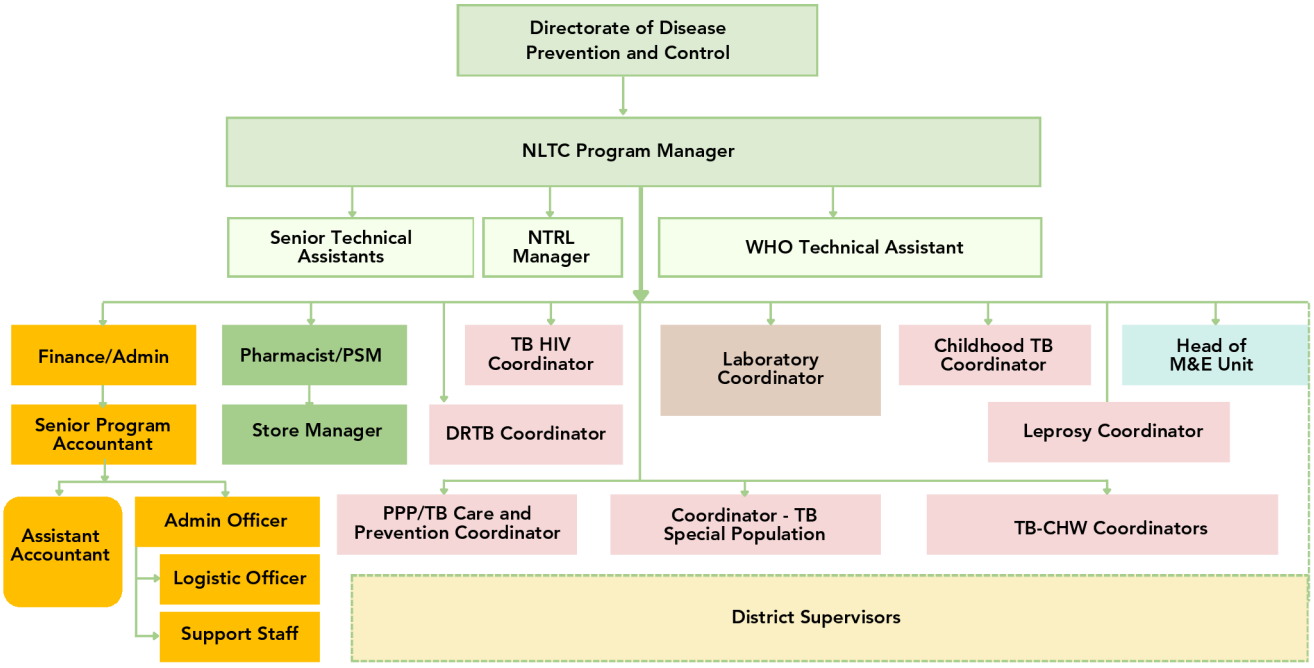
It is estimated that 7.5 million children and young adolescents aged under 15 years are newly infected with M. tuberculosis each year. Cumulatively, about 67 million children and young adolescents aged under 15 years are infected with M. tuberculosis, including 2 million with MDR-TB and 100 000 with extensively drug-resistant tuberculosis (XDR-TB) strains, and therefore at risk of developing TB disease

In Sierra Leone, TB remains a major public health problem posing significant deleterious health impacts by affecting the productive segment of the population. The country is among the 30 high TB burden countries globally, with an estimated TB incidence rate of 286/100,000 (WHO, 2022). Based on the global TB report (WHO 2021), TB mortality has declined by 40% compared to the 2015 baseline and Sierra Leone has already met the 2020 milestone of the End TB strategy. However, the incidence of TB has remained fairly stagnant, with only 5% reduction compared to the 2015 baseline putting the country off track to the 2030 End TB targets.

2.2 Structure of the NLTCP

The programme's organogram shows the chain of command, responsibility, and accountability (Figure 1). The program staff with different capacities and skill sets are distributed along the national, district, facility, and community levels. To function efficiently, the central unit of the program is subdivided into thematic units with specific focal points.

Figure 1: TB programme organogram



2.2.1 Responsibilities of key staff is attached in Annex 2.

2.3 Goal and Objectives of the NLTCP

Goal - Sierra Leone is free from Tuberculosis; that is zero deaths, zero disease and suffering and zero stigma and discrimination due to TB.

Objectives of the NLTCP

The programme objectives as contained in the 2020-2025 strategic plan are:

1. 90% of all people with TB is notified and placed on appropriate therapy first line and second line therapy by 2025.
2. 85% of the key population, the most vulnerable, underserved and at-risk population is reached with access quality TB treatment and care by 2025.
3. To detect and diagnosed 90% of MDR-TB cases and treat with WHO recommended regimens by 2025.
4. Treatment success rate is maintained at over 90% for all people diagnosed with TB through affordable treatment services, adherence to complete and correct treatment and social support by 2025
5. TB affected families facing catastrophic costs due to TB is reduced by 50% by 2025
6. 90% of eligible PLHIV and children aged <15 years who are household contacts of cases started on TB preventive treatment (TPT)

2.4 Strategies of the National TB Programme

The strategies are in line with the WHO End TB Strategies as seen below:

Table 1: END TB strategies

PRINCIPLES	
1.	Ensure government stewardship and accountability i.e. Reinforce government commitment and discharge of responsibilities effectively by all levels of government (National, Regional and District)
2.	Promote strong coalition with civil society organizations and communities
3.	Ensure protection and promotion of human rights, ethics and equity
4.	Adapt the End TB Strategy and targets at all levels of government, with global collaboration
PILLARS AND COMPONENTS	
1. INTEGRATED, PATIENT-CENTERED CARE AND PREVENTION	
A.	Early diagnosis of TB, including universal drug-susceptibility testing and systematic screening of contacts and high-risk groups
B.	Treatment of all people with TB, including drug-resistant TB, and patient support
C.	Collaborative TB/HIV activities, and management of co-morbidities.
D.	Preventive treatment of persons at high risk, and vaccination against TB.
2. BOLD POLICIES AND SUPPORTIVE SYSTEMS	
A.	Political commitment with adequate resources for TB care and prevention.
B.	Engagement of communities, civil society organizations, and public and private care providers
C.	Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control.
D.	Social protection, poverty alleviation and actions on other determinants of TB.
3. INTENSIFIED RESEARCH AND INNOVATION	
A.	Discovery, development and rapid uptake of new tools, interventions and strategies.
B.	Research to optimize implementation and impact, and promote innovations.

The TB Programme in Sierra Leone summarizes its strategies as follows:

1. Early case finding and proper case management.
2. Decentralization and Integration of TB services into the general health services.
3. Promoting Public-Public and Public Private Partnerships (PPP) in TB control.
4. Engagement of communities and all stakeholders.
5. Behavioural Change Communication.
6. Collaboration with NGOs, bilateral and multi-lateral partners.
7. Functional commodities management system.
8. Human Resource Development at all levels of government.
9. Research and new innovation

2.5 Milestones of the National TB Programme

The miles stones will be in line with that of the End TB Strategy as seen in the table below:

Table 2: Milestones and targets for END TB strategies.

Vision	Sierra Leone free of TB, expressed as "zero death, disease and suffering due to TB"			
Goal	End TB Epidemic in Sierra Leone			
Indicators	**Milestones**		**Targets**	
	2020	**2025**	**SDG 2030**	**END TB 2035**
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100,000)	50% (<55/100,000)	80% (<20/100,000)	90% (<10/100,000)
Percentage of TB patients and their households experiencing catastrophic costs due to TB	N/A	N/A	0%	0%

2.6 Finding Missed TB cases

The country has an estimated 5000 missed people with TB annually. This is according to WHO estimate for the country. Majority of missed cases are believed to concentrate among the poor, vulnerable and underserved communities. Addressing the missed cases does not only have an epidemiological implication but also raises human right and equity issues.

Enhanced efforts with targeted strategies are much needed by recognizing the needs of vulnerable and underserved communities as key affected population for TB to accelerate the national TB control efforts towards TB control and elimination.

2.7 Addressing the dual TB and HIV burden

TB is the leading cause of mortality and morbidity among PLHIV globally. In Sierra Leone, the TB-HIV co-infection rate is about 14%. PLHIV have up to 20 times higher risk of developing active TB compared to those without HIV infection. TB screening should be offered to all PLHIV enrolled in care at diagnosis and all follow-up visits, and HIV testing should be routinely offered to all patients with TB and presumed to have TB. PLHIV with active TB need both TB treatment and antiretroviral therapy (ART). WHO recommends that ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 count, except when signs and symptoms of meningitis are present. PLHIV without active TB must receive TB preventive treatment to reduce the risk of developing active TB.

2.8 Emergence of threats of Drug resistant TB

Emergence of Tuberculosis that is resistant to essential TB medicines (i.e. Rifampicin with or without Isoniazid) has further impeded the promising gains to control the TB epidemic. In the face of lack of national capacity to perform universal DST for all incident TB cases, the country is underperforming in ensuring early diagnosis and administering appropriate therapy.

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 to 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, which 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, 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, extreme age groups and the malnourished, are at higher risk of developing Active TB as they fail to contain the latent TB infection from progressing to active disease.

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.

Pathogenesis: primary infection occurs in persons without previous exposure to tubercle 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 after 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 disease are usually infectious and may spread the bacteria to other people.

3.3 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.

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 an infectious TB case, and presence of documented recent weight loss may indicate the presence of TB in such patients to warrant investigation.

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

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.

NB: In TB program setting, a TB patient with both pulmonary and extra-pulmonary TB is classified as a pulmonary TB patient since this category is of public health importance.

Table 3: Most common types of extra-pulmonary tuberculosis

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 persons with advanced stages of HIV infection.
	Cervical Lymph nodes is the commonest site 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: decreased chest movement with stony dullness on percussion on the side of the effusion.
	CXR findings may include: tracheal and mediastinal shift away from 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 sequelae.
	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 pressure, 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 micro nodular infiltrates (miliary pattern) in two-thirds of patients that assist in the diagnosis of military TB.

4. DIAGNOSIS OF TUBERCULOSIS AND TB CASE FINDING

Diagnosis of Tuberculosis employs the use of various diagnostic methods that are organized in various algorithms for appropriate investigations of patients that are triaged for TB diagnostic evaluation. This section discusses the nationally recommended TB diagnostic methods, TB cases finding strategies and the national TB and DR-TB diagnostic policies and algorithms.

4.1 Tuberculosis Diagnostic Methods

Laboratory methods for identification of TB and anti-microbial resistance are broadly classified into:

a) Molecular and new technologies

- Xpert MTB/RIF ultra
- Xpert MTB/XDR Assay
- Truenat
- Line Probe Assay
  - 1st and 2nd line
  - Identification of Microbacteria Other Than TB/Non-Tuberculous Microbacteria (MOTT/NTM)
- Sequencing (Next Generation Sequencing)

b) Microscopy

- Light-emitting diode (LED Fluorescent microscopy)
- Conventional light microscopy

c) Phenotypic culture for detection and identification of TB

- Liquid culture system and Solid media

d) Drug susceptibility testing

- DST first line and DST second-line

e) Rapid identification tests

- TB LAM Urine test for PLHIV

f) Immuno diagnostic tests used for Latent TB

- Interferon Gamma Release Assay (IGRA)

Other investigative Methods

- Imaging – X-ray, ultrasound, CT-scan, Magnetic Resonance Imaging (MRI)
- Histology – Tissue histology and fine needle aspiration cytology.

Note:

- **The Xpert MTB/RIF ULTRA assay is the primary diagnostic tool for the investigation of all presumptive TB in the NLTCP.**
- Where Xpert MTB/Rif ultra assay is not accessible, AFB Smear Microscopy may be used.

4.2 Description of laboratory tools for TB diagnosis.

Health care workers should try as much as possible to make a laboratory confirmation of TB diagnosis in all patients with presumptive TB. This is important for monitoring of treatment response. It is also important for TB reporting and monitoring of TB control efforts. However, a clinician can still make a diagnosis of TB even in the absence of laboratory confirmation.

4.2.1 Xpert MTB/RIF/Ultra and MTB/XDR Assay

A WHO recommended Rapid, DNA-based, molecular technologies available for the diagnosis and management of TB are the GeneXpert machines and the line probe assays (LPA). The rapid detection of drug-resistance can facilitate early initiation of correct treatment and appropriate measures to prevent TB transmission.

The GeneXpert test is an automated assay used for rapid detection of M. tuberculosis and gene mutations that are associated with Rifampicin and Fluoroquinolone resistance at the same time. The test is called Xpert® MTB/RIF/ultra and MTB/XDR and the instrument is a GeneXpert machine. It is approved for use directly on raw or processed sputum specimens, cerebrospinal fluid, gastric lavage/aspirates, lymph node tissue/aspirates, and other tissue samples. Results may be available within 2 hours of test initiation. An advantage of this test is that it uses an enclosed cartridge therefore reducing the risk of cross contamination and human error. Limitations of this test include the following:

- It cannot be used for monitoring treatment because it does not differentiate between live or dead bacilli.
- A small proportion of Rifampicin resistance detected with ten color Xpert MTB/ XDR may not correlate with phenotypic (culture based) resistance (leading to discordance between Xpert and phenotypic DST results or clinical outcome).

Simple one step (SOS) Stool Testing for children

Updated WHO Guidelines in 2020 includes the use of Xpert MTB/RIF/ultra on stool as an initial diagnostic test for detection of TB and rifampicin (RIF) resistance in children with signs and symptoms of pulmonary TB. In case of a negative result on the initial test, and there is strong clinical evidence of TB, repeated testing with the Xpert MTB/RIF/Ultra assay has been endorsed by the National Leprosy and Tuberculosis Programme of Sierra Leone as recommended from WHO in management of TB among children.

Figure 2: Diagrammatic indication of SOS stool method by GeneXpert ultra method

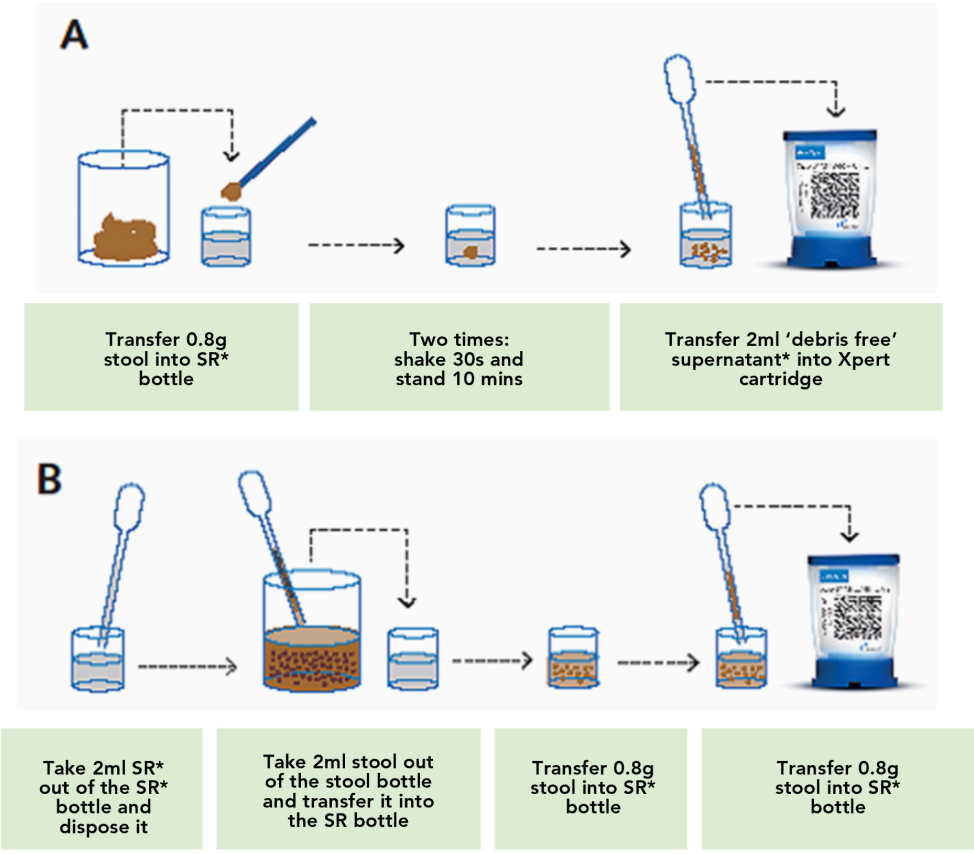


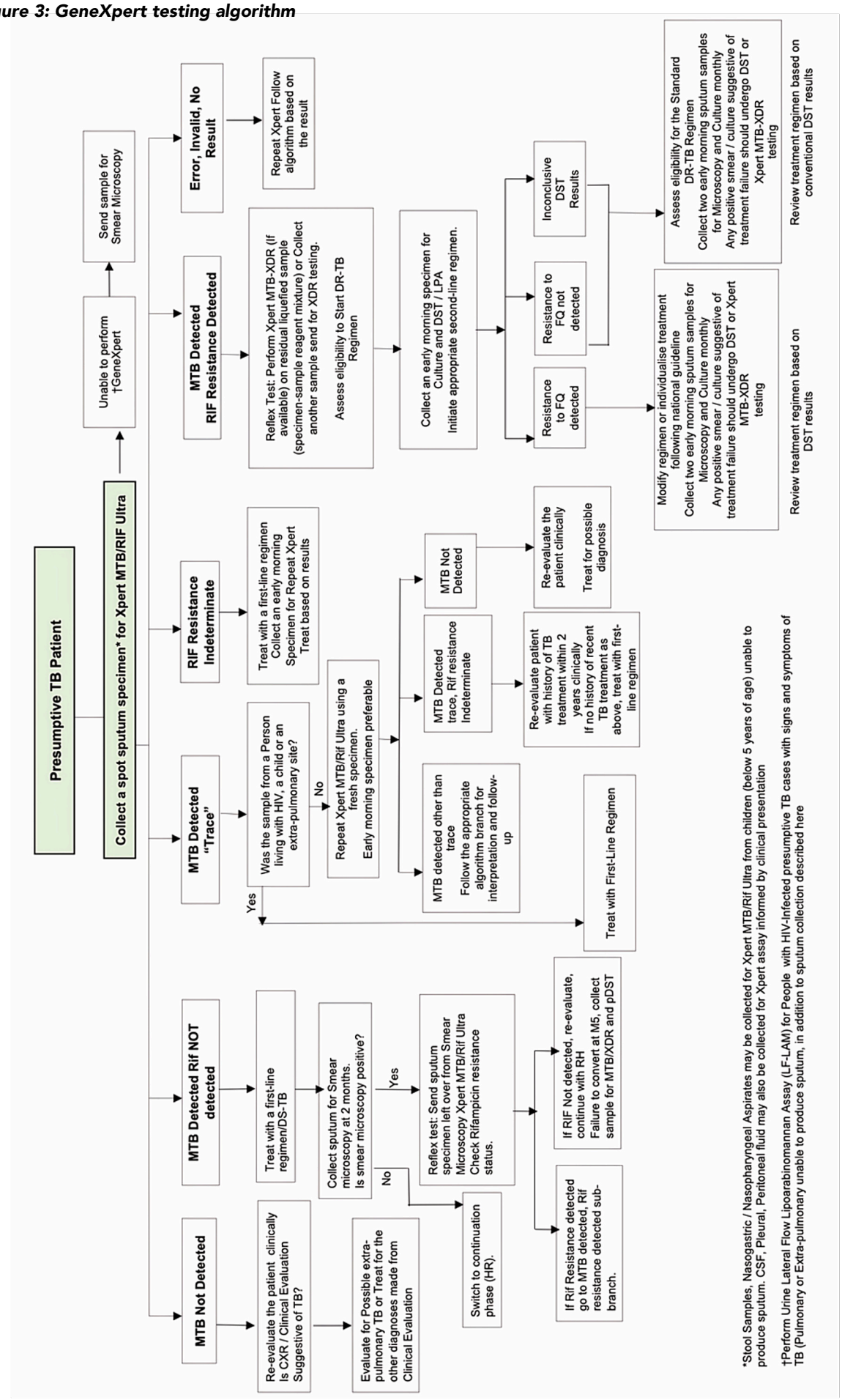
Table 4: Interpretations of Xpert/MTB RIF Ultra Assay results

Result	Interpretation	Action
MTB (Mycobacterium tuberculosis) not detected	Negative result for TB	Evaluate further
MTB detected and Rifampicin (RIF) resistance not detected	Positive result for TB with no resistance to Rifampicin	Treat for drug susceptible TB
MTB detected and Rifampicin resistance detected	Positive result for TB with resistance to Rifampicin	Treat for drug resistant TB
MTB detected and Rifampicin resistance indeterminate	Positive result for TB with inconclusive result on Rifampicin	Obtain another sample and repeat the test
MTB detected "trace" RIF resistance indeterminate (Xpert Ultra)	HIV-infected patients, children and EP specimens: a "trace" result should be considered as positive Adults with history of TB in the previous 5 years: a "trace" result cannot be interpreted	Culture should be performed. If suspected resistance to Rif or other TB drugs: perform Phenotypic DST, Adjust treatment according to DST. No interpretation of RR is possible.
Invalid result	Result not valid	Obtain another sample and repeat the test
Error	Error occurred in the sample processing	Obtain another sample and repeat the test
No result	Insufficient information for the machine to generate result	Obtain another sample and repeat the test

Table 5: Interpretations of Xpert MTB/XDR results

RESULT	ACTIONS
Invalid/Error/No result	Perform a 2nd test on a new specimen.
MTB detected	After a positive Xpert MTB/RIF, an "MTB detected" result is expected because Xpert MTB/XDR and Xpert MTB/RIF have similar detection limit.
MTB not detected No resistance detected	• After a positive Xpert MTB/RIF: perform a 2nd test on a new specimen. If the 2nd test is negative, it can be performed on culture isolates. • After a "trace" result with Ultra, a negative result is expected because the Xpert MTB/XDR has a higher detection limit than Ultra.
MTB detected No resistance detected	• Treat according to the result of Xpert MTB/RIF or Ultra. • Resistance cannot be ruled out because other resistance-conferring mutations are not detected by Xpert MTB/XDR (e.g. only 30% of Eto resistance conferring mutations are detected). • Perform pDST for resistance to other TB drugs and monitor treatment.
MTB detected • Low INH resistance detected • INH resistance detected • Low FLQ resistance detected • FLQ resistance detected • ETH resistance detected • AMK, KAN and/or CAP resistance detected	Evaluate risk factors of resistance for each drug: • High risk of resistance : consider as resistant to the drug. ○ If low-level H resistance detected (inhA mutation and no katG mutation): Hh can be used, but not counted as a likely effective drug. ○ If low-level resistance to FQs detected: Mfxh can be used, but not counted as a likely effective drug. ○ Resistance to Eto can be detected (inhA mutation). However, a negative result does not rule out resistance. ○ Perform DST for resistance to other TB drugs and monitor treatment. • Low risk of resistance : perform a 2nd test on a new specimen . If the 2nd test shows: ○ Drug susceptibility: treat with the drug. Drug resistance: consider as resistant (see above for "High risk of resistance to the drug).
MTB detected Drug resistance indeterminate	Perform a 2nd test on a new specimen. If still "indeterminate": treat with likely effective drug(s) while investigating resistance with pDST or other gDST (second-line LPA, genome sequencing).

Figure 3: GeneXpert testing algorithm



4.2.2 Smear Microscopy for AFB

Microscopy used to be the most common method used to diagnose TB. Patients suspected of having PTB (i.e. those with suggestive signs and symptoms or with chest X-ray findings suggestive of TB) should have two spot sputum specimens submitted to the laboratory for microscopic examination with same day results. A patient with one positive AFB sputum smear is considered a bacteriologically-confirmed case of smear-positive PTB. Staining for the AFB can be done using Ziehl – Neelsen (ZN) or Fluorescent Microscopy (FM) using auramine O stain. Microscopy can also be done on specimens obtained from extra pulmonary sites, which includes pleural fluids, cerebrospinal fluid (CSF), and fine needle aspiration of lymph nodes.

Interpretations of smear results

A smear result is positive if at least one tubercle bacillus (acid-fast OR fluorescent) is detected in one or more smears.

Table 6: Interpretation of smear (AFB) microscopy result

Positive AFB Result:	
Specimen 1	Specimen 2
+	+
+	Sc
+	0
Sc	0
0	+
Sc	Sc
Sc	0
0	Sc

Negative AFB Result:	
Specimen 1	Specimen 2
0	0

Scanty refers to:
1-9 AFB per 100 oil immersion for ZN Staining OR 1 -29 AFB per /20x of 30 Field for Auramine Staining

When recording, ensure to record all bacteriological results into the **TB Laboratory Register, Presumptive TB register, TB treatment card and in the Facility register.**

All positive results should be recorded with **red ink.**

4.2.3 External Quality Assessment

External quality assessment (EQA) refers to a system in which laboratory results are scrutinized objectively by an outside agency in order to get a general impression of the standard of laboratory practice and to achieve inter- laboratory comparability. There are different ways of doing EQA i.e. on-site evaluation (supervisory visits), panel testing (PT) and blinded checking.

A laboratory can adopt one or more of the stated EQA approaches for every laboratory test performed. This is in line with the clinical laboratory improvement Act CLIA requirement. This helps the laboratory identify errors which are not detected by the internal quality program (IQA) as well as comparing its performance with other laboratories participating in the same.

4.2.4 Culture

Sputum liquid and solid cultures are the "gold standard" for the diagnosis of TB. It is more sensitive than microscopy -since it can detect small number of bacilli in a sample. Liquid culture shows results after 7–10 days as opposed to solid culture which can take between 4–6 weeks. It is an important tool especially in patients with low bacterial load, which can be seen in patients with HIV and children. Indications for TB culture and drug susceptibility testing (DST) include the following;

- Patients with a history of previous TB treatment (interrupted, loss to follow-up, relapse, failed) who remained smear positive at the end of the intensive or continuation phases or who failed to improve.
- High-risk patients including those with contact to a drug-resistant TB case, health personnel, military and prisons inmates and personnel.
- Patients with positive Rifampicin resistance on GeneXpert (for susceptibility testing of other TB drugs).
- Persistent negative smear in co-infected patients (HIV, viral hepatitis or others) with signs and symptoms of TB

4.2.5 Line Probe Assay

Line Probe Assays LPAs are rapid nucleic acid amplification test (NAAT) capable of detecting M. tuberculosis and carrying out drug susceptibility testing (DST) for first-line and second-line anti-tuberculosis drugs. The GenoType MTBDRplus® and MTBDR sl (Hain Life-science) have been endorsed by WHO since 2008 and 2015 respectively. This test has the advantage of simultaneous molecular detection of M. tuberculosis and the most common genetic mutations associated with resistance to rifampicin, isoniazid, fluoroquinolones and the injectables. This technology can diagnose MDR-TB directly from sputum smear- positive samples or culture isolates, providing results within 5 hours of test initiation. Like GeneXpert, it does not differentiate between live and dead bacilli, thus cannot be used for treatment monitoring and a small proportion will not correlate with culture or microscopy due to sensitivity. Reference laboratory conditions (intended for use where culture, biosafety, and PCR facilities exist) are required to perform LPA.

4.2.6 Loop Mediated Isothermal Amplification (TB LAMP)

The TB-LAMP assay is designed to detect MTBC directly from sputum specimens. It provides results in less than 1 hour, does not require sophisticated instrumentation and can be used at the peripheral health centre level, given biosafety requirements similar to those for sputum-smear microscopy. TB-LAMP does not detect resistance to anti-TB drugs. WHO recommends that TB LAMP may be used as a replacement for microscopy for the diagnosis of pulmonary TB in adults with signs and symptoms of TB. TB LAMP may also be considered as a follow-on test to microscopy in adults with signs and symptoms of pulmonary TB, especially when further testing of sputum smear-negative specimens is necessary.

4.2.7 LF-LAM

According to the WHO operational handbook for rapid diagnosis of TB, the urine-based lateral flow lipoarabinomannan (LF-LAM) assay is recommended to diagnose active TB in HIV positive adults, adolescents and children with signs and symptoms of TB (Pulmonary or Extra-pulmonary, with advanced HIV disease; who are seriously ill; or who have a CD4 cell count of less than 200 cells/mm3, irrespective of signs and symptoms of TB and unable to produce sputum.

4.2.8 Truenat

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

> Apart from sputum, other body fluids such as cerebrospinal, peritoneal, pleural, urine, gastric and joint aspirates can be used for diagnosis of TB using Xpert MTB Rif, LPA and Culture.

4.3 Radiology

The following radiological investigations are approved for aiding in the diagnosis of TB.

4.3.1 Chest X-ray

A chest X-ray is not necessary in most cases of smear-positive PTB but can support diagnosis. A chest X-ray is suggestive of active TB if there is upper lobe infiltrate, cavitation, pleural effusion, miliary pattern or in HIV- positive patients with non-specific patchy infiltrates with or without hilar lymphadenopathy. It can be use in the screening of high-risk groups for TB such as PLHIV, contacts of bacteriologically positive TB patients, diabetics, prison inmates, health care workers or during prevalence surveys.

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. Although recent diagnostic strategies have given specific prominence to bacteriology, CXR can be used for selecting individuals for referral for bacteriological examination, and the role of radiology remains important when bacteriological tests cannot provide a clear answer.

The x-ray findings must be interpreted in the light of the patient's history and clinical findings. Where it is available and feasible in the outpatient care setting, CXR can be used as an effective primary screening and triage test for those clinical high risk groups seeking care with any complaints. Persons with unexplained chest x-ray findings that are suggestive of PTB should be evaluated with bacteriologic techniques to confirm TB.

4.3.2 Ultrasound

Used as supplementary test for diagnosis of extra-pulmonary TB, especially in the abdomen or middle of the chest area, to detect lymphadenopathy, hepatosplenomegaly and ascites.

4.3.3 Advanced Imaging studies (Computerized Tomography (CT scan) and Magnetic Resonance Imaging (MRI))

CT scan and MRI can be useful for imaging tuberculosis lesions especially EPTB.

4.3.4 Histology

Histopathological examination may be conducted on tissue specimen, but this is not considered to be bacteriological confirmation of disease. The multiplication of tubercle bacilli in any site of the body causes a specific type of inflammation, with formation of characteristic granuloma that can be found on

histopathological examination. Samples can be submitted using fine needle aspiration or tissue biopsy. This provides another means of diagnosing TB especially EPTB using specimens from other tissues and organs such as lymph nodes, abdominal organs, skin etc.

Table 7: Appropriate specimens for diagnosis of EPTB

Suspected Diagnosis	Specimen Needed
Extra-pulmonary TB	Depending on the site, other clinical specimens may be necessary, such as: • Urine – Renal TB • Cerebrospinal fluid – TB of the meninges • Effusions – pleural, pericardial, joints, etc • Pus or other aspirated fluid – TB of the abdomen etc. • Biopsy specimens – TB of the lymph nodes

Diagnosis of EPTB is based on the result from at least one specimen with confirmed M. tuberculosis by WRDs (Xpert MTB/RIF, TB LAM, Tru NAT and LPA), smear microscopy, culture or histology. However, diagnosis can be made based on strong clinical evidence consistent with active EPTB, followed by clinician's decision to treat with a full course of anti TB medicines.

As a policy of the NLTCP:

Any person presumed of having extra-pulmonary TB should be referred to a senior clinician for evaluation.

All presumptive EPTB patients should be offered an HIV test.

4.4 Tuberculosis Case finding strategies

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 and communities
- Screening and evaluation of self-presented persons with TB symptoms
- Screening all clients entering a health facility for TB symptoms
- Integrating TB screening at service delivery points like IMNCI, HIV clinics, etc.

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

Table 8: Key TB at-risk population groups

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. • Internally displaced persons. • Homeless/street persons and families.

4.4.1 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 (Active Case Finding):** Health extension workers at health facility implement community based TB care package whereby they screen all individuals presenting to the health facility and during regular home visits for Tuberculosis symptoms, and identify close contacts of an infectious TB patient, and refer to the catchment health centers for clinical evaluation and investigation for TB.
- **Identification at Health facility level (Passive Case Finding):** 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 should routinely conduct TB screening services for household/close contacts of infectious TB patients registered to receive TB treatment.

4.4.2 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) 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 investigations to rule out active TB and to provide preventive therapy for contacts without TB disease that have increased susceptibility to develop Active TB disease.

C) 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:

- 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 individuals who meet the clinical criteria of presumptive TB (individuals with symptoms suggestive of TB), conducting proper evaluation for TB and other conditions followed by investigations with sensitive confirmatory bacteriological tests.

5.1 Diagnosis of Pulmonary Tuberculosis in Adult and Adolescents

Presumptive TB case: Any person who presents with symptoms or signs suggestive of TB. The most common symptom of pulmonary TB is a productive cough for 2 weeks or more, which may be accompanied by other respiratory symptoms.

Other respiratory symptoms may include:

- Shortness of breath
- Chest pain
- Coughing up blood (haemoptysis)

There may be constitutional symptoms such as:

- Loss of appetite
- Fever
- Weight loss
- Night sweats
- Tiredness

However, any person living with HIV (PLHIV) is considered a presumptive TB if he/she presents with cough of any duration.

Confirmed TB Case: A confirmed TB case is a person for which a health worker (clinician or other medical practitioner) has diagnosed TB and has decided to treat with a full course of TB treatment.

> Any person given treatment for TB should be recorded as a TB case.
>
> Clinical "trial" TB treatment should not be used as a method for diagnosis.

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

Bacteriologically-confirmed TB case: TB diagnosed with a biological specimen using a WHO-Recommended Rapid Diagnostics (WRD) such as Xpert MTB/RIF, Tru NAT and TB LAM or culture (or by smear microscopy, where the WRDs or cultures are not available).

5.2 Methods of collecting sputum specimen

For good quality specimens to be obtained, patients must be instructed on how to produce sputum.

All presumptive PTB should be requested to submit sputum specimens using the approach below:

A. Before collecting sputum:

The Health worker should educate the presumptive TB on the following:

- The reason for collection of specimens.
- How to cough deeply (demonstration may be necessary) to produce sputum.
- The number of specimens to be submitted for examination in the laboratory for processing to identify TB bacteria/organism; and
- That if the bacteria/organisms are seen in the specimen, the patient will receive treatment and be cured.

The Health Worker should:

- Fill the NLTCP Presumptive TB Register,
- Fill a Request form for Microscopy, GeneXpert, Culture and DST as described in the program tools.
- Write the name and patient identification number on the side of the specimen container according to the Presumptive TB Register.
- The specimen collection container should be transparent, wide-mouth, screw cap container for GeneXpert/Microscopy and Sterile 50ml conical tube for Culture.
- Ensure that specimen collection occurs in a well-ventilated area or in an open field (the collection must be supervised)
- Ensure that the patient understands the instructions for specimen collection: the health worker must not stand in front of the patient during the sputum production,
- The patient spits gently into the specimen container without contaminating the outer part.

If the specimen is not suitable, e.g. saliva, repeat the sputum collection process immediately to produce a better sample.

B. During collection of sputum:

The Health worker should:

a. Ensure that patients who have chewed anything just before specimen collection rinse their mouth with water.

b. Inform the patient that the best specimens come from deep inside the lungs after coughing

c. Demonstrate how to cough deeply to the patient.

d. Inform the patient to:

- Inhale deeply 2 to 3 times and to breathe out hard each time,
- Cough deeply from the chest,
- Place the opened container close to the mouth to collect the specimen,
- Spit the specimen carefully into the container to avoid spillage of the specimen on the outside part of the container,
- Screw the lid tightly after producing the specimen,

- Return the sample to the laboratory where possible or to the health worker.

e. The volume of the specimen should be at least 3-5 ml

C. After collecting sputum:

The Health worker should:

a. Double check to ensure that the container is labelled properly.

b. Ensure that the container is firmly closed using the lid.

c. Ensure that both hands are washed with soap and water (including the patient's).

d. Ensure that all specimens are immediately sent to the laboratory. In situations where specimen cannot be shipped immediately to the laboratory, do the following;

- Store the specimens preferably in a refrigerator or in a cool, safe and dark place,
- Ensure the specimens are sent to the laboratory within 48 hours,
- Ensure the specimens for culture are sent to the laboratory, not later than 24 hours after collection if cold chain is not maintained.

e. Ensure that each specimen is accompanied with a completed specimen examination request form that is kept separately from the sputum container.

Number of sputum specimens for Xpert MTB/RIF Ultra and smear microscopy

- For Xpert MTB/RIF Ultra, one spot specimen is required under supervision
- For sputum microscopy, two specimens are required ('spot-spot' approach) as outlined in the table below

Note: Patient should rinse mouth with water before production of sputum specimen

Table 9: Approach for specimen collection for smear microscopy

Day	Specimen number	Approach to specimen collection
Day 1	2 Specimens	Patient provides 2 "on the spot" specimen under supervision and present them to the laboratory.

Note: Patient should rinse mouth with water before production of sputum specimen

D. Labelling of specimen container:

a. It is important that specimen containers are labelled on the side of the container and not on the cover, to avoid mix up of specimens in the laboratory.

b. The number on the specimen container is derived from the Presumptive TB register thus: Clinic code/Serial Number of the patient to be examined in the current month from the presumptive register/current calendar month/number of specimens.

E. Transportation of sputum:

The Health worker should ensure that:

a. The TB specimen form should be filled by the health worker delivering the specimen to the

laboratory,

b. Specimens that require transportation are packed carefully, preferably in a transport box (3-level packaging) before transportation.

c. Cold chain is maintained throughout the transportation process, especially when sending specimens for culture and DST.

5.3 Specimen other than sputum (SOTS)

5.3.1 Nasopharyngeal Aspirate (NPA)

- Nasopharyngeal Aspirates are approved for diagnosis among in children and patients who cannot produce sputum or may swallow it. Where the equipment and the skills to perform the skills exist at Health Facility level, NPA should be attempted in all children less than 5 years and the resulting specimen tested with Xpert® MTB/RIF/ultra
- Ask patient to sneeze & clean nostril area with normal saline.
- Connect the sputum trap to the suction machine.
- Measure the distance to the nasopharynx by placing the end of the tube at tragus of the ear and extending it to the tip of the nose.
- Mark the length on the tube.
- Insert the tube through the nares into the nasopharynx.
- If the patient does not have teeth, you can introduce the tube into the oropharynx via the mouth.
- If the patient coughs during the tube insertion and produces good quality sputum, collect the sputum in the sterile sputum container.
- If ≥ 2 mL of sputum has been produced, sputum collection is complete.
- If the patient does not produce a sputum specimen, insert the tube from the sputum trap into the nasopharynx until you reach the marked length.
- Use caution to avoid causing undue trauma.
- Ensure that the sputum container is tightly sealed and correctly labeled

5.3.2 Laryngeal Swab

Laryngeal swabs may be useful in children and patients who cannot produce sputum or may swallow it.

- Collect laryngeal swabs in the early morning, before patients eat or drink anything.
- Use a sterile absorbent cotton swab for collection.
- Transport each specimen in a container with a few drops of sterile 0.9% saline solution in order to keep the swab wet.

5.3.3 Other respiratory specimens

Trans bronchial and other biopsies taken under sterile conditions should be kept wet during transportation by adding a few drops of sterile 0.9% saline to the tissue.

5.3.4 Stool specimens

Stool collection is a non-invasive method. Mycobacterium tuberculosis complex (MTBC) can be detected in stool specimens because sputum is coughed up and subsequently swallowed, and then

passes through the gastrointestinal system. Since 2021, the World Health Organization (WHO) has recommended stool as a new specimen type for both Xpert MTB/RIF and Xpert Ultra as the initial diagnostic test for TB and the detection of rifampicin resistance in children aged under 10 years with signs and symptoms of pulmonary TB.

Stool collection ideally takes place at the health care facility. However, to obtain a specimen on demand is often challenging; therefore, stool is collected at home and the patient or caregiver needs to return the sample to the facility for testing. Different types of containers can be used; but should generally be wide-mouthed to make it easy to add the stool, and it should be able to hold at least 3–5 g of stool. Note: Sputum containers can also be used for stool collection. The stool container should be provided in a plastic bag containing absorbent material, to keep the container clean during transport to and from the child's home. The absorbent material will absorb any substances that may leak out of the container if it is not closed properly. The patient or caregiver should be instructed by the laboratory staff or other health care worker on how to collect the stool sample in the following steps.

a. Ideally, collect the stool sample during the first daily bowel movement. If possible, first empty the bladder, to avoid mixing urine with the stool sample.

b. Put some clean plastic sheeting on the spot where the stool will be dropped, to ensure the collection of a clean sample. Avoid contamination of the plastic with soil, detergent or disinfectant from the toilet.

c. If the stool sample needs to be collected from a child that uses a diaper (i.e. a nappy), then either collect the stool directly from the diaper as soon as possible after defecation, or put a plastic sheet in the diaper to avoid (prolonged) contact between the stool and the surface of the diaper (diapers may contain substances that inhibit the test).

d. Fill the stool container with the stool sample up to half full, using (for example) the spoon provided with some types of containers, a clean plastic bag, a clean piece of cardboard or a clean spoon. Do not fill the container to the brim.

e. Close the container tightly, place the container in the plastic bag provided (preferably a self-sealable bag) and close the bag. Leave the absorbent material in the plastic bag so that this material can absorb any substances that may leak out of the container.

f. As soon as the stool sample has been collected, store the plastic bag containing the stool container in a clean, cool place (e.g. in a fridge if possible), avoiding exposure to direct sunlight. Do not freeze the sample.

g. Take the plastic bag containing the stool container to the health care facility, preferably on the same day that you collected the stool sample.

For transport and storage of stool specimens, the same conditions apply as for transport and storage of sputum specimens for GeneXpert testing described in section 5.2. Allow the stool sample to warm up to room temperature.

5.3.5 Gastric aspirate

Gastric aspirates often contain MOTT and are therefore rarely used for adults; they are indicated for children, however, who are not likely to produce sputum. An early morning specimen is highly recommended especially when the patient has an empty stomach.

After specimen collection, add 100 mg of sodium bicarbonate to the gastric aspirate to neutralize it and transport immediately to the laboratory or store at 2-8 °C.

5.3.6 Other extra-pulmonary specimens

The laboratory may receive a variety of specimens for diagnosis of EPTB -body fluids, tissues, stool etc. All these samples should be sent for GeneXpert, and culture and DST. These specimens may be broadly divided into two groups which are processed in different ways:

Specimens collected from sterile sites

These include CSF, pericardial, synovial and ascitic fluid, blood, bone marrow etc. which are usually free from contaminating flora.

- All liquid specimens should be collected in sterile glass containers without using any preservative.
- Specimens can be inoculated directly into liquid vials and transported to the laboratory for culture.
- Specimens must be transported to the laboratory immediately; they should be processed as soon as possible or kept at 2–8 °C.

Specimens collected from non-sterile sites

- A urine specimen should consist of a single, early-morning, midstream sample.
- Skin tissues, pus swabs and pus aspirates
- Stool samples from children for GeneXpert using the SOS methods as described in the stool sample collection SOP.

Table 10: Types of specimen for every test method and the handling procedures

Test	Specimen Type	Type of container	Specimen volume	Transport/storage conditions
Microscopy	Sputum, CSF, Aspirates, Biopsies, Pus/ swabs	A wide-mouthed, unbreakable, leak-proof container	3 - 5 ml	2 – 8^{0}C
MTB Rif Assay (Gene Xpert)	Sputum, CSF, Gastric aspirate, Nasopharyngeal aspirate, Pleural fluid, Pericardial fluid, Ascitic fluid, FNA, Lymph node biopsy, Stool, skin snips, pus aspirate, bone tissue.	50 ml falcon tubes	2 - 3 ml	2 – 8^{0}C
TB culture / DST	Sputum, CSF, Aspirates, Biopsies, pleural effusions, urine, Laryngeal swab, gastric aspirates, pus swabs	50 ml falcon tubes,	Sputum (5–10ml), Pleural effusions (5-10 ml) CSF-(1-3ml) Urine(10ml)	2 – 8^{0}C
IGRA (QuantiFERON) Assay	Blood	Whole blood collected in EDTA tubes	4 - 6 ml	2 – 8^{0}C
LPA	Sputum, CSF, Aspirates, Biopsies, pleural effusions, laryngeal swabs, gastric aspirate pus swabs, culture	50 ml falcon tubes	5 - 10 ml of sample	2 – 8^{0}C

5.4 Special Sample Packaging and Transport

The basic packaging system for local surface transport of all specimens consists of triple packaging systems while ensuring that the biohazard labels are attached on the outer shipping package as per IATA regulations.

Basic triple packaging system consists of three layers as follows;

1. Primary receptacle. A labelled primary watertight, leak-proof receptacle containing the specimen. The receptacle is wrapped in enough absorbent material to absorb all Fluid in case of breakage.
2. Secondary receptacle. A second durable, watertight, leak-proof receptacle to enclose and protect the primary receptacle(s). Several wrapped primary receptacles may be placed in one secondary receptacle. Sufficient additional absorbent material must be used to cushion multiple primary receptacles.
3. Outer shipping package. The secondary receptacle is placed in an outer shipping package which protects it and its contents from outside influences such as physical damage and water while in transit.

Note: All samples should be transported in cold chain (cool box, 2-80C ice packs and if possible, with thermometers to monitor the temperature from packaging to reception of the sample).

Transport conditions

Specimens collected should be transported to the laboratory as soon as possible. If a delay of a few days cannot be avoided, keep specimens cool (refrigerated 2-8°c) up to 3 days in cold conditions will not significantly affect the positivity rate of smear microscopy and will be suitable for culture.

Quality specimen is a key to quality results hence, samples should be accepted when:

a) Sample acceptance

- Collected in a leak proof container
- The volume is adequate (3-5ml)
- Duly completed request form
- Specimen packed appropriately (triple packaging)
- Accurately labelled for identification (Patient's name, IP/OP/TB No, facility name, date).

b) Samples are rejected when:

- The request form is not received with the specimen or it's not correctly filled.
- There is a mismatch of information details on the request form with details on the specimen container.
- Container used is not appropriate
- Specimen unlabelled.
- Specimen container is broken.
- Specimen leaked.
- Specimen volume is not sufficient.
- Specimen not appropriately packed (triple packaging).

5.5 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 histopathologic tests if indicated) to reach to proper diagnosis of the patient's condition.

5.5.1 Considerations for clinical diagnosis of pulmonary TB

In patients in whom index of clinical suspicion remains high despite non-revealing results from confirmatory methods, the care provider may continue investigating the patient for TB with the aid of supportive methods including imaging and histopathologic techniques. Treatment for common infections with antibiotics, other than anti-TB drugs, 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 non-bacteriologic evidences from supportive tests and with aid of sound clinical decision by a clinician or TB expert.

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 has at least one positive result on AFB microscopy

Clinically diagnosed PTB Case is defined as:

- A person who has 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 Anti-TB regimen is made with the help of evidences from supporting tests and with aid of sound clinical decision.

5.5.2 Diagnosis of extrapulmonary TB (EPTB) in adult and adolescents

Symptoms or signs of EPTB depend on the site(s) involved. See Table 10 below.

Table 11: Symptoms of EPTB disease

Pulmonary	Constitutional Symptoms:	Extra-pulmonary
• Cough • Coughing up sputum or blood • Pain in the chest when breathing or coughing • Shortness of breath	• Weight loss • Chills • Fever • Night sweats • Loss of appetite • Weakness or easy fatiguability • Malaise (a feeling of general discomfort or illness)	• TB of the spine may cause pain or swelling/deformity in the back. • TB of the kidney may cause blood in the urine. • Meningeal TB may cause headaches, fever, neck stiffness, vomiting, irritability, convulsions or loss of consciousness. • TB of the Lymph nodes (Lymphadenitis) may cause painless lymph node swelling, often at the base of the neck and may drain pus • Abdominal TB may cause abdominal swelling, ascites and abdominal mass • Osteo articular TB (TB of the bones/ joints) may cause bone/joint pain, bone swelling and limitation of movement

Diagnosis of EPTB is based on the result from at least one specimen with confirmed M. tuberculosis by WRDs (Xpert MTB/RIF, TB LAM, Tru NAT and LPA), smear microscopy, culture or histology. However, diagnosis can be made based on strong clinical evidence consistent with active EPTB, followed by clinician's decision to treat with a full course of anti TB medicines

As a policy of the NLTCP:

Any person presumed of having extra-pulmonary TB should be referred to a senior clinician for evaluation.

All presumptive EPTB patients should be offered an HIV test.

Features of EPTB can be summarized in Table 11 below:

Table 12: Typical clinical features and evaluation of EPTB

Disease site	Typical Clinical Presentation	Investigation
TB adenitis	• Asymmetrical, painless, non-tender lymph node enlargement for more than one month • +/- discharging sinus • Most commonly in neck area	• Xpert MTB/RIF assay, culture and cytology using fine needle aspiration or excisional biopsy when possible • TST or Interferon Gamma Release Assay (IGRA) usually positive - not necessary for diagnosis • If axillary node enlargement is on same side with the site where BCG vaccine was administered, consider BCG disease and refer or manage as applicable
Pleural TB	• Signs of respiratory distress • Reduced breath sound and chest movement on affected side • Dullness to percussion on affected side • +/-chest pain • Pleural friction rubs on affected side • The severity of the signs and symptoms are related to the amount of fluid in the pleural space	• Investigate for PTB • Chest x-ray • Pleural fluid analysis (Xpert MTB/RIF assay, culture, protein content, white blood cell (WBC) count, cytology, adenosine deaminase assay (ADA) • If pleural tap yields pus, consider empyema and refer or manage as appropriate.
TB Meningitis/ CNS	• Headache • Irritability/abnormal behaviour • Vomiting (without diarrhoea) • Lethargy/reduced level of consciousness • Neck stiffness • High-pitched cry in under-5 children • Bulging fontanelle in children <2 years • Photophobia (aversion to light) • Signs and symptoms of cranial nerve palsies (e.g diplopia, squint) • Focal neurological deficits (deafness, blindness, weakness of the limbs) • Convulsions • Paraplegia (spastic or flaccid paralysis) • Loss of consciousness	• Lumbar puncture and cerebrospinal fluid (CSF) analysis: • Gross findings: CSF may look clear, occasionally cloudy or may form spider web if left for a few hours • Xpert MTB/RIF assay • Microscopy: The WBC count is usually < 500/mm3 with lymphocyte predominance • Culture • Chemistry: High protein and low glucose levels • Computerized tomography (CT) scan and magnetic resonance imaging (MRI) of the brain may show features of intra-cranial collections and Tuberculoma • Chest x-ray
Miliary TB	• Features depend on the site/organ affected but may be usually non-specific • Lethargy • Fever • Wasting • Failure to thrive in children	• Chest x-ray • CT scan and MRI may show features specific to lesions in the site/organ affected • Collect any available specimen depending on site/organ affected and send for investigations as appropriate

Abdominal TB	• Abdominal swelling with or without ascites • Palpable masses • Diarrhoea • Malabsorption • Cachexia (severe weight loss) • Fever • Night sweat •	• Abdominal USS • Ascitic fluid analysis • Xpert MTB/RIF assay • AFB smear microscopy • Culture • Cytology • Chemistry • Biopsy (peritoneal, lymph node, liver etc) • Xpert MTB/RIF assay • Histology • Advanced imaging (CT scan, MRI)
Spinal TB	• Deformity of spine e.g. gibbus (hunch back) • Lower limb weakness/paralysis • Urinary and/or stool incontinence • Paraesthesias (tingling sensations, numbness, etc.) • Loss of skin sensations (pain and touch)	• X-ray of the spine • Spine MRI • Spine CT scan
Pericardial TB	• Signs and symptoms of cardiac failure • Apex beat difficult to palpate • Distant heart sounds • Pericardial friction rub	• CXR • Echocardiography • ECG • Pericardial fluid analysis (Xpert MTB/RIF assay, culture, protein content, WBC count and cytology)
TB of the bones and joints	• Bone/joint pains • Swelling of the joints and/or bones with or without limitation of movement • Unilateral effusion (common in knee or hip joints) • Dactylitis (swelling of the bones of hands and feet) in children • Discharging sinuses especially when osteomyelitis is present	• X-ray of the corresponding bone/joint • Joint fluid analysis (Xpert MTB/RIF assay, culture, protein content, WBC count and cytology) • Analysis of any discharge from sinuses (Xpert MTB/RIF assay, culture, protein content, WBC count and cytology)

After clinical and laboratory investigation of the presumptive TB case, the following algorithms can be used to guide the management.

5.5.3 Diagnosis of TB among HIV positives

TB is one of the main causes of death among HIV positives. The mortality rate among HIV-infected tuberculosis patients is higher than that of non-HIV-infected tuberculosis patients, particularly for those with smear-negative pulmonary and extra-pulmonary tuberculosis. The rates of smear-negative pulmonary and extra-pulmonary TB 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 people living with HIV who have smear-negative pulmonary and extra-pulmonary TB. 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 the 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.
- 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.
- Molecular WRDs (Xpert MTB/RIF test, Xpert Ultra, Trunat, TB-LAMP, and LF-LAM among advanced HIV disease) are the preferred initial confirmatory diagnostic tests among PLHIV.
- Chest X-rays, when available, should be performed early in the course of investigation of TB in seriously sick HIV positives.
- Pathologic studies should be considered from the appropriate specimen.
- In patients with negative sputum smears, sputum culture should be encouraged when possible as part of the diagnostic procedure for people living with HIV.
- 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.
- 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.

5.6 Diagnosis of Drug Resistant Tuberculosis

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

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

Diagnosis of DR-TB should be confirmed using molecular tests like GeneXpert. All presumptive TB cases should have access to these tests. For sites without GeneXpert, it is important to identify presumptive DR-TB cases including those with positive AFB and refer samples to GeneXpert sites. Initiation of appropriate treatment for confirmed DR-TB cases should be done promptly

Diagnosis includes history taking, clinical examination and laboratory investigations. The clinical presentation of DR-TB in adults, adolescents and children is similar to that of DS-TB. A high suspicion is required in people who are contacts of a known DR-TB case. With Xpert MTB/RIF used as the initial diagnostic test of presumptive TB cases, detection of Rifampicin resistance strains can be identified. Timely detection of DR-TB prevents further morbidity, mortality and transmission in the community.

Diagnosis of DR-TB using Xpert MTB/RIF Ultra

Any presumptive TB case should be requested to submit 1 clinical specimen e.g. sputum for Xpert MTB/RIF Ultra on the spot and managed according to guidelines. Interpretation of Xpert MTB/RIF Ultra results

The results of Xpert MTB/RIF assay should be interpreted as shown in the algorithm in Table 5.

Other diagnostic tests for DR-TB

- Xpert MTB/XDR- This will test for additional resistance to H, FQs, Eto, Injectables
- Line Probe Assay (LPA): Rapid molecular tests for identifying MTB bacilli and detecting resistance to first- and second-line anti-TB medicines.
- Culture and DST: Involves growing the organism in a medium (liquid or solid) before proceeding to test for resistance.

Table 13: Recommendations for DST

First Line DST is recommended for
• Presumptive/confirmed TB patients with prior TB treatment history for one or more month • Patients with presumed or confirmed TB with contact history with RR/MDR-TB • Presumptive TB in patients from health care settings or congregated settings or other known high MDR-TB prevalent settings • TB patients who remain smear positive at end of second months or later on TB treatment. • All bacteriologically confirmed TB patients at time of registration to TB treatment if not done as initial diagnosis. • FL-DST including for INH using FL-LPA or Trunat is also indicated for all TB patients who are smear positive at the end of second month of treatment or later and in whom RIF resistance is ruled out (see section under Hr-TB for details). The tests are also indicated for all presumptive TB cases or confirmed TB cases who are close contacts of confirmed Hr-TB cases.
Second line DST is recommended under the following conditions:
• All bacteriologically confirmed RR/MDR-TB patients at baseline, before initiation of RR/MDR-TB regimens • All Hr-TB patients at baseline, before initiation of treatment. • Confirmed TB patients who are contacts of patients with documented RR/MDR-TB • Symptomatic contacts of patients with documented RR/MDR-TB • Smear/culture positivity at the end of 4th month of treatment or later for patients on RR/MDR-TB regimens • Smear/culture reversion to positive after initial conversion in a patient on RR/MDR-TB Regimen. • Patient in whom the current SL regimen is seriously compromised because of drug intolerance • All patients being evaluated for treatment after loss to follow up from RR/MDR-TB regimens for more than one month. • All RR/MDR-TB patients coming from areas with high rates of second line drug resistance or unfavorable treatment outcomes • All RR/MDR-TB patients with clinical and radiological deterioration/non-response despite adequate RR/MDR-TB regimens

6. DIAGNOSIS OF TUBERCULOSIS IN CHILDREN

6.1 Integrated childhood TB care service

TB in young children often present with non-specific clinical presentations that are not managed within the context of TB care services but rather in the RMNCAH platform that provides care to the sick child based on major childhood illnesses which systematically excludes TB.

As a result health professionals often overlook TB and repeatedly treat them erroneously as a sick child not improving to standard treatment in RMNCAH. An important step towards improving the prevention and management of TB in children is the provision of integrated care.

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 Miliary and 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 Diagnosis of 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 specimen is usually not feasible, but bacteriological confirmation should be sought whenever possible by testing biological specimen with Xpert® MTB/RIF/ultra. These specimen should also be sent for microscopy, and or culture.

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 clinics 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.

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;
- Children 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. (Please see box below for the approaches to diagnose TB in children).

Approaches to diagnosis of 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 (AFB microscopy, Xpert MTB/RIF assay & culture)
- 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

i. Persistent Cough for two weeks or more
ii. Prolonged Fever for 2 weeks or more
iii. Poor weight gain for 1 month or more: defined as weight loss, or very low weight (weight-for-age less than -3 z-score), or underweight (weight-for age less than -2 zscore), or confirmed weight loss (>5%) since the last visit, or growth curve flattening, or Mid Upper Arm Circumference (MUAC) measurement in the red color code.
iv. History of a close or household contact with an individual who has PTB.
v. Reduced playfulness, poor feeding or decreased activity in the presence of any of the above symptoms 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, always 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 confirm diagnosis of TB in a child using specimens and laboratory facilities available. Bacteriological confirmation whenever possible: 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 Ultra, or AFB microscopy, or culture. Appropriate clinical specimens include sputum, nasal pharangeal aspirates, gastric aspirates, stool 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
- HIV infection
- complicated or severe cases of TB disease
- uncertainty of the diagnosis
- history of prior TB treatment.

To aid in the diagnosis of TB in children, the use of stool has been recommended. Refer to Simple one Step Stool testing method for children - TB diagnostic methods in chapter 4.

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 mWRDs (e.g. Xpert MTB/RIFUltra), AFB microscopy or culture from biologic specimen.

B) Clinical diagnosis of TB based on 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.

6.3.4 Diagnosis of Tuberculosis in HIV Positive Children

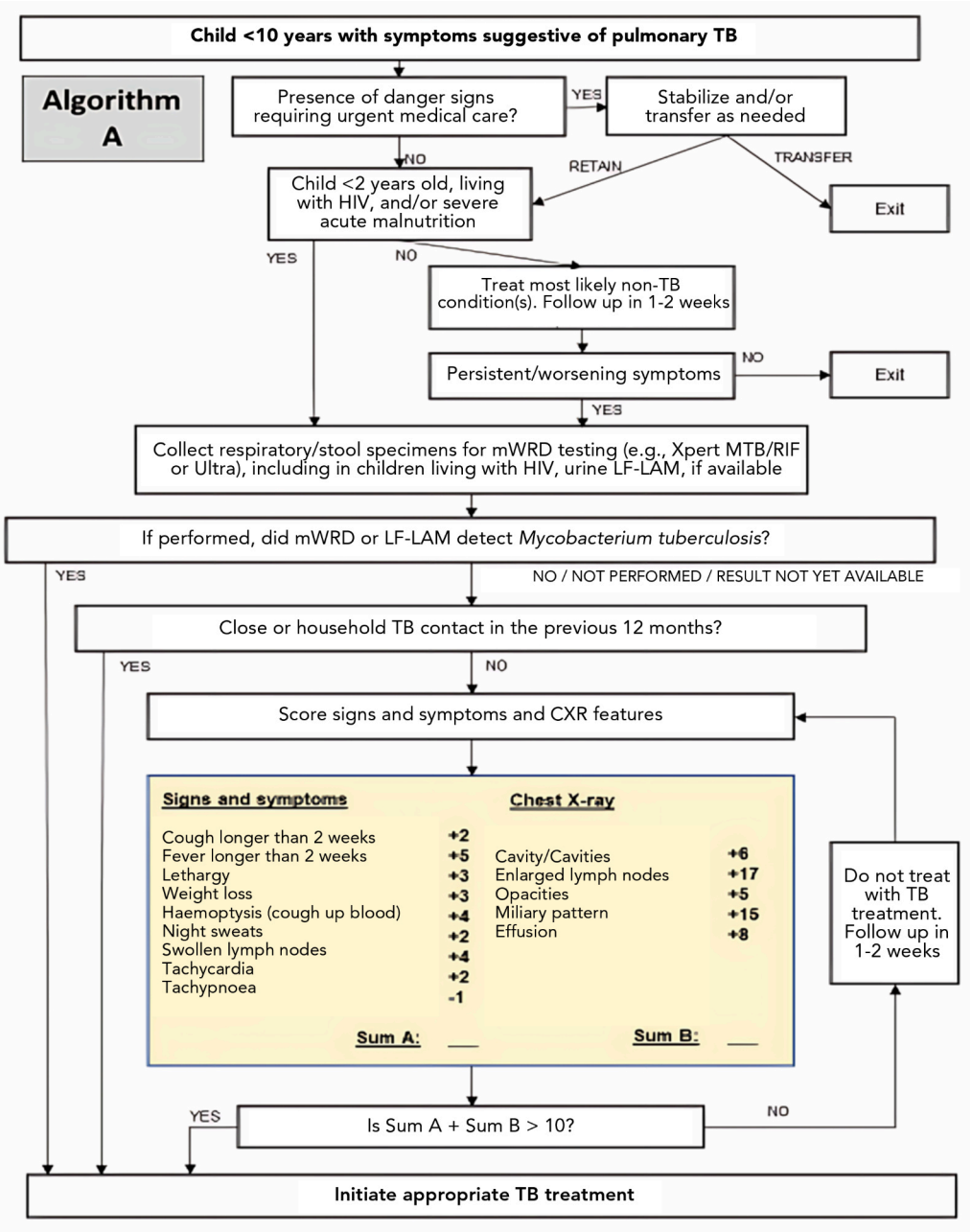
Incidence of tuberculosis in HIV-infected children is much higher compared to HIV negative children. In HIV infected children, tuberculosis is often severe, progressive and likely to involve extra-pulmonary sites. All HIV-exposed and infected children should be screened for TB using symptom-based TB 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 Diagnosis of TB in HIV-infected children: 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.

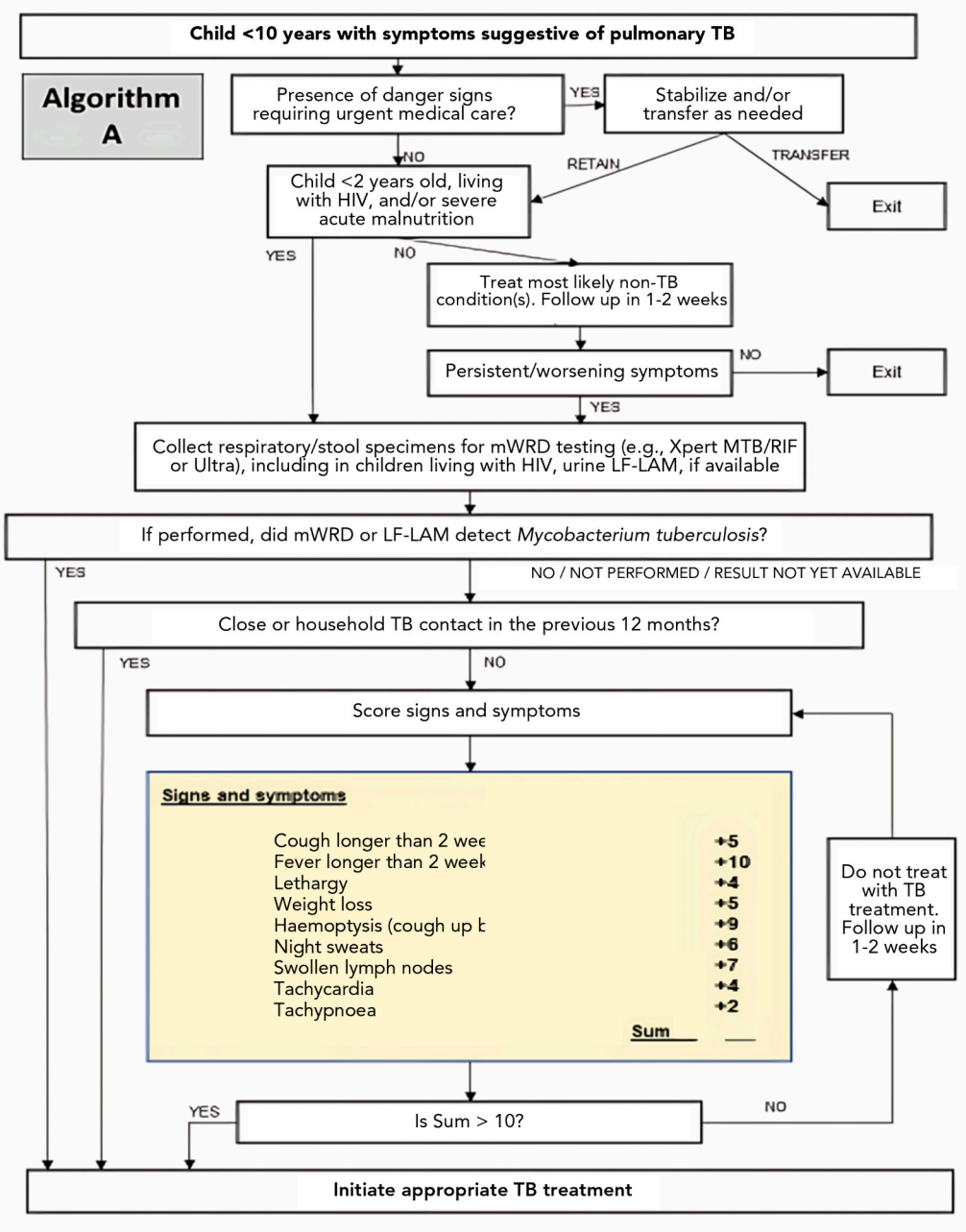
Use of the TB diagnostic algorithm is a simplified approach recommended to evaluate both HIV negative and HIV-infected children who fulfill symptom screen criteria to reach to the diagnosis of TB. (See figures 2 and 3 below).

Figure 4: Diagnostic algorithm for children below 10 years in facilities with X-ray



In setting where X-ray may not be available, the algorithm below will be useful for decision making in the management of the child.

Figure 5: Diagnostic algorithm for children below 10 years in facilities with no X-ray



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)

LTBI is a state of persistent immune response to stimulation by Mycobacterium Tuberculosis antigens with no evidence of active TB. There is no gold standard test for direct identification of Mycobacterium tuberculosis infection in humans. The vast majority of infected people have no signs or symptoms of TB but are at risk for active TB disease.

Testing for latent tuberculosis infection

Test for LTBI using either of the following;

- TST e.g. Mantoux
- IGRA e.g. QuantiFERON®-TB Gold (QFT G)

People living with HIV who have a positive test for LTBI benefit more from preventive treatment than those who are negative;

The LTBI testing is not a requirement for initiating preventive treatment in people living with HIV or child household contacts aged < 5 years (active TB should be ruled out)

TPT Regimens:

The following medicines are used for TPT;

- Isoniazid (6H) – daily dosage for 6 months
- Rifampicin and Isoniazid (3RH) – daily dosage for 3 months
- Rifapentine and Isoniazid (3HP) – weekly dosage for 3 months
- Rifapentine and Isoniazid (1HP) – daily dosage for 1 month

(See dosage tables below)

The decision to prescribe one regimen rather than the other should take into consideration:

- Drug-susceptibility of the strain of the presumed source patient, if known.
- Co-morbidities (e.g. HIV infection, pre-existing hepatic disease or neuropathy).
- Risk of drug interactions (especially with antiretrovirals), tolerability, length of treatment and likelihood of adherence.
- Individual characteristics (e.g. age, pregnancy, living conditions, individual preference).
- Epidemiological and programmatic aspects (e.g. HIV prevalence, available drugs, national recommendations).

7.2 Priority groups for TPT

All persons who are in close contact with a diagnosed TB case should be screened for TB. Those without active TB should be placed on TPT (formerly IPT). Priority should be given to the following groups:

- Children aged less than 5 years (<5 yrs) who are contacts of an infectious index TB case
- Children aged 5 years and above, adolescents and adults who are contacts of an infectious index TB case

- All HIV infected persons

Screen all contacts of an infectious index TB case for TB and place all eligible contacts on TPT.

7.3 Administering TPT for children

Children <5 years of age and persons of any age with HIV infection who are close contacts of a bacteriologically diagnosed TB patient and who, after careful evaluation by a trained clinician, do not have active TB, should receive TPT.

Points to note regarding TPT in children

- Administer TPT after ruling out active tuberculosis (regardless of BCG vaccination status), and contraindications to TPT
- To avoid treatment interruption, pre-pack the necessary amount of medication to cover the period required for the chosen regimen at the commencement of therapy and dispense monthly or as appropriate
- Weigh the child every month (during follow up visit) and adjust dosage according to the weight (refer to tables below on how to calculate the appropriate dosages)
- For children with HIV or other medical conditions, TPT appointment date should be aligned with other clinic visits
- Fill the TPT card and facility TPT register accordingly

Discontinue TPT in any child who develops active TB, and commence full TB treatment.

Table 14: Dosage of 6H and 3RH for prophylaxis in children

Weight band	Isoniazid daily dose	H 100 mg*tablet	H 300 mg tablet	RH 75/50 Fixed Dose Combination
4-7 kgs	50 mg	0.5	-	1
8-11 kgs	100 mg	1	-	2
12-15 kgs	150 mg	1.5	-	3
16-24 kgs	200 mg	2	-	4
≧ 25 kgs	300 mg	3	1	Use adult formulations

Dispersible formulations for Isoniazid are preferred

Table 15: Dosage of Rifapentine, INH (3HP) for children 2-14 years

Weight band	Isoniazid (H) weekly dose	Rifapentine (P) weekly dose	HP 300/300 mg tablet
10-14 kgs	300 mg	300 mg	1
15-24 kgs	450 mg	450 mg	1.5
25-29 kgs	600 mg	600 mg	2
30 kgs or more	900 mg	900 mg	3

Rifapentine has a bitter taste, for young children who cannot swallow, crush the tablet and mix with small amount of multivitamin syrup

Daily regimen for 1 month HP

- Child 13 years and over and adult: 600 mg once daily

Steps for monitoring a child on TPT.

- Review for signs and symptoms of active TB during monthly drug refills
- Ask for side-effects;
- Evaluate adherence and counsel appropriately
    - Any child who does not come a week after his/her TPT appointment day should be traced and reviewed for signs and symptoms of active TB. If active TB is excluded, continue TPT for the duration to complete as per the selected regimen.
- If a child develops symptoms suggestive of active TB during the course of TPT:
    - Discontinue TPT
    - Assess for active TB
    - Commence anti-TB treatment if active TB is confirmed
    - Refer to medical officer/specialist if not sure of diagnosis.
    - If child is on ART, assess for adherence to ART/ART failure.

7.4 Algorithms for identification and management of those eligible for TPT

In clinical settings, two critical considerations are important in initiating treatment for LTBI.

- Active TB disease should be excluded before offering TPT. Clinical screening using symptom-based criteria can safely be used to identify those eligible for TPT.
- The routine 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 affordable.

Figure 6: Algorithm for initiating TPT in adults and adolescents ≥15 years living with HIV

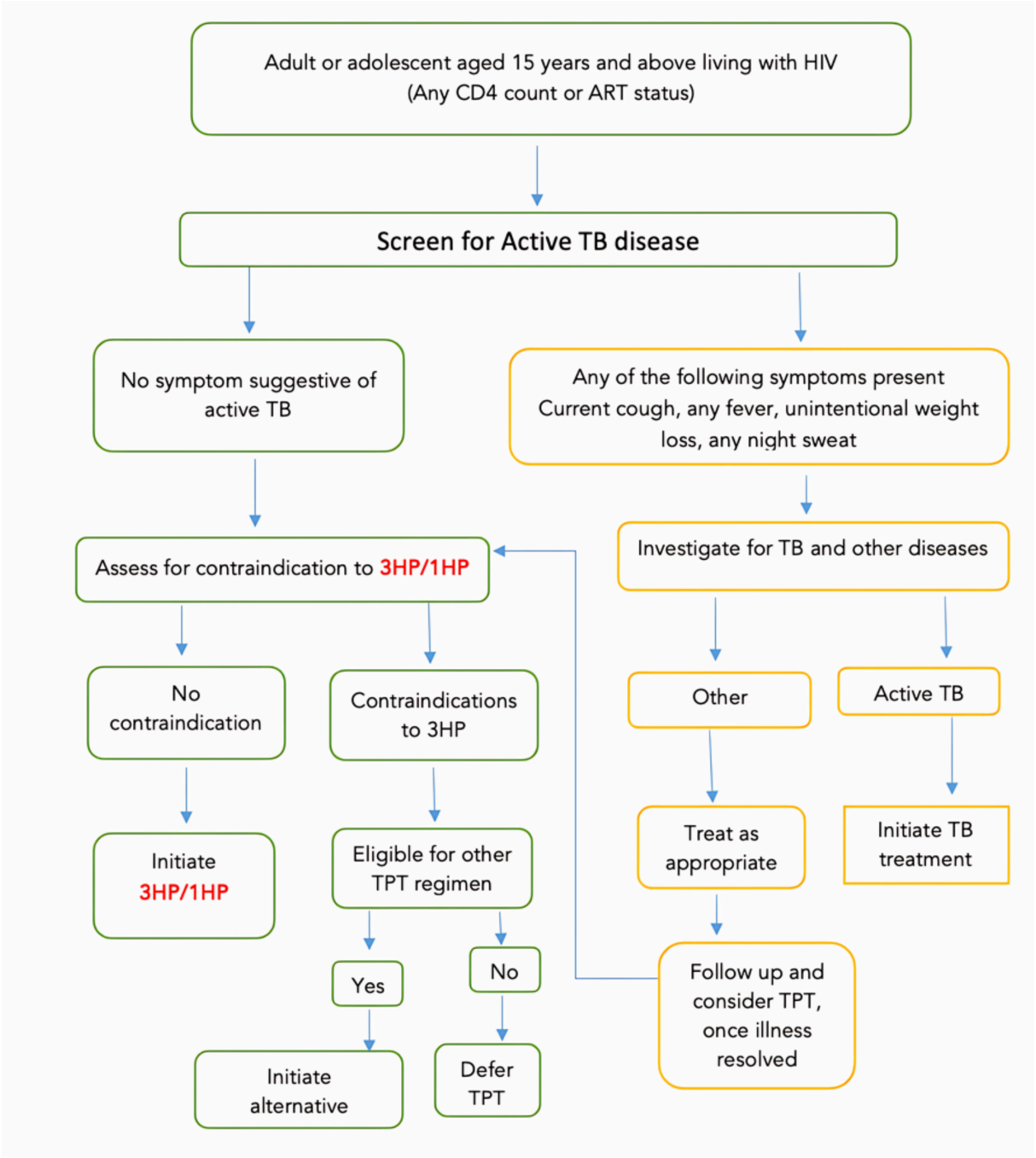


Figure 7: Children < 15 years living with HIV and without household TB exposure

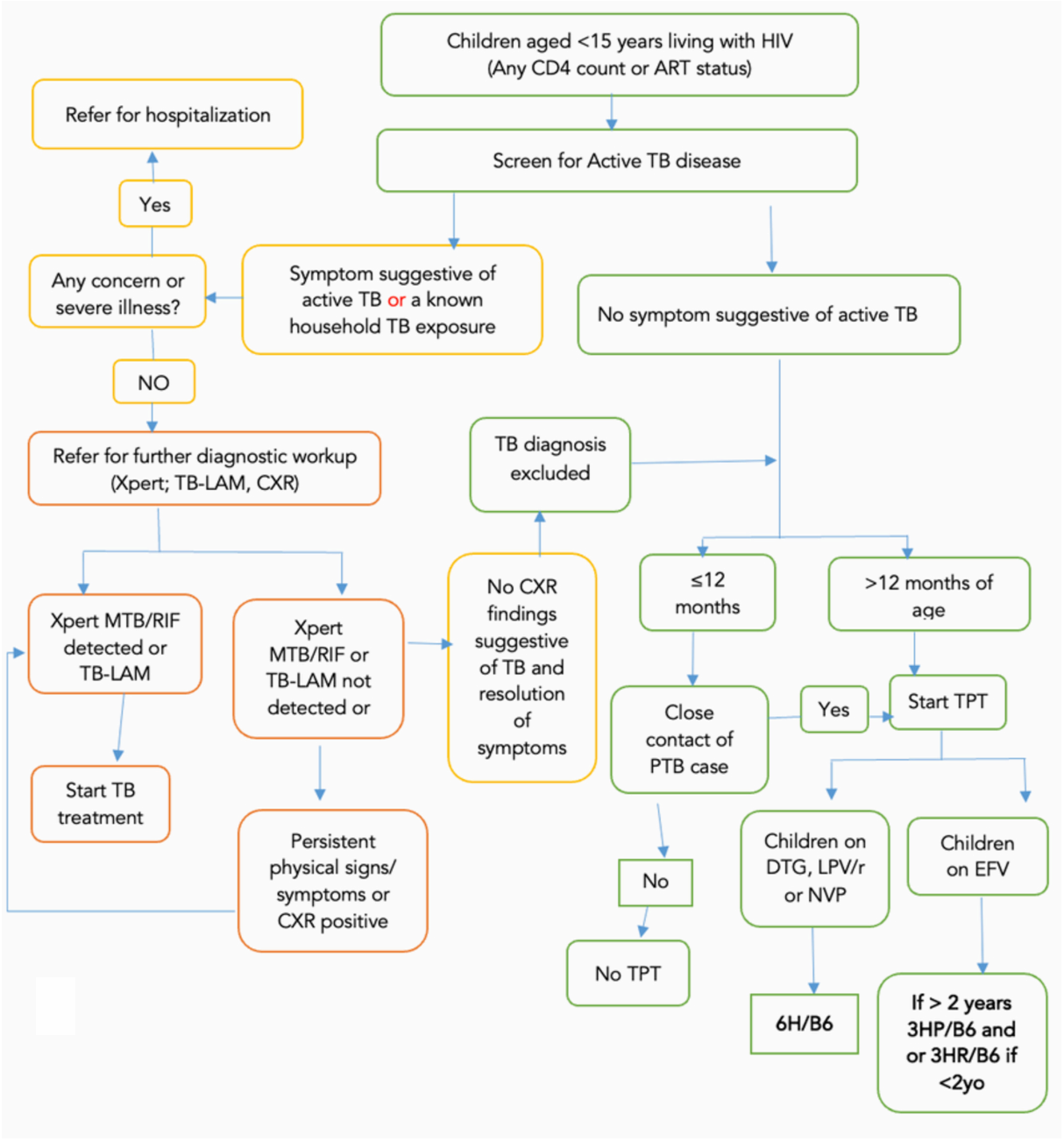
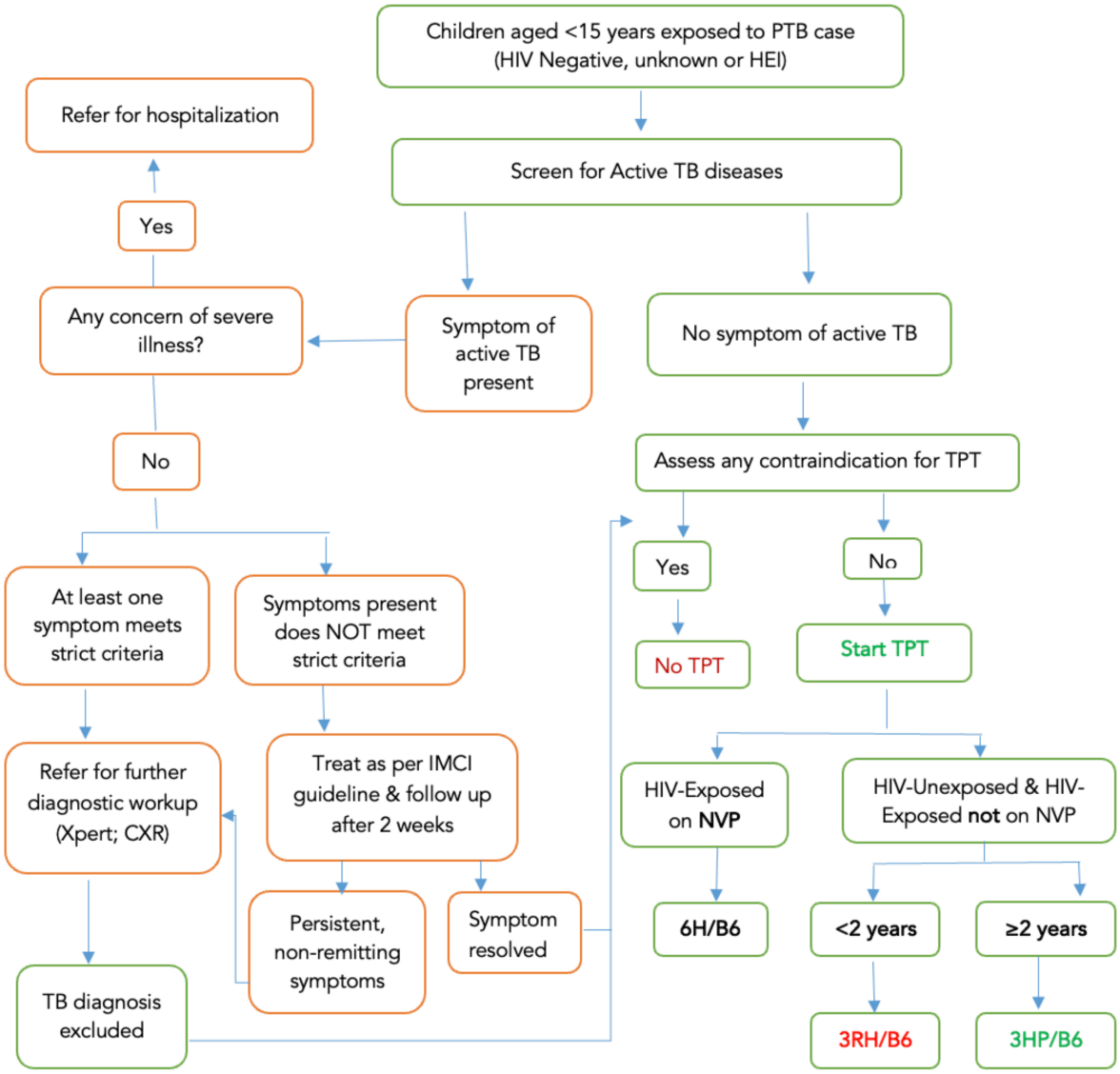


Figure 8: HIV negative and HIV-exposed children <15 years of age with household exposure to PTB case



Preventive Treatment for house hold contacts of MDR-TB index patient

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

Contacts of people with rifampicin-resistant TB (RR-TB) are usually treated as for MDR-TB unless isoniazid-susceptibility in the index case is reliably confirmed, in which case TPT may be effective. In case of Isoniazid-resistant and Rifampicin sensitive TB, little evidence on the choice of TPT exists, but 4R may be an option.

Table 16: Dosing for Levofloxacin 6 months (for selected household contacts of MDR-TB index patient)

Age/Weight Ranges(kg)	Dose Given (mg)
Age < 15 (approx. 15 – 20mg/kg/day)	
5 – 9kg	150 mg/day
10 – 15 Kg	200 - 300 mg/day
16 – 23 Kg	300 - 400 mg/day
24 – 34 Kg	500 - 750 mg/day
Age >14 years	
<46Kg body weight	750 mg/day
>45kg body weight	1gm/day

7.5 Treatment initiation, monitoring and clinical care

Treatment initiation

The selection of treatment options for LTBI by programs and clinicians 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. An RCT showed that self-administered treatment of the 3-month regimen of weekly rifapentine plus isoniazid is not inferior to directly observed treatment. Shorter regimens are more preferable than longer ones for the individuals receiving treatment, clinicians providing treatment and program managers.

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. Weekly/daily 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.

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.

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/1HP is a safe and effective treatment for latent TB infection. Clinically significant drug reactions are rarely experienced by patients taking 3HP/1HP, 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, in general: *If an AE occurs while a patient is taking 3HP/1HP, 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.*

Minor adverse events are likely to occur in a small proportion of individuals/patients. Rarely serious adverse events may occur, and hence both the health care provider and patient should be vigilant and manage such events rapidly.

Table 17: Management of adverse events

Drug reactions	• The most common drug reactions with 3HP/1HP are: Liver toxicity (less common than for TPT) and Flu-like reactions (more common than for TPT). • 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 3HP/1HP. • 3HP/1HP is currently not recommended in Pregnancy and children with age <2 years. • Information on baseline liver function is important in the following: ○ HIV+ (done as part of ART assessment) ○ Daily alcohol consumption ○ Liver disorders including viral hepatitis ○ Postpartum period (≤3 months after delivery) ○ Concomitant use of other hepatotoxic substances • Individuals at higher risk of peripheral neuropathy should be offered vitamin B6 (pyridoxine) supplementation with 3HP/1HP; if B6 is not available this should not delay starting a course of 3HP/1HP.
Counseling for AEs	• Red/orange discoloration of urine and other body fluids while taking 3HP/1HP is normal and completely harmless. • If patients experience any symptoms concerning for an AE: ○ Do not take any further doses of 3HP/1HP ○ Contact a healthcare provider for advice • Only continue taking 3HP/1HP if advised to do so by a healthcare provider Individuals should be alert to the following symptoms: ○ Weakness, fatigue, loss of appetite, persistent nausea (early symptoms of hepatotoxicity) ○ Flu-like, or other acute symptoms appearing shortly after taking a dose of 3HP/1HP ○ Symptoms of active TB (appendix 1)

Adherence support and monitoring

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, HCWs 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.

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

Interrupted treatment or incomplete treatment is defined as the loss of at least one-third of the intended LTBI treatment regimen (a lapse in treatment that lasted at least 1 or 2 months consecutively depending on the TPT regimen employed)

For any client who misses appointment:

- Trace the client/care giver
- Find out the reason for missed appointment and address as appropriate
- Offer adherence counseling
- Evaluate to rule out active TB disease
- Make up for the missed doses
- Manage as outlined below

Table 18: Management of interruption of IPT

Length of interruption	Evaluate for TB	Outcome of TB evaluation	Action
<8 weeks	Yes	Confirmed TB	Discontinue TPT and commence TB treatment
		If no active TB	Continue TPT and extend duration of treatment to compensate for missed doses
> 8 Weeks	Yes	Confirmed TB	Discontinue TPT and commence TB treatment
		If no active TB	Re-commence TPT for a complete duration of therapy

Management of interruption of INH+Rifapentine Preventive Therapy

The general principle to manage children whose TPT is interrupted while on short course TPT regimen are as follows;

- If the interrupted period is ≤1 month
    - Continue the TPT and compensate for the missed doses.
- If the interrupted period is >I month or if the treatment period lapse is the duration of the regimen (interrupted for 3 months) or if the child is immunocompromised especially due to HIV infection and interrupts for any length of time
    - Restart the TPT regimen for a complete duration of 3 months

**If attempt to complete LTBI treatment fails after 3 attempts, no further effort should be made.*

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 from receiving TPT, since isoniazid and rifampicin, the medicines commonly used in preventive treatment, are considered safe for use in pregnancy. WHO conducted a systematic review for the 2019 update of LTBI guidelines, to assess evidence in support or against a recent report from one RCT showing increased risk of adverse pregnancy outcomes with TPT. However, review of all other existing evidence did not reproduce an association of TPT with adverse pregnancy outcomes, such as foetal/neonatal death, prematurity, low birth weight, congenital anomaly. Similarly, no statistically significant risks for maternal hepatotoxicity, grade 3 or 4 events or death were reported. Therefore, deferral of TPT to the postpartum period may not be required, and preventive treatment 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, 6H and 3RH 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.

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 newborns

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, TPT should be started. TPT with RH and HP cannot be given along with nevirapine prophylaxis since rifampicin decreases 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 contact investigation and preventive therapy register.

Preventive therapy for PLHIV should be part of a comprehensive care for HIV positive individuals; therefore, patients should be initiated on preventive therapy and monitored at the ART clinic and relevant information should be documented in the patient follow up card, Pre-ART/ART register, and performance data will be reported using HMIS reporting formats.

The key indicators for monitoring of TPT include:

- Initiation of TPT among PLHIV disaggregated by age and regimen type
- Initiation of TPT among HIV negative children and adolescents aged < 15 years exposed to PTB cases disaggregated by regimen type
- Completion of TPT among PLHIV disaggregated by age and regimen type

- Completion of TPT among HIV negative children and adolescents aged < 15 years exposed to positive TB case disaggregated by 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 3RH, and 10 consecutive days for 1HP
- **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 no record of TPT completion

8. DEFINITION OF TERMS AND PATIENT REGISTRATION

8.1 Case Definitions

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

i) Case definitions for drug-susceptible TB:

- **Presumptive TB Case:** Any person who presents with symptoms and/or signs suggestive of TB, in particular cough of two weeks or more duration is a presumptive TB case. The most common symptom of pulmonary TB is a productive cough for more than 2 weeks, which may be accompanied by other respiratory symptoms (shortness of breath, chest pains, and hemoptysis) and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats, and fatigue).
- **TB Case:** refers to a patient in whom TB has been bacteriologically confirmed or diagnosed by a clinician.
- **A Bacteriologically Confirmed TB Case:** Refers to a patient from whom at least one biological specimen is positive for mycobacterium tuberculosis by either smear microscopy, Xpert MTB/RIF Ultra, culture or other WHO approved bacteriologic detection test.
- **A Clinically Diagnosed TB Case:** A patient who does not fulfill the criteria for a bacteriologically confirmed case but, has been diagnosed with active TB by an experienced 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 tuberculosis.

NB: Clinically diagnosed cases subsequently found to be bacteriologically positive (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 diagnosed of active TB and with either medium or high- risk to harbor Drug-resistant TB.
- **Bacteriologically Confirmed DR-TB:** refers to those cases with documented laboratory DST (phenotypic or molecular) results for DR-TB.
- **Clinically Diagnosed DR-TB Case:** refers to a person who is diagnosed to have DR-TB without documented DST result but the clinical panel team decided to empirically treat with SLD regimen. Mainly reserved for small children as obtaining specimen is not feasible.

8.2 Classification of TB

Bacteriologically confirmed or clinically diagnosed cases of TB 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.

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

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

8.2.2 History of previous treatment:

New: patients that 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.

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 (RR TB): resistance to Rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs.

Multi-drug-resistant TB (MDR TB): Resistance to at least Isoniazid and Rifampicin.

Pre- Extensively Drug-Resistant TB (Pre-XDR TB): this refers to multi-drug resistant (MDR) and rifampicin-resistant TB (MDR/RR-TB) and which are also resistant to any fluoroquinolone.

Extensively Drug-Resistant TB (XDR-TB): is TB that is resistant to any fluoroquinolone and at least one additional Group A drug (levofloxacin, moxifloxacin, bedaquiline and linezolid) in addition to multi-drug resistance.

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 enrollment 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 now diagnosed with a recurrent episode of TB.

Treatment after failure: refers to patients who were declared treatment failure in their most recent course of treatment as per national protocol.

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

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

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

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.

a. "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*

Table 19: Definitions of Treatment Outcome for DS TB and DR TB (WHO 2021)

Outcome	Definition
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[a] 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.
Treatment failure	A TB patient whose treatment regimen needed to be terminated or permanently changed[b] to a new regimen or treatment strategy.
Died	A patient who died[c] before starting treatment or during the course of treatment.
Lost to follow up (LTFU)	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[d].
Treatment success	The sum of cured and treatment completed.
Moved to MDR-TB	TB Patients who were found to have RR-TB or MDR-TB before fifth month of treatment and who were referred to MDR TB unit and started on a full MDR-TB treatment regimen (i.e. patient is moved to the second-line treatment register).

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.*

b. Reasons for the change include:

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

c. Patient died for any reason.

d. This includes cases "transferred out" to another treatment unit and those whose treatment outcome is unknown; however, it excludes those lost to follow-up.

9. TREATMENT OF DRUG SUSCEPTIBLE TB

9.1 Objectives of TB treatment

The aims of treatment of TB are to:

- cure the patient of TB and restore quality of life and productivity
- prevent death from active TB or its late effects
- prevent relapse of TB
- reduce transmission of TB to others
- prevent the development and transmission of drug resistant TB
- achieve all above with minimal cost and toxicity.

In order to ensure quality TB treatment and reduce drug resistance, the following principles should guide treatment:

- **Directly observed therapy (DOT) by health workers or treatment supporter** to ensure that TB patients take the right medicines, in the right doses at the right times under supervision.
- All previously treated TB patients should immediately have access to Xpert MTB/RIF Ultra in order to determine the correct treatment regimen to offer to the patient.
- All patients diagnosed as DS-TB should be managed as in Table 10.
- DOT must be ensured for all TB regimens through a patient centered approach

Directly Observed Therapy (DOT)

The health worker or treatment supporter watches the patient swallow the tablets throughout the whole duration of treatment.

First line anti-TB medicines

The first line anti TB medicines used in the country include:

- Rifampicin (R)
- Isoniazid (H)
- Pyrazinamide (Z)
- Ethambutol (E)

The medicines are used in various combinations in a standardized regimen to treat various forms of TB as described below.

9.2 Standard treatment regimens for DS-TB

Two standardized treatment regimens have been adopted for the treatment of all susceptible TB cases. These regimens are as follows:

a. **Regimen one - 6-month treatment (2(RHZE)/4(RH):** for all forms of TB (PTB and EPTB cases – both new and previously treated) with the exception of TB meningitis Osteo-articular, CNS/ meningeal and miliary TB cases.
b. **Regimen two - 12-month treatment (2(RHZE)/10(RH):** for all cases of TB Meningitis (TBM)/other forms CNS TB, osteo-articular and miliary TB cases.

Note

1. It is recommended that TB patients who are living with HIV should receive the same duration of TB treatment as HIV-negative TB patients.
2. ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV.

The medicines come in fixed dose combinations (FDCs) and each regimen is divided into two phases (intensive and continuation). The use of fixed dose combination (FDCs) of anti-TB drugs are thought to prevent acquisition of drug resistance due to monotherapy, which may occur with separate ("loose") drugs. Prescription errors are likely to be less frequent because dosage recommendations are more straightforward, and adjustment of dosage according to patient weight is easier.

Regimen one: Six-month treatment 2(RHZE)/4(RH)

Regimen one consists of 2 months of intensive phase and 4 months of continuation phase.

Refer to the table below:

Table 20: Regimen and dosages for adults with susceptible PTB/EPTB cases*

Regimen 1	Pre-treatment weight				
	25-<30 kg	30-<35 kg	35-<50 kg	50-<65 kg	65 kg +
Intensive phase (2 months): Combined tablet of RHZE (150mg+75mg+400mg+ 275mg)	2	3	4	4	5
Continuation phase (4 months): Combined tablet of RH (150mg + 75mg)	2	3	4	4	5

**Refers to all PTB and EPTB cases with the exception of miliary TB, TB meningitis and TB of bones/joints*

Regimen two (Twelve Months Regimen) for adult: 2(RHZE)/10(RH)

Regimen two consists of 2 months of intensive phase and 10 months of continuation phase.

Refer to the table below:

Table 21: Regimen and dosages for adults with miliary TB, TB meningitis and Osteo-articular TB

Regimen 2	Pre-treatment weight				
	25-<30 kg	30-<35 kg	35-<50 kg	50-<65 kg	65 kg +
Intensive phase (2 months): Combined tablet of RHZE (150mg+75mg+400mg+ 275mg)	2	3	4	4	5
Continuation phase (10 months): Combined tablet of RH (150mg + 75mg)	2	3	4	4	5

Note:

Patients who are put on Regimen 2 will need more RH because continuation phase is longer (10 months). The extra drugs (RH) needed should be taken into account in the supply box.

9.2.1 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.

9.3 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
- Administer pyridoxine for children with severe malnutrition, or taking ART
- 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.

DS-TB treatment regimen in Children and Adolescents

This can be summarized in the table below:

Table 22: Anti-TB Treatment for children and adolescents

Age and severity of disease	Duration and composition of treatment	
	Intensive	Continuation
Infants age < 3 months or weight <3kg		
PTB of any severity	2HRZ or 2HRZE	4HR
Children and adolescents aged 3 months to <12 years		
Non-severe PTB	2HRZ or 2HRZE	2HR
Severe PTB	2HRZE	4HR
Adolescents aged 12–<16 years		
Non-severe PTB	2HRZ or 2HRZE	2HR
Severe PTB	2HRZE	4HR
Adolescents aged 16–<20 years		
PTB of any severity	2HRZE	4HR

9.3.1 Regimen 1 (Four Months Regimen): 2(RHZ+E)/2(RH)

1. In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used
2. Children and adolescents who do not meet the criteria for non-severe TB should receive the standard six-month treatment regimen (2HRZE/4HR), or recommended treatment regimens for severe forms of extrapulmonary TB.

9.3.2 Regimen 2 (Six Months Regimen): 2(RHZ+E)/4(RH)

1. Start all children with severe PTB and EPTB (except TB meningitis, Osteo-articular and miliary TB) weighing < 25kg on Regimen 2
2. Eligible children weighing ≥ 25kg should receive adult Regimen 2 irrespective of age
3. The treatment of DSTB in children as in adults comprises two phases: intensive and continuation.
    - Intensive phase involves the use of 4 drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) for the first 2 months
    - Continuation phase involves the use of 2 drugs (isoniazid, rifampicin) for 4 months.

- DOT should be used throughout the period of treatment either through direct supervision by the health worker or through the engagement of a treatment supporter. Refer to SOP for the engagement of a treatment supporter in Annex 1.

*Table 23: Drug dosing (tablets) for children with susceptible PTB/EPTB cases**

Daily Regimen	Pre-treatment weight (Kg)					
	<4	4- <8	8- <12	12- <16	16- <25	≥ 25
Intensive phase (2 months):						
Combined tablet of RHZ (75mg+50mg+ 150mg)	1/2	1	2	3	4	Adult tablets
Ethambutol tablet (100mg)	1/2	1	2	3	4	
Continuation phase (4 months):						
Combined tablet of RH (75mg + 50mg)	1/2	1	2	3	4	
Continuation phase (2 months):						
Combined tablet of RH (75mg + 50mg)	1/2	1	2	3	4	For no severe cases of PTB

**Refers to all PTB and EPTB cases except TB meningitis, miliary TB and TB of bones/joints*

9.3.3 Regimen 3 (12 Months Regimen): 2(RHZ + E)/10(RH)

1. Start all children with TB meningitis, other forms of CNS TB, osteo-articular and miliary TB weighing ≤25kg on treatment Regimen 3.
2. Eligible children weighing > 25kg should receive adult Regimen 3 irrespective of age
3. Regimen 3 also comprises two phases: intensive and continuation.
   a. Intensive phase involves the use of 4 drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) for the first 2 months
   b. Continuation phase involves the use of 2 drugs (isoniazid, rifampicin) for 10 months.

Table 24: Drug dosing (tablets) for children with TB meningitis, miliary and Osteo-articular TB

Daily Regimen	Pre-treatment weight (Kg)					
	<4	4- <8	8- <12	12- <16	16- <25	≥ 25
Intensive phase (2 months):						
Combined tablet of RHZ (75mg+50mg+ 150mg)	1/2	1	2	3	4	Adult tablets
Ethambutol tablet (100mg)	1/2	1	2	3	4	
Continuation phase (10 months):						
Combined tablet of RH (75mg + 50mg)	1/2	1	2	3	4	Adult tablets

9.3.4. Adjunctive treatment

1. **Pyridoxine (Vitamin B6):** The use of pyridoxine is recommended for all adult patients started on TB treatment to prevent peripheral neuropathy most commonly caused by isoniazid. The dose of pyridoxine: 25mg daily for adults, 5mg for infants, and 10mg for older children. If patient develops peripheral neuropathy at any stage during TB treatment, the dose can be increased to 50 – 75mg (up to maximum of 200mg) until the symptoms subside, then reduce to 25mg daily.
2. **Steroids:** Steroids have a supportive therapeutic effect and have been shown to improve survival in patients with specific forms of TB disease (meningeal, pericardia, laryngeal, gonadal and adrenal TB). The conditions requiring steroid use in children is same as adults except that considerations should be given for dosage. Prednisolone should be administered at a dosage of 1-2 mg/kg/day (maximum dose of 60 mg) for three weeks, followed by a stepwise reduction in regimen over three weeks.

9.4 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.

9.5 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.

9.5.1 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 card or 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.

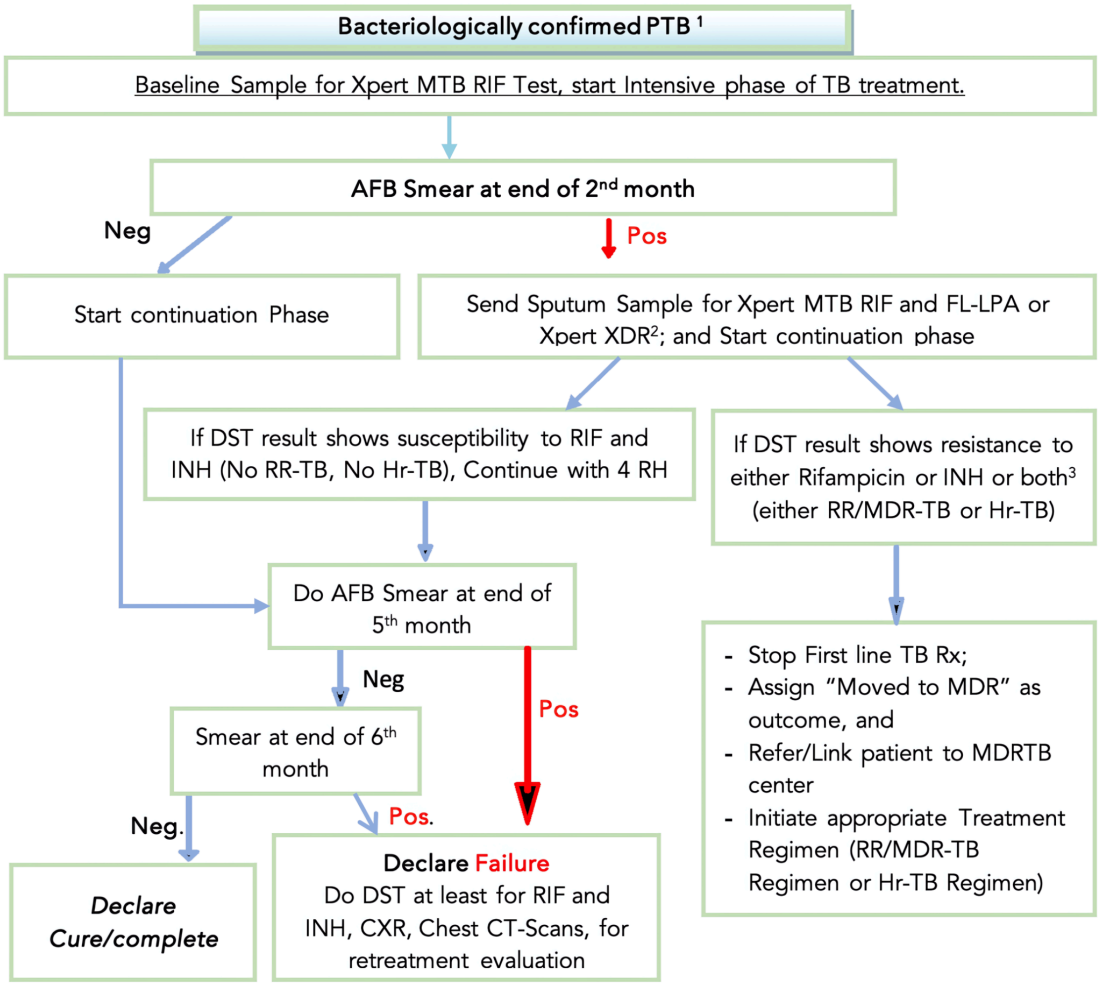
Unsatisfactory response to treatment beyond two months of treatment should alarm the possibility of drug resistance or alternative diagnoses.

9.5.2 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 Ultra or culture) need their sputum 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 6 below).

Molecular techniques like Xpert MTB/RIF assay cannot be used to monitor treatment response, the technique may give false positive result as it identifies genetic material of dead bacilli.

Figure 9: Sputum AFB follow-up for bacteriologically confirmed PTB patients

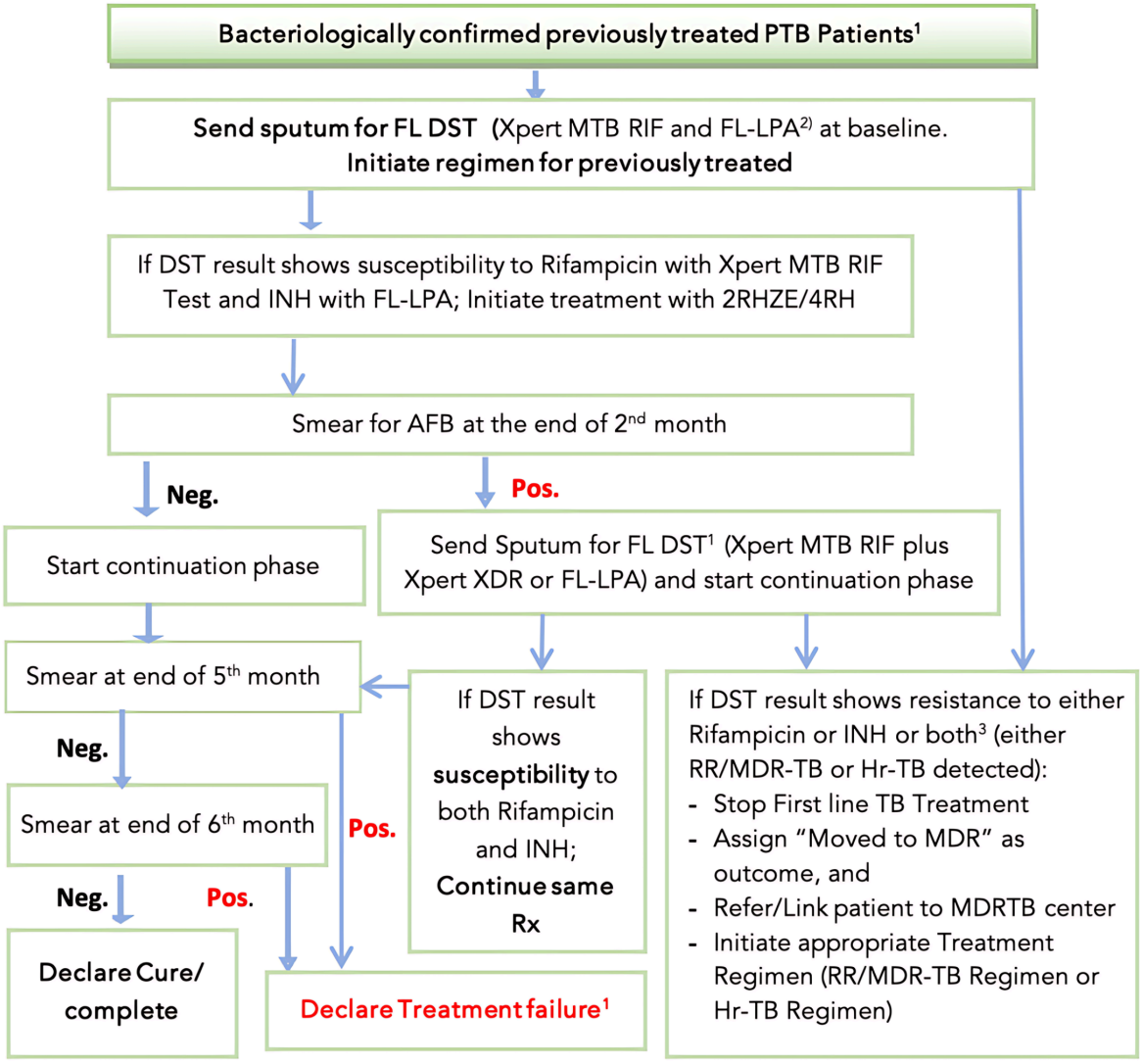


[1] *Bacteriologically confirmed TB patients include those diagnosed by positive result on either AFB microscopy, Xpert MTB/RIF Assay or culture;*

[2] *DST may be performed from one sputum sample using Xpert MTB/RIF, Xpert XDR, SL-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.*

Figure 10: Flow chart for Sputum AFB follow-up for bacteriologically confirmed previously treated PTB patients



[1] *Refer a patient who has failed second course of full TB treatment to MDR-TB center for further evaluation and decision. Such patients require chest imaging, full DST for FLDs, and further workup.*

[2] *DST may be performed from one sputum sample using Xpert MTB/RIF, Xpert XDR, LPA or conventional DST based on availability. Information on rifampicin and INH DST may be enough to decide on next action.*

9.5.3 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. Some drug-induced side-effects can be prevented, for example isoniazid-induced peripheral neuropathy. This usually presents as numbness or a tingling or burning sensation of the hands or feet and occurs more commonly in pregnant women and in people with the following conditions: HIV infection, alcohol dependency, malnutrition, diabetes, chronic liver disease, renal failure. These patients should receive preventive treatment with pyridoxine, 10 mg/day along with their anti-TB drugs.

A symptom based approach, as seen the Table 23 below:

Table 25: Managing side-effects of TB drugs:

Side effect	Drug responsible	Management
Major		
Skin rash, with or without other symptoms	Streptomycin, isoniazid, rifampicin, pyrazinamide	Stop all anti-TB drugs. See section 4.x for step-wise re-introduction in adults
Jaundice, or signs of liver toxicity*	Pyrazinamide, Isoniazid, Rifampicin	Stop all anti-TB drugs and manage according to figure 4.1. See section 4.x for step-wise reintroduction
Confusion (suspect drug induced hepatitis if accompanied by jaundice)	All TB drugs	Stop all anti-TB drugs. Restart once confusion settled for 2 weeks and hepatotoxicity excluded
Shock, multiple bruises, renal failure	Rifampicin	Stop all anti-TB drugs and refer to district centre
Visual impairment/ change in colour vision	Ethambutol	Stop all anti-TB drugs. Refer to district centre
Minor		
Nausea, decreased appetite, abdominal pains	Pyrazinamide, rifampicin, isoniazid	Take drugs with small meals or just before bedtime, advise to swallow pills slowly with small sips of water. If symptoms worsen or any vomiting of blood, refer urgently to Doctor
Joint pains	Pyrazinamide	Advise oral analgesia, paracetamol or anti-inflammatory
Burning, numbness or tingling of feet or hands.	Isoniazid	Give Pyridoxine 50 mg/day
Drowsiness	Isoniazid	Take medication before bedtime
Red/orange urine	Rifampicin	Reassure patient that is normal and due to medication

**Signs of liver toxicity: Loss of appetite, nausea, vomiting, abdominal pain, passing dark urine, jaundice and tenderness over the liver area*

9.6 Management of Treatment Interruption

Patients who have not received their treatment for two consecutive months either in the intensive or continuation phase should be regarded as having interrupted treatment and should be traced.

Managing interruption of treatment

During enrollment of a patient, the HCW should record and confirm the patient's full address, other relevant addresses such as those of family members and if possible, the patient's or a family member's mobile phone number in case there is need to contact or track the patient arises. Should a patient miss a scheduled appointment, action must be taken within three days of the date the patient was due for his or her scheduled appointment or medicine collection. It is the responsibility of the HCW and the District TB Supervisors to ensure a sound defaulter-tracking plan is in place and implemented at facility and district level. It is the responsibility of the HCW, the District Supervisor and the CBOs in the community/ community health workers and/or other stakeholders to locate a patient who has interrupted treatment. The table below summarizes action to be taken by the health worker:

Table 26: Managing treatment interruption

Length of interruption	Do Xpert MTB/RIF Assay	Result of Xpert MTB/RIF	Length of treatment	Action to be taken
< 1 month	No			Continue treatment and prolong to compensate for missed doses
1-2 months	Yes: Collect and send sample for Xpert MTB/RIF assay	MTB not detected or	Any duration of treatment	Continue treatment and prolong to compensate for missed doses; If EPTB, continue treatment and prolong for missed doses
		MTB detected, Rif resistance not detected		
		MTB detected Rif resistance detected	Any duration of treatment	Manage for DRTB (see DRTB section)
2 or more months	Send one sample for Xpert MTB/RIF assay	MTB not detected	1 month or more	Clinical decision on individual basis whether to restart or continue treatment, or no further treatment; If EPTB, continue treatment and compensate for missed doses.
		MTB detected	1 month or more	Declare as return after loss to follow-up; Manage according to Xpert MTB/RIF assay.

9.7 Transferring a TB patient while on TB treatment

Managing transferred-in and transferred -out

When a patient is transferred out to another treatment facility, it should be indicated in the facility/ District TB register and ensure you do the following;

- All patients transferred out should be given medicines that will last them for only two weeks and their remaining medicines should be returned to the supply box in the health facility where they started treatment
- Similarly, all transferred-in-patients should be continued on treatment on arrival to their new treatment centre provided they have a properly filled referral/transfer form and should be given their medicines from the supply box.
- The date of transfer out and the new treatment facility must be indicated in the transfer form.
- A copy of the referral/transfer form must accompany the patient and must be sent to the HCW of the receiving District and hence the new treatment facility.
- A copy of referral/transfer form must be kept at the original treatment unit in a dedicated folder.
- When patients are transferred in from another facility, they should be registered in the facility/ District TB register as transfer in patients.
- The patient's treatment outcome must be entered in the facility/District TB register and results must be communicated to the original treatment unit.
- All transferred patients to continue treatment in another District/Region should not be given a new identification number by the receiving facility/District (but should retain the identification number from the originating Facility/District.

Referral:

When a patient is sent to another facility/district, the receiving facility/district should register and notify such patients through the routine reporting system as transferred in.

10. DRUG RESISTANT TB

Key Considerations in Drug Resistant TB management

The following are key areas that should be looked at critically when running a DR-TB program:

- Access to reliable, quality assured DST, informs the use of the WHO-recommended regimens.
- Rapid molecular testing should be available and accessible, to ensure DST for at least rifampicin and fluoroquinolones, given that DST for both of these agents is essential for selecting the most appropriate initial regimen.
- Local TB drug resistance surveillance (DRS) data should provide accurate estimates of the frequency of resistance to at least rifampicin and isoniazid in new patients, and to fluoroquinolones among MDR/RR-TB cases, as well as some information about the frequency of resistance in relevant subgroups of re-treatment cases (e.g. recurrence or failure after a first-line anti-TB regimen and return after loss to follow-up).
- WHO recommends the use of the approved rapid molecular DST 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.
- No rapid molecular testing is currently available for ethambutol.
- High complexity reverse hybridization NAATs are recommended as rapid test for pyrazinamide resistance. This is reserved for use on M. tuberculosis culture isolates only from people with bacteriologically confirmed
- Results from Xpert XDR and LPA typically become available within a few hours/days of testing and can thus be used to decide upon the initial regimen for treatment of Hr-TB, or some other forms of mono-resistant or poly-resistant TB.
- Apart from its rapidity, Xpert XDR and LPA can also provide information on the mutation patterns, which can influence the choice of treatment (e.g. if only the inhA mutation is present, it is likely that isoniazid can still be effective at high dose, whereas if the katG mutation alone or both inhA and katG are present, isoniazid is no longer effective, even at high dose).
- If rifampicin resistance is detected, rapid molecular tests for resistance to isoniazid and fluoroquinolones should be performed promptly, to inform the decision on which regimen to use for the treatment.
- Establish DST for all TB medicines for which there are reliable and reproducible methods (e.g. bedaquiline, linezolid, clofazimine, delamanid and pyrazinamide).
- If available, targeted or whole genome sequencing (or sequencing of the pncA gene) should be used as a reference method to detect pyrazinamide resistance.
- Susceptibility to ethionamide/prothionamide can be inferred from the results of molecular testing for isoniazid resistance (i.e. presence of mutations in the inhA promotor region) using LPA.
- Phenotypic DST for cycloserine/terizidone, ethambutol, ethionamide/prothionamide, imipenem/meropenem or p-aminosalicylic acid is not routinely recommended because results may be unreliable.
- 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.
- If DST for second-line TB medicines is not yet available, the clinician or the TB program needs to estimate 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.

- The DST results are generally used to guide the choice of chemotherapy in TB and MDR-TB regimens. When based on externally quality-assured laboratory work, DST to isoniazid, rifampicin and fluoroquinolones is most useful for clinical purposes.

10.1 Safety monitoring and management, provision of patient support

All treatment delivered should align with WHO-recommended standards, including patient-centred care and support, informed consent where necessary, principles of good clinical practice, active TB drug safety monitoring and management (aDSM), and regular patient monitoring to assess regimen effectiveness.

Health care providers must offer careful clinical and bacteriological follow-up to assess TB treatment response, with general laboratory support to monitor and manage adverse events and comorbidities.

The provision of social support is essential to enable adherence to treatment.

An appropriate schedule of laboratory tests and clinical examinations should be included in the patient's treatment chart to identify adverse events.

Patient support is critical for good adherence and improved outcomes.

10.2 Principles of Drug Resistant Tuberculosis Treatment

- Detect RR-/MDR-TB early and initiate effective treatment promptly,
- RR/MDR-TB diagnosis must be confirmed for rifampicin and if possible for isoniazid using rapid molecular DST techniques, to initiate treatment consisting of second line medicines,
- Bacteriologically confirmed RR/MDRTB TB patients are recommended to have baseline screening DST for core-second lines medicines at least for FQs using Xpert XDR or SL-LPA.
- Pulmonary RR/MDR TB patients must submit sputum specimen for Xpert XDR or SL-LPA before or within seven days of treatment initiation with DR-TB treatment.
- Xpert XDR or SL-LPA must be performed directly from the sputum specimen that is 2+ and above on microscopy.
- 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).
- 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 8 weeks period.

10.3 Classification of DR-TB

The classification of drug resistant Tuberculosis is done based on two major categories:

1. Classification based on drug resistance pattern.
2. Programmatic classification (described in the section 8.2)

10.3.1 Classification based on drug resistance pattern.

DR-TB cases are categorized based on drug susceptibility testing of clinical isolates confirmed to be Mycobacterium tuberculosis:

- **Isoniazid-resistant TB (Hr-TB)** is caused by Mycobacterium tuberculosis strains resistant to isoniazid and susceptible to rifampicin.
- **Rifampicin-resistant TB (RR-TB)** is caused by M. tuberculosis strains that are resistant to rifampicin. RR-TB strains may be susceptible to isoniazid or resistant to it (i.e. MDR-TB), or resistant to other first-line or second-line TB medicines.
- **Mono resistant TB:** Is caused by M.tuberculosis strains that are resistant to one first-line anti-TB drug only.
- **Poly drug resistant TB:** Is caused by M.tuberculosis strains that are resistant to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).
- **Multidrug-resistant TB (MDR-TB)** is caused by M. tuberculosis strains that are resistant to at least both 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.
- **Pre-XDR-TB:** Is caused by M. tuberculosis strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone
- **Extensively drug-resistant TB (XDR-TB)** is tuberculosis that fulfils the definition of MDR/RR-TB and that is also resistant to any fluoroquinolone and at least one additional Group A drug (Bedaquiline or Linezolid)

10.3.2 Programmatic classification of DR-TB cases.

A DR-TB case could also be classified based on previous exposure to anti-TB drugs.

1. **Drug resistance among new cases:** Is the presence of resistant strains of MTB in the clinical isolates of a newly diagnosed patient who has never received anti-TB drugs or has received treatment with them for less than one month
2. **Drug resistance among previously treated cases:** Is the presence of resistant strains of MTB in the clinical isolates of a patient who has previously received at least one month of anti-TB drugs.

10.4 Risk groups for DR-TB

These include:

- All known symptomatic contacts of a confirmed DR-TB patient.
- Sputum AFB positive smears at month two (2) in patients taking first line treatment.
- Any failure to first line treatment
- Re-treatment cases

a. Relapse
b. Treatment after failure
c. Treatment after loss to follow-up
d. Other previously treated patients

In addition to screening all presumptive TB cases and the priority groups above, the NLTCP has identified a second priority group to expedite early diagnosis and improve the quality-of-service delivery. This group includes:

- All persons living with HIV (PLHIV) who present with symptoms of TB.
- All health care personnel who present with symptoms of TB
- Consider people who may be exposed to TB/DR-TB in congregate settings like correctional service centers.
- Also consider people with history of using anti-TB drugs of poor or unknown quality.
- All children who present with symptoms of TB

10.5 Preventing DR-TB

Early detection and high-quality treatment of drug-susceptible TB remains a core pillar in the prevention of DR-TB. These elements can be summarized as follows:

1. **Early detection and high-quality treatment of drug susceptible and drug resistant TB:** Early diagnosis and prompt treatment of all persons of all ages with any form of drug susceptible or drug-resistant TB is fundamental. Sierra Leone has endorsed the GeneXpert as a primary test for all presumptive TB in all settings. This is both for adults, adolescents and children. To ensure universal access to drug susceptibility testing for timely detection of all drug-resistant TB cases and achieve impact, an important investment is necessary to improve access to GeneXpert testing for presumptive TB cases including an effective sample transportation system from non-GeneXpert sites to sites with GeneXpert.
2. **Quality-assured, uninterrupted drug supply:** The uninterrupted supply of quality anti-TB drugs and proper storage in all DOT facilities is crucial in preventing drug resistance.
3. **Compliance to treatment protocols:** Compliance with management guidelines as recommended by the National Leprosy and Tuberculosis Control Programme ensures that adequate drugs, in the correct combinations and dosages, are prescribed for the correct period of time.
4. **Patient adherence and supervision of therapy:** Adherence refers to how well patients complete the full course of prescribed medication. This often depends on adequate counselling, ongoing support, and access to the facility and attitudes of heath care staff. Directly observed therapy (DOT) during (at the very least) the intensive phase of treatment is the national policy. Excellent adherence during the intensive phase of treatment, during which time the total bacterial load in the patient is being reduced, is crucial to the prevention of drug-resistant TB. This is especially true for bacteriologically-positive patients who have a high bacterial load. DOT in the follow-up phase is also important to help prevent relapse.
5. **Effective implementation of infection control measures:** TB infection control measures aim at minimizing the risk of TB transmission within populations. Sierra Leone has well formulated infection control policies which will be implemented at every level of health service delivery, including the correctional facilities and at the household level.
6. **Strengthening and regulation of health systems:** The NLTCP will continually assess health system barriers to identify bottlenecks that can be addressed through either TB-specific interventions or in collaboration with other programmes/sectors. Opportunities for integration of health service delivery, sharing of resources and joint actions to develop human resources, and efforts to improve diagnostic capacity and drugs supply management with other public health programmes will be explored.

- It is particularly important to ensure quality and availability of both first- and second-line drugs and to restrict their use to those facilities where quality of prescription and treatment management can be assured. In particular, banning of over-the-counter sales of anti-tuberculosis drugs should be enforced.
- It is also important to make TB a notifiable disease and to enforce this regulation. This is key to both enabling proper surveillance of TB as well as identifying where TB (including DR-TB) is being diagnosed and managed.

7. **Addressing underlying risk factors and social determinants:** Optimal diagnosis and treatment of known TB cases are essential; however, they are not sufficient to manage or prevent drug-resistant TB. One of the most critical immediate intervention for prevention of drug-resistant TB is to assess social and financial barriers to adherence and access to health-care services and to address them accordingly. This includes providing all TB diagnostic and treatment services free of charge to patients, minimizing the costs of other related clinical services (such as diagnosis and management of comorbidities and HIV infection) and indirect cost of care (for example those costs associated with transport and loss of income). Indirect costs are often catastrophic even if diagnosis and treatment is provided free of charge. The NLTCP will advocate for the development of social protection schemes, disability funds, and/or cash transfers in favour of TB patients in order to reduce risk of poor treatment outcomes leading to development of drug-resistant TB.

10.6 Treatment of Drug -Resistant Tuberculosis

Effective treatment of TB, including its drug-resistant forms, relies on the use of approved medicines administered in combination for an adequate duration of time.

Aims of treatment

The aims of TB treatment are to achieve the following:

- Cure the DR-TB patient and restore quality of life and productivity.
- Prevent death from active TB or its late effects.
- Reduce transmission of resistant strains of TB bacilli to other persons.
- Prevent the further development and transmission of drug resistance.
- Achieve all these with minimal cost and toxicity.

Eligibility criteria for starting DR-TB treatment regimens

- Patients (adults, adolescents and children) with confirmed rifampicin resistance.
- All patients enrolled in care in the implementation sites who have been diagnosed with DR-TB (RR/MDR/FQ Resistance/XDR-TB) are eligible for the DR-TB treatment.
- Other patients at high risk for RR-TB to be considered for enrollment. In the absence of bacteriological confirmation of DR-TB, the following are eligible for second-line treatment after considering all circumstances around the patient:
    - Young children who are diagnosed with active TB, with a close contact, (especially a parent or caregiver) who has bacteriologically confirmed DR-TB
    - PLHIV with active TB who are close contacts of known DR-TB patients
    - EPTB patients who are in close contact of a known DR-TB patient
    - Failure of first-line TB treatment.

10.6.1 Management of DRTB at the treatment centre

The management of DR-TB at the treatment center is a team approach comprising a multidisciplinary team of at least; a physician, nurse(s), social worker, CHW etc, who will support in assessing, monitoring, and providing care both before and after initiation of treatment.

1. Nursing care for DR-TB patients before admission to the DR-TB treatment centers

A patient-centered approach is important to alleviate fears and anxiety, which is common for patients who are about to initiate DR-TB treatment. As the first clinical point of contact for most patients will be a nurse, DR-TB treatment center nurses should:

- Receive patients warmly;
- Ask why the patient is at the center, and provide further patient education as appropriate;
- Explain the purpose and benefits of DR TB treatment, admission; and
- Obtain patient's consent for baseline evaluations, admission, and treatment.
- Explain to the patient that their DR TB regimen will be discussed and guided by the results of baseline evaluations and tests.

2. Baseline evaluation/pre-treatment screening

The initial evaluation serves to establish a baseline and may identify patients who are at increased risk for adverse effects or poor outcomes. The monitoring of patients with pre-existing conditions has to be more intensive. The following should be done for DR-TB patients on arrival at the treatment unit:

- Detailed clinical history
- Baseline physical exam
- Laboratory/radiology investigations

i. Take a detailed clinical history

This includes obtaining the following information from the patients:

- Demographics
- Detailed history about the illness, including duration and treatment received so far (including a list of all TB medications received to date and the length of treatment)
- Past medical history
- Any previous adverse reactions to medications
- A social history
- Any other medical problems in the family
- A complete review of systems

ii. Physical assessment

This should include the following:

- General comprehensive physical examination
- Mental health assessment
- Vision assessment

iii. The baseline laboratory/radiology investigations should include:

- Full blood count (Hb, WBC, and platelets)
- Serum potassium, creatinine, urea, and glucose
- Thyroid stimulating hormone (TSH) for STR

- Liver function tests (AST, ALT)
- HIV test
- HBsAg, HCV antibody
- Pregnancy test (for women of childbearing age)
- Urinalysis
- Sputum smear for AFB
- Culture and DST/second-line LPA/Xpert MTB/XDR
- Chest x-ray
- Electrocardiogram

Fill in the information on examination results on the DR-TB patient card.

iv. Care for DR-TB patients on admission

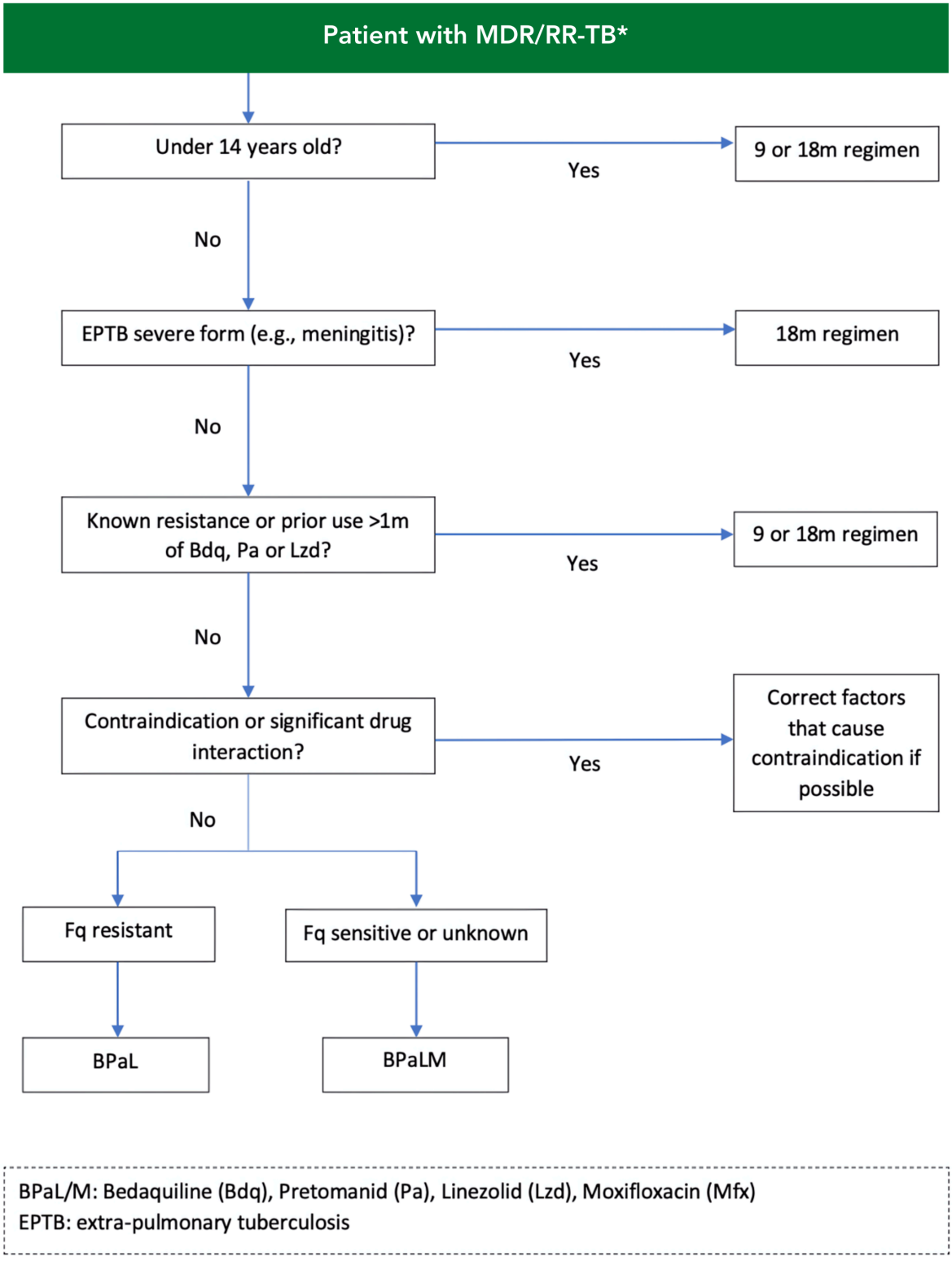
Treating physicians and nurses should provide the following care before admitting the patients to the ward:

- Inform the patient about the dosage and the duration of the drugs prescribed;
- Inform the patient about the common side effects of the drugs and request that he or she report any side effects immediately;
- Educate the patient on the importance of treatment adherence;
- Provide information on nutrition and feeding in the treatment center and encourage patients to eat regularly;
- Educate patients on the use of a face mask and the importance of putting the face mask on when moving around;
- Educate the patient on cough etiquette, and encourage him or her not to spit on the floor, sink, or indiscriminately around the premises;
- Ask the patient to keep windows open to enhance cross-ventilation;
- Show patient the available services such as the toilet, the recreational area, and others meant for use of the patient; and
- Engage patients' family members to assist patients in cooperating with the clinical plan throughout the period of admission.

Patient triage approach to select the appropriate DR-TB regimen

- All patients with DR-TB are eligible to start DR-TB treatment without delay.
- A systematic approach must be followed to determine if the patient should be treated with the shorter DR-TB regimens or all-oral longer DR-TB regimen. Figure 9 shows algorithm to guide choice of regimen
- The approach includes clinical evaluation to determine the patient's risk of resistance or intolerance to Second Line TB Drugs (SLDs) and bacteriological testing of pre-treatment specimens to determine if the strain is not resistant to FQ or other SLDs.
- Before starting treatment, two sputum samples must be sent for SL-LPA or Xpert MTB/XDR assay and culture, as well as first line and second-line phenotypic drug susceptibility tests.
- Ensure availability of all the component second line drugs for the appropriate regimen.
- Ensure timely availability of DST and other baseline investigation results to allow one to re-evaluate the initial regimen and adjust to the appropriate regimen if necessary.

Figure 11: Algorithm to guide choice of regimen



BPaL/M: Bedaquiline (Bdq), Pretomanid (Pa), Linezolid (Lzd), Moxifloxacin (Mfx)
EPTB: extra-pulmonary tuberculosis

The following scenarios should be considered after receiving second-line DST results:

- For patients that started with the shorter regimens, if genotypic second-line, DST results reveal no additional resistance to FQ and/or other SLDs and are tolerating well then, the shorter regimen can be continued.
- For patients that started with the shorter regimen and genotypic results show additional resistance/intolerance to FQ, the patient should switch to (starting from the beginning of the treatment duration) all-oral longer regimen (based on the culture and DST results).
- For patients with intolerance/toxicity to any drug in STR, the patient should be switched to individualized regimen (the composition of the regimen should be guided by DST results).
- For patients that started with BPaL or all-oral longer regimen based on intolerance/resistance to FQ and other SLDs, the regimen should be re-evaluated and put on individualized regimen based on the phenotypic DST results.
- For patients that started with an individualized regimen based on resistance for FQ and/ other SLDs which is not confirmed by phenotypic DST results, they should continue the treatment whilst consulting experts on potential regimen adjustment based on DST results and clinical status.

All detected TB patients should be tested for both FL and SL resistance. If not feasible, SL DST could be limited to only those TB patients who have detected Rifampicin resistance. Treatment initiation for DR-TB patients should not be delayed while waiting for results with a 2-weeks cut-off timeframe .

If the patient is detected to be Isoniazid resistant with both inhA and katG resistant mutations present, then they should not receive the all-oral STR.

All DR-TB patients should be tested for resistance to FQ and/or other SLDs before starting any DR-TB treatment, and efforts should be made to ensure that rapid molecular DST for FQ and other SLDs is available for all DR-TB patients with prompt turn-around time of results.

10.6.2 DR-TB treatment regimens

TB medicines to be used for treatment of MDR/RR-TB are categorized into Groups A, B and C. This 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).

Table 27: WHO grouping of medicines recommended for DR-TB regimens:

Group A		**Group C**	
Levofloxacin	Lfx	Ethambutol	E
Moxifloxacin	Mfx	Delamanid	Dlm
Bedaquiline	Bdq	Pyrazinamide	Z
Linezolid	Lzd	Imipenem-Cilastin	Imp-Cln
		Meropenem	Mpm
Group B		Amikacin	Am
Clofazamine	Cfz	Prothionamde/ Ethionamide	Pro/ Eto
Cycloserine or Terizidone	Cys/Trd	P-aminocyclicacid	PAS

WHO recommends a number of treatment regimen options. The regimen notations used throughout this document highlight the number of months for which a relevant combination of medicines is used and if certain drugs are used for a different duration this is also noted using subscript in brackets. The following are examples of regimen notations:

- **Regimen for isoniazid-resistant TB:** *6 (H)REZ-Lfx* (6-month treatment regimen composed of rifampicin, ethambutol, pyrazinamide, levofloxacin. Isoniazid can be added if 4-drug FDC (HREZ) will be used.
- **Standardized Shorter all-oral regimen for MDR/RR-TB:** *4–6 Bdq(6m)-Lfx/Mfx-Cfz-Z-E-Hh-Pto/Eto / 5 Lfx/Mfx-Cfz-Z-E*
- **Standardized BPaLM regimen for MDR/RR-TB** without quinolone resistance: *6–9 Bdq-Pa-Lzd-Mfx* (6–9-month treatment regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin)
- **Standardized BPaL regimen for MDR/RR-TB** with quinolone resistance: *6–9 Bdq-Pa-Lzd* (6–9-month treatment regimen composed of bedaquiline, pretomanid and linezolid)
- **Standardized all oral longer regimen:** *18 Bdq(6m)-Lfx/Mfx-Lzd-Cfz ± Z* (18-month treatment regimen composed of bedaquiline for the first 6 months and levofloxacin or moxifloxacin, linezolid, clofazimine and pyrazinamide for 18 months).

Table 28 below shows the different RR-TB/MDR-TB regimen compositions and eligible populations.

Table 28: Regimen for RR-TB/MDR-TB

Regimen	Composition	Duration	Eligible population
Standardized BPaLM regimen	6Bdq-Pa-Lzd-Mfx	6-9 Months	Patients with RR/MDR-TB in whom resistance to FQ has been excluded
Standardized Shorter all-oral regimen	4-6Bdq-Mfx/Lfx-Cfz-Hh-Pto/Eto-E-Z/ 5 Mfx/Lfx-Cfz-E-Z	9-11 months	Patients with RR/MDR-TB in whom resistance to FQ has been excluded
Standardized all oral longer regimen	6Bdq-Mfx/Lfx-Cfz-Lzd ± Z/ 12Mfx/Lfx-Cfz-Lzd ± Z	18-20 months	For patients who do not fulfill the criteria for the all oral shorter MDR-TB regimen
Standardized BPaL regimen	6 Bdq-Pa-Lzd	6-9 months	For Pre-XDR-TB with fluoroquinolone-resistance
Rifampicin Susceptible, Isoniazid Resistant TB	6(H)RZE-Lfx	6 months	Rifampicin Susceptible, Isoniazid Resistant TB
Individualised longer regimen	Regimen designed according to DST results	18-20 months	For pre-XDR not eligible for BPaL regimen XDR-TB with Lzd resistance XDR-TB with Bdq resistance

10.6.3 Bedaquiline, Pretomanid, Linezolid, Moxifloxacin (BPaLM) regimen

This is a 6-month treatment regimen composed of Bedaquiline, Pretomanid, Linezolid and Moxifloxacin (BPaLM). It is the preferred regimen for all confirmed RR-TB/MDR-TB patients particularly when susceptibility to fluoroquinolones is documented or presumed.

Composition and Dosages

In the BPaLM regimen, the following drugs are administered:

Table 29: BPaLM regimen and doses

Drug	Dose
Bedaquiline (100 mg tablet)	400 mg once daily for 2 weeks, then 200 mg 3 times per week afterwards OR 200mg daily for 8 weeks, then 100mg daily
Pretomanid (200 mg tablet)	200 mg once daily
Linezolid (600 mg tablet)	600 mg once daily
Moxifloxacin (400 mg tablet)	400 mg once daily

Eligibility criteria for BPaLM regimen

1. All people with RR-TB/MDR-TB regardless of HIV status
2. People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving CNS, osteoarticular and disseminated (Miliary) TB.
3. Adults and adolescents aged 14 years and older.
4. Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.
5. Patient is not pregnant or breastfeeding or, if the patient is a pre-menopausal woman, and on effective contraception.

Exclusion criteria for BPALM regimen include:

1. Known intolerance to any of the drugs in the regimen.
2. TB involving the CNS, joints and miliary TB
3. Children under 14 years.
4. Pregnant women or breastfeeding mothers
5. Confirmed XDR TB

Duration of treatment with BPaLM/BPaL

- Patients that are susceptible to FQs can be started on the BPaLM regimen for 6 months (26weeks) with possibility of extending to 9 months as decided by a clinical review committee. Extension of BPaL can occur under following conditions
    - Lack of culture conversion between months 4 and 6 of treatment
    - Lack of clinical response between months 4 and 6 of treatment (based on clinical judgement)
- In case resistance to FQs is identified after initiation of BPaLM, Moxifloxacin may be discontinued and regimen continued as BPaL.
- If the regimen is BPaL from the start or is changed to BPaL, it can be extended to 9months (39weeks)- continuing from the start date of BPaLM or BPaL. Extension of BPaL can occur under following conditions

- Lack of culture conversion between months 4 and 6 of treatment
- Lack of clinical response between months 4 and 6 of treatment (based on clinical judgement)

- One month can be added to the overall treatment duration if there is need to make up for missed doses
- Temporary suspension of the regimen is allowed for suspected drug-related toxicity.
- Reintroduction of the full regimen can be considered after a cessation of no more than 14 days of consecutive treatment interruption or up to a cumulative 4 weeks of nonconsecutive treatment interruption

Modification of the BPaLM treatment regimen

- Modification of bedaquiline and pretomanid is not recommended
- Dose modification of linezolid is acceptable after the first 9 weeks of treatment in cases of adverse events.
  - this principle should however not override the need to avoid permanent disabilities.
  - After 9 weeks of consecutive administration of Linezolid, the dose of Lzd can be reduced to 300mg in case of toxicity.
- The following principles guide cessation of any component drug of the BPaLM/BPaL in case of severe toxicity
  - if either bedaquiline or pretomanid needs to be permanently discontinued, the entire BPaLM/BPaL regimen should also be discontinued and an individualized regimen started.
  - if linezolid is permanently discontinued during the initial 9 consecutive weeks of treatment, the entire regimen should be discontinued;
  - if linezolid is with held in the later weeks of the regimen, with the total remaining duration of the regimen not exceeding 8 weeks, the regimen can be considered to be completed with the remaining component drugs; and
  - o if moxifloxacin alone is discontinued, the regimen can be continued as the BPaL regimen.

Linezolid dosing in the BPaLM/BPaL regimen

- Although it is preferred to continue Linezolid at the full dose for the entire duration, the dose of linezolid can be reduced to 300 mg or discontinued (and restarted when possible) if there is significant toxicity. In general, action should be taken in the following manner for the common toxicities associated with linezolid:
- for optic neuritis diagnosed at any grade, discontinue Linezolid permanently
- for peripheral neuropathy Grade 2, reduce the dose of Linezolid to 300 mg per day with a possible drug holiday for 1–2 weeks before dose reduction;
- for peripheral neuropathy Grade 3 or 4, permanent suspension of Linezolid will be needed;
  - in some cases, after a 1–2-week drug holiday and reversion to Grade 2, the Linezolid can be restarted and tolerated, provided it does not revert back to a Grade 3 or 4 (caution is warranted with this approach because patients can be left with a severe painful and disabling permanent peripheral neuropathy);
- myelosuppression (even of Grade 3 or 4) is often reversible with a short 1-to-2-week drug holiday followed by reducing the dose of Linezolid to 300 mg per day

Contraindications to the BPaL(M) regimen

There are no absolute contraindications for the use of any drug in the treatment of MDR-TB and MDR-TB with fluoroquinolone resistance. However, there are relative contraindications for the BPaL(M) regimen, and some of the most relevant of these are listed in Table 30. If the clinician judges that the potential benefits outweigh the potential risk (also considering alternative treatment options), then treatment may proceed with caution. In these situations, advice should be sought from the DR-TB Expert committee.

Table 30: Relative contraindications to BPaL regimen use for treatment of 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 x ULN Total bilirubin > 2.0 × ULN Albumin < 32 g/L
Severe renal failure	Serum creatinine > 3.0 x 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

ALT: alanine transaminase; AST: aspartate transaminase; BPal: bedaquiline, pretomanid and linezolid for 6-9 months; CYP: cytochrome; MDR/RR-TB multidrug- or rifampicin-resistant TB; PI: protease inhibitor; ULN: upper limits of normal

Treatment monitoring (BPaLM)

Table 31: Schedule of baseline, routine and post-treatment monitoring examinations for BPaL regimen

Examination	Baseline	2 weeks	Monthly	End of treatment	6 and 12-months post-treatment
Clinical evaluation					
Clinical assessment®	x	x	x	x	x
Psychosocial assessment»	x	x	x	x	x
Weight/BMI	x	x	x	x	x
Performance status	x				
Peripheral neuropathy screen	x	x	x	x	
Visual acuity and colour discrimination screen	x	x	x	x	
Assessment and follow-up of adverse events	x	x	x	x	x
Outcome consultation				x	x
Bacteriological evaluations					
Sputum smear	x		x	x	x
Sputum culture	x		x	x	x
Sputum drug susceptibility testing	x	If smear or culture positive			
Other samples (smear/culture/DST)	x	If no documented response to treatment			
Radiology, ECG & laboratory evaluations					
Chest X-ray	x			x	x
ECG	x	x	x	x	
Full blood count	x	x	x	x	
Liver function tests (AST, ALT, bilirubin)	x	x	x	x	
Serum electrolytes	x				
Urea, creatinine	x				
Pregnancy test	x				
HIV/HBV/HCV tests	x				
BSL/HbA1c	x				

ALI: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index BSL: blood sugar level; DST: drug susceptibility testing; ECG: ECG: electrocardiography Hb: haemoglobin; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; TB: tuberculosis.

- Vital signs, TB symptom screen, pain, nausea, appetite and nutrition, diarrhoea, candidiasis. Clinical assessment should focus on a) monitoring response to treatment and b) addressing common symptoms associated with TB treatment and long-term antibiotic use, with the goal of supporting adherence.
- Food security, housing, mental state, substance use. Psychosocial assessment should offer an opportunity to assess supportive factors for treatment adherence and should be directly linked to relevant interventions wherever possible per country specific questionnaires.
- Xpert MTB/RIf, Hain GenoType MTBDRsi, culture-based second-line DST, next generation sequencing. If available, this should include Xpert/DR and DST for the BPal component drugs.

10.6.4 Standardized Shorter all-oral regimen for MDR/RR-TB

WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded

Composition and duration of regimen

- The shorter all-oral MDR/RR-TB regimen contains bedaquiline, levofloxacin/moxifloxacin, clofazimine, Prothionamide/Ethionamide, ethambutol, isoniazid (high dose) and pyrazinamide for 4 months (with the possibility of extending to 6 months if the patient remains sputum smear or culture positive at the end of the fourth month). This is followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide.
- Bedaquiline use in this regimen is for 6 months.
- Access to rapid DST for ruling out fluoroquinolone resistance is required before starting a patient on this regimen but should not delay initiation of treatment.

Regimen: 4-6 Bdq (6m) - Mfx/Lfx-Cfz-Pto/Eto-Z-E-Hh/ 5 Mfx/Lfx-Cfz-E-Z

Initial Phase: 4-6 Bdq (6m) - Mfx/Lfx-Cfz-Pto-Z-E-Hh

Continuation Phase: 5 Mfx/Lfx-Cfz-E-Z

The standardized shorter all-oral 9-month regimen can be modified as follows.

Regimen: 4-6 Bdq (6m) - Mfx/Lfx-Cfz-Lzd (2m) - Z-E-Hh/5 Mfx/Lfx-Cfz-E-Z

Initial Phase: 4-6 Bdq (6m) - Mfx/Lfx-Cfz-Pto-Z-E-Hh

Continuation Phase: 5 Mfx/Lfx-Cfz-E-Z

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

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:

- Two months of linezolid (600 mg) can be used as an alternative to 4 months of ethionamide/ Prothionamide.
- Bedaquiline is used for 6 months.
- Prothionamide may be used instead of ethionamide.
- Moxifloxacin may be used instead of levofloxacin.
- 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 continuation phase remains fixed at 5 months regardless.

If a patient is started on the shorter all-oral 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.

- Repeat DST at that point to guide the composition of the longer regimen.

If a patient is placed on a longer regimen and later found to be eligible for the shorter regimen he/she 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.

Eligibility Criteria

The 9-month all-oral regimen (with either Prothionamide or linezolid) may be offered to the following patients with MDR/RR-TB (where resistance to at least rifampicin has been confirmed and resistance to fluoroquinolones has been ruled out):

- no documented resistance or suspected ineffectiveness of bedaquiline, clofazimine, or prothionamide/Ethionamide or linezolid (whichever is considered for inclusion in the regimen);
- no exposure to previous treatment with bedaquiline, fluoroquinolones, clofazimine, or prothionamide/Ethionamide or linezolid (whichever is considered for inclusion in the regimen) for more than 1 month – when prior drug exposure is greater than 1 month, patients may still receive this regimen if resistance to the specific medicine with such exposure has been ruled out;
- no extensive or severe TB disease and no severe extra pulmonary TB
- women who are pregnant or breastfeeding: these patients may be considered eligible for the linezolid-containing 9-month regimen, but they should not receive the 9-month regimen containing prothionamide/Ethionamide
- children and adults without bacteriological confirmation of TB or resistance patterns but who require MDR/RR-TB treatment based on clinical signs and symptoms of TB (including radiological findings) and history of contact with someone with confirmed MDR/RR-TB: these patients may be eligible for this regimen based on the drug resistance profile of the isolate obtained from the most likely index case

If the Standardized Shorter all-oral MDR-TB regimen cannot be used, the patient should be reassessed for a longer all-oral MDR-TB regimen.

The health care provider may opt for a Standardized all oral longer regimen even in patients who are eligible for the shorter all-oral MDR-TB regimen. This could be motivated by uncertainty about drug susceptibility while the patient's condition requires an immediate start of treatment and cannot wait for DST results.

Considerations for Implementation

Assessment of extent of TB disease:

- Extent of TB disease is important to determine the regimen options, in addition to the DST and other considerations mentioned above. Chest radiography is important for decision to use or not to use this regimen. Patients with extensive disease on CXR should not use this regimen.
- Severe extrapulmonary TB is defined as the presence of miliary TB or TB meningitis. 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. Patients with severe forms of EPTB should not be started on this regimen.

DST results:

- Testing for susceptibility to at least fluoroquinolones is recommended before the start of a standardized shorter all-oral MDR-TB regimen, to ensure exclusion of resistance to fluoroquinolones.
- First-line LPA (MTBDRplus) or XpertMTB/XDR can determine mutations in the inhA promoter or katG regions. Both of these mutations confer resistance to isoniazid with low-level resistance when inhA mutations are present, or high-level resistance when mutations in the katG gene are present. Mutations at the inhA promoter are also associated with resistance to ethionamide and prothionamide. The presence of both mutations (i.e. inhA promoter and katG) suggests that isoniazid at high dose and thioamides are not effective, and that the shorter regimen may therefore not be used.

Table 32: Standardized shorter all-oral MDR/RR-TB regimen in special populations

Sub-group	Recommendations
PLHIV	• The standardized shorter all-oral MDR-TB regimen can be used in PLHIV, including those who are receiving ART. • For PLHIV with pulmonary disease, there may be a potential for overlapping, additive toxicities or for drug–drug interactions between some antiretroviral medicines and TB drugs such as ○ Efavirenz and bedaquiline. Bdq should not be given with Efavirenz. Efavirenz should be substituted with Dolutegravir which has no interaction with Bdq. ○ Ritonavir may also increase bedaquiline exposure, which could potentially increase the risk of bedaquiline-related adverse reactions. Avoid combination of Bedaquiline with ritonavir or combined use should be with caution • ART regimens need to be initiated early, in accordance with WHO recommendations. ○ Give prophylaxis for other OIs, ○ Support for TB and antiretroviral medication adherence, ○ And close monitoring of the biomarkers of immune status.
Children:	• The standardized shorter all-oral regimen can be used in children of all ages under programmatic conditions. • 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 in case a child-friendly formulation is not available.
Pregnant and lactating women:	• The regimen contains ethionamide, which is usually contraindicated in pregnancy • These patients may be considered eligible for the Linezolid-containing 9-month regimen, but they should not receive the 9-month regimen containing Prothionamde • Individualized longer regimens can be designed and should be prioritized to avoid known toxicities in case they are not eligible for the standardized shorter all-oral bedaquiline-containing MDR-TB regimen.
Rifampicin-resistant TB without MDR-TB:	• All patients with rifampicin-resistant TB in whom isoniazid resistance is not confirmed may be treated with the shorter all-oral MDR-TB treatment regimen.

Sub-group	Recommendations
Severe extra pulmonary TB disease:	• This regimen can be used in some forms of EPTB, but cannot be used in severe forms of extrapulmonary TB disease including CNS, Osteo-articular and Miliary TB • In severe forms of EPTB, use the longer regimen.
Patients with diabetes mellitus:	• There are no data on the use of the standardized shorter all-oral regimen among people with diabetes mellitus. • Although the standardized shorter all-oral regimen may be considered as an option, monitor closely for hepatotoxicity among this patient group. • Monitor RBS closely as thionamides may destablise the sugar control
Patients with extensive disease:	• In patients with extensive disease, preference should be given to the standardized all-oral longer regimen and BPaLM regimen.

10.6.5 Monitoring treatment response and outcome assignment

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

- reliable DST results show resistance to key medicines in the standardized shorter all-oral MDR-TB regimen:
    - this may reflect the actual situation at the start of treatment (that was unknown at that time) or the acquisition of additional resistance during treatment;
- there is a lack of response to treatment (e.g. no sputum smear conversion from positive to negative by 6 months, or deterioration of clinical condition despite treatment);
- treatment of a patient is interrupted for 2 months or more after being treated for more than 1 month. If the interruption is for less than 2 months, the clinician needs to decide whether the standardized shorter MDR-TB regimen can be continued based on clinical condition and repeat laboratory test results, and whether the missed doses will be added to the rest of the treatment or a longer regimen should be started; or
- another disqualifying criterion emerges (e.g. pregnancy, intolerance or toxicity to a medicine in the regimen, or clinical deterioration).

Monitoring treatment response

- The monitoring schedule for this regimen is similar to that of the longer all-oral MDR-TB regimen. Monitoring is done monthly using sputum **smear microscopy** and **culture**.
- The treatment outcome definitions and reporting framework for patients on the standardized shorter MDR-TB regimen are the same as those for patients on the longer MDR-TB regimens.

Decision to switch to continuation phase

- The criteria to shift to the continuation phase is based on smear conversion and clinical response.
- The patient should have smear-negative results and be clinically improving. All attempts should be made to send monthly samples for culture and trace results.
- It is important to have FL-LPA, SL LPA, culture, and SL phenotypic DST or XpertMTB/XDR results available, to exclude resistance to FQ, FL and other SLD.
- If the smear conversion is not achieved at month four, the intensive phase shall be extended to a maximum total duration of six months (until smear conversion and one negative culture result is

achieved).

- If the patient remains smear and/or culture-positive at six months, will be declared as a treatment failure and switched to an individualized regimen.
- Failure declaration and a switch to an individualized treatment will be considered earlier than six months in patients with a clear lack of response (clinically, smear grading, culture).
- The decision to switch earlier must be made by a committee of experts.

Figure 12: Treatment response monitoring chart for patients on standardized shorter all-oral MDR/RR-TB regimen

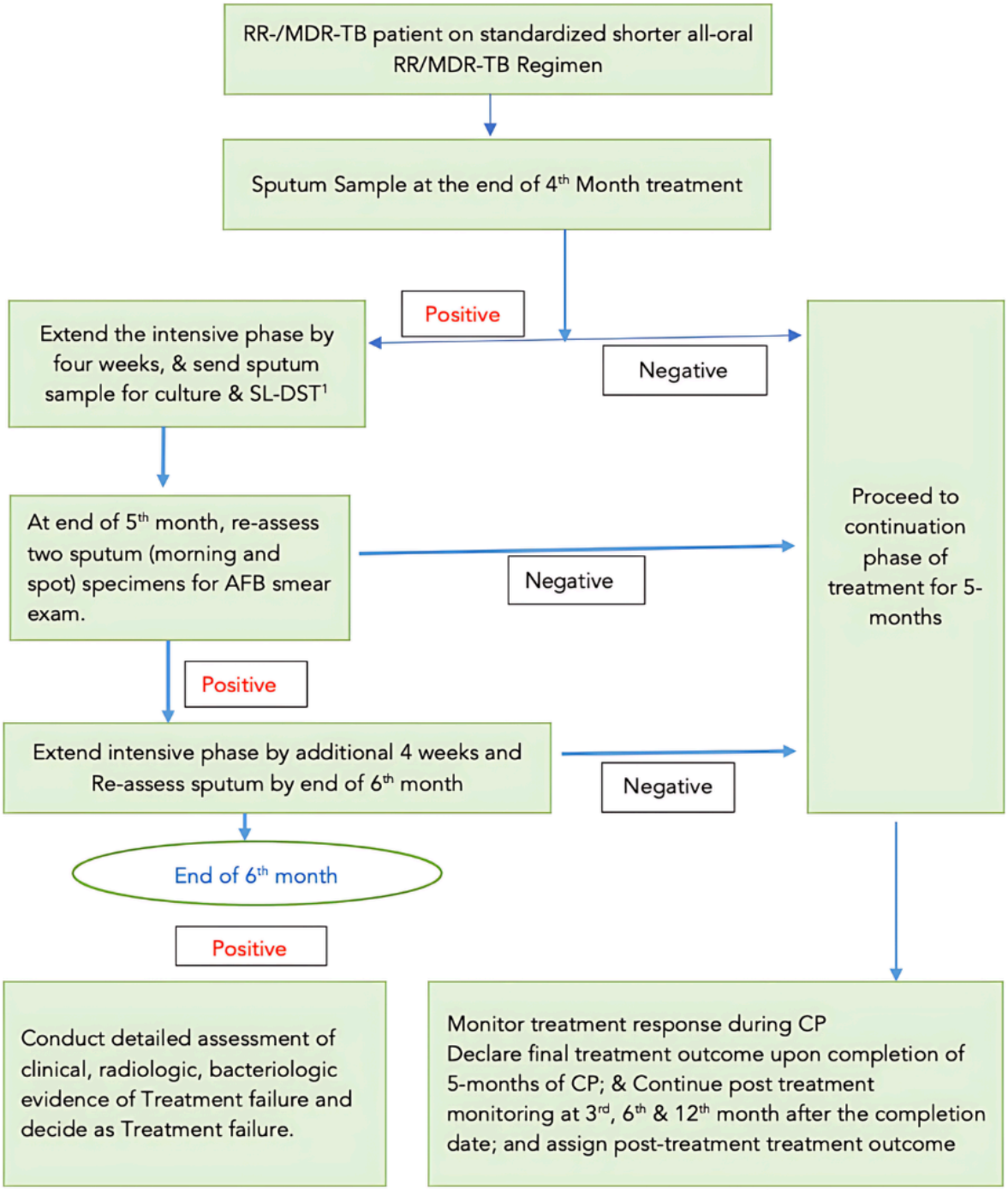


Table 33: Treatment monitoring schedule for standardized shorter all-oral regimen

***Prompt action on abnormal clinical or laboratory findings is mandatory** ****Circle any parameter carried out**												
Patient Name: **DR-TB No:** **Age:** **Sex:**												
Month/Year												
Examination	**Baseline**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Clinical symptoms and exam	X	X	X	X	X	X	X	X	X	X	X	X
Toxicity symptoms and signs	X	X	X	X	X	X	X	X	X	X	X	X
Educational and psychosocial	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X
Height &BMI (wt/ht^2)	X											
Xpert MTB/RIF	X											
1st and 2nd line drugs LPA or XpertMTB/XDR	X				Repeat if smear and/or culture positive or presumption of failure							
Sputum AFB	X	X	X	X	X	X	X	X	X	X	X	X
Sputum culture	X	X	X	X	X	X	X	X	X	X	X	X
Phenotypic DST	X				Repeat if smear and/or culture positive or presumption of failure							
X-Ray	X						X					X
ECG[6]	X & week 2	X	X	X	X	X	X	X	X	X	X	X
Haematology (FBC, diff)[1]	X											
Creatinine and potassium[2]	X	X	X	X	X	X	X					
LFTs (ALT/AST)	X	X	X	X	X	X	X	X	X	X	X	X
TSH[3]	X						X					
Fasting blood sugar	X											
Vision test charts[4]	X											
HIV test[5]	X											
Hepatitis B, C	X											
Pregnancy test[7]	X											
HIV positive patients												
CD4 count	X						X					
Viral load	X						X					

1. *Repeat FBC as necessary if HIV-infected (special care in patient on AZT)*
2. *Creatinine, potassium should be requested monthly*
3. *TSH:If replacement with levotyroxine is required, repeat TSH every 30-45 days to adjust the dosage.*
4. *For patient on long term Ethambutol request vision test. Repeat if any change/complain in acuity or color vision*
5. *HIV test can be repeated if indicated (consider repeat every 6 months).*
6. ***ECG is mandatory for patients** at baseline, week 2 and then continue monthly ECG in patients receiving more than one QT prolongation drugs (Bdq, Mxf, Cfz & Dlm). More frequent monitoring is required in patient with low albumin (<3.4 g/dl), low electrolytes, hypothyroidism or heart conditions.*
7. *Pregnancy test: at baseline, then offer use of appropriate effective contraceptives.*

Monitoring safety

Even though the standardized shorter all-oral regimen is well tolerated, the safety profile of some medicines used concomitantly may present concerns. For instance, concomitant use of clofazimine, bedaquiline and high-dose moxifloxacin – all of which prolong the QT interval – may make it more important to monitor for additive cardiotoxicity (using ECG) for these drug combinations than it is for other drug combinations. Any adverse events for patients on treatment need to be reported primarily to the **pharmacy board** which is responsible for pharmacovigilance, within the framework of aDSM.

A functional aDSM system at all the treatment centers is required at the time of starting patients on the standardized shorter all-oral MDR/RR-TB regimen.

Two key elements need to be in place so that the essential safety data are collected for all patients from the moment that they are started on treatment:

- Preparations for the collection of data in paper or electronic format and staff properly trained to collect these data. 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.

10.7 Longer all-oral regimens for MDR/RRTB

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. In MDR/RR-TB patients on longer regimens, the total treatment duration is 18–20 months for most patients. However, the duration may be modified according to the patient's response to therapy. Treatment duration of 15–17 months after culture conversion can also been considered depending on the patient's bacteriologic response.

A longer regimen is usually denoted using abbreviations for the individual agents and the duration of use in months; for example:

6Bdq(6 m or longer)-Lfx-Lzd-Cfz /12Lfx-Lzd-Cfz +/- Z

In this example, the first 6 months of treatment comprises four second-line agents. The remaining 12 months includes the same agents except for bedaquiline, bringing the total duration to 18 months. All medicines apart from bedaquiline are given 7 days a week. Bedaquiline, when prescribed on-label, is given daily for the first 2 weeks and three times weekly thereafter.

Medicines used in longer MDR-TB treatment regimens

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 34 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. Therefore, clinicians should be guided by these recommendations in designing treatment regimen.

Table 34: Medicines recommended for the treatment of RR/MDR-TB:

Group	Medicine and abbreviation	
Group A Include all three medicines	Levofloxacin/	Lfx
	Moxifloxacin	Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B Add one or both medicines	Clofazimine	Cfz
	Cycloserine or Terizidone	Cys/Trd
Group C Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-Cilastatin or Meropenem	Imp-Cln or mpm
	Amikacin or Streptomycin	Am or S
	Prothionamde/ Ethionamide	Pro/ Eto
	P-aminosalicylic acid	PAS

Considerations in the designing a longer treatment regimen:

- In MDR/RR-TB 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.
- 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 of all age groups.
- Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens.
- 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 of all age groups.
- 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.

Note

- Group A and B are considered core second line anti TB drugs whereas the group C drugs are add on agents (added to the regimen if effective regimen cannot be composed with only group A and B drugs).
- 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. 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 being considered for the standardized longer MDR-TB treatment regimen should have a laboratory-confirmed diagnosis of MDR/RR-TB before embarking on a regimen using second-line medicines. This is needed because erroneous treatment with an MDR-TB regimen exposes patients to an unnecessarily lengthy and toxic treatment that could be less effective than the rifampicin-based regimens recommended for patients with drug-susceptible TB.

10.7.1 Eligibility

A standardized longer regimen is expected to be used in the following situations:

- severe extrapulmonary TB;
- additional resistance to key medicines of the BPaLM/BPaL regimen (except moxifloxacin) or the standardized 9-month all-oral regimen;
- lack of response to shorter treatment regimens (e.g. treatment failure due to no bacteriological conversion, no clinical response, emerging resistance or loss to follow-up);
- drug intolerance to the component medicines of the BPaLM/BPaL regimen (except moxifloxacin) or standardized shorter 9 months all-oral treatment regimen; and
- pregnant and lactating women who could not benefit from the standardized shorter 9-month all-oral regimen owing to certain clinical conditions, or children aged below 14 years who could not be treated with BPaLM/BPaL or who, for any reason, cannot opt for a standardized shorter 9-month regimen.

Any patient eligible for a standardized all-oral longer regimen should undergo a pretreatment assessment to optimize the drug selection, reduce the chances of adverse events and thus increase the probability of the favourable treatment outcomes. The pretreatment assessment includes:

- a detailed clinical history (including all comorbidities, medications and known intolerances), a physical examination, a blood test, chest X-ray or other imaging and bacteriological tests; and
- a list of current effective TB medicines available based on a clinical history of drugs taken before this treatment episode and guided by the DST results or sequencing of the most recent sample from the patient (or the index case).

In addition to the eligibility criteria and preclinical assessment, a clinician should also consider:

- development of a personalized treatment approach (patient-centered approach) and close follow-up, including food support if needed, to increase bioavailability of drugs, improve nutritional status and facilitate adherence;
- provision of advice on contraception for women of childbearing age;
- availability of ancillary medications (e.g. corticosteroids in the case of disseminated TB or TB meningitis or pericarditis, pretreatment blood transfusion in the case of severe anaemia and
- nutritional support) and other interventions (e.g. intravenous [IV] medication in the case of severe malnutrition and malabsorption, insertion of peripheral or central catheter, or surgery in the case of restricted options and meeting criteria for intervention); and
- provision of counselling, depending on the patient's comorbidities (e.g. HIV or diabetes) or pre-existing conditions

Note

- 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.
- 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.
- In the absence of DST guidance for regimen design, 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.
- Any patient with rifampicin-resistant TB in whom isoniazid resistance is absent or unknown, needs to be treated with a recommended MDR-TB regimen. High-dose isoniazid has also been shown to be an important component in shorter all oral 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 regimens for RR/MDR-TB

When designing longer regimens, a number of basic principles should be followed

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

- If bedaquiline is stopped at month 6, the regimen will still have three effective agents for the rest of the treatment duration. However, if another agent needs to be stopped because of toxicity, then that medicine would need to be replaced by another one, or bedaquiline could be continued throughout the treatment under "off-label" use. If the choice is to replace a medicine, instead of prolonging the use of bedaquiline, the replacement medicine would be chosen either from Group

B (unless both clofazimine and cycloserine/terizidone are already included) or from Group C. The choice from Group C is usually determined by the order in which the medicines are ranked, and by the individual circumstances of the patient and setting.

- Observational data has shown no additional safety concerns when bedaquiline was used for longer than 6 months.
    - The clinicians may therefore consider continuing bedaquiline 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 effective agents instead of four. This increases the pill burden and chances of adverse reactions, but may be justified, particularly when:
    - 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.
- 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
- 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.
- Resistance testing 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.
- Resistance to fluoroquinolones remains an important finding for all regimens hence it should be tested.

10.7.3 Steps in longer MDR/RR-TB Regimens Design

Patient triaging will be the first step in the regimen design for the standardized all-oral longer DR-TB treatment regimen. Patients not eligible for shorter all oral DR-TB treatment or BPaLM at the beginning of the treatment and those who are found to have resistance to any of the second line TB drugs in the shorter all oral DR-TB regimen are best candidates to receive the longer all oral DR-TB treatment.

Drugs are grouped according to their order of usual preference from group A down to group C. Choice of the drugs from each group depends on the following rationale:

- Expected balance of effectiveness and harm
- Result of drug susceptibility testing (DST result)
- Reliability of the DST for drug considered to be used
- Population level drug surveillance of each particular drugs (if there is)
- History of previous use by the patient
- Drug tolerability by the patient and
- Potential drug-drug interaction (between anti TB drugs or between TB drugs and other non anti TB drugs in case of comorbidities).

Table 35: Step-by-step directions for designing an effective longer MDR/RR-TB regimen

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

Table 36: Factors to consider in choosing individual medicines for longer MDR-TB regimens

Results of DST, preferably performed from externally quality assurance, 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. For migrants, it may be necessary to consider the current and historical patterns of medicine use in the migrant's country of origin, as well as the country of residence 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. In some settings, facilities to monitor adverse events of certain medicines may not be available; however, it is not necessary for patients to wait for all operational elements to be in place for them to start benefiting from life-saving treatment.
Potential for, or past history of, toxicities, intolerance (other than allergy) and drug– drug interactions.
In children, age of the child and formulations available.

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. These drugs can be extended until the entire length of treatment if required especially if bedaquiline and delamanid are the only effective drugs.

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

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

Proper ECG monitoring is important where Bdq and Dlm are combined in the same regimen or prolonged beyond 24 weeks.

Dosage of medicines used in longer MDR-TB regimen

- Dosages of individual medicines are often determined by body weight separately for adults and children.
- Doses may need to be adjusted because of accompanying medicines or comorbidities.
- 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 gradually over a 2-week period.

- 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.
- 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.
- 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.
- If a dose of Bdq is missed during the first 2 weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule
    - From the third week onwards, if a 200 mg dose of Bdq 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.

10.7.5 Duration of longer MDR/RR-TB regimens

- In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; 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 15–17 months after culture conversion is suggested for most patients; 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; the duration may be modified according to the patient's response to therapy.

Note

- The duration of use of different medicines will depend on the following conditions:
    - Clinical indication (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).
    - 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 applies to all patients on longer all oral treatment regimens (standardized or individualized).
    - 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

10.7.6 Use of All Oral Longer regimens in special populations

Children

- Children who are not eligible for the standardized shorter all-oral regimen include those
    - without bacteriological confirmation (e.g. with a clinical diagnosis)
    - without fluoroquinolone resistance ruled out (in their own specimens)
    - with drug-resistant EPTB other than peripheral lymphadenopathy
    - with extensive pulmonary disease
    - with prior exposure for more than 1 month to the medicines in the shorter regimen.

These children should be treated with longer, individualized treatment regimens. In general, the treatment principles for MDR/RR-TB in children follow those recommended for adolescents and adults.

The following treatment considerations apply specifically for children with MDR/RR-TB

- Child-friendly formulations should be used whenever possible.
- Individualized regimens should consist of at least four medicines to which the organism is likely to be susceptible.
    - Most medicines will be used for the duration of treatment, but some may be used for shorter periods, such as bedaquiline (recommended for 6 months) or linezolid (often used for shorter durations because of its potential for severe adverse effects).
    - Children and adolescents with extensive forms of MDR/RR-TB may benefit from an additional fifth medicine at least at the beginning of treatment, with the duration depending on the extent of disease, response to treatment, number and efficacy of companion medicines in the regimen, and potential for adverse effects
- Group A and Group B medicines should be prioritized in the construction of the treatment regimen, as well as delamanid and other Group C medicines.
- For children of all ages, bedaquiline is recommended to be included as part of individualized treatment regimens.
    - The recommended standard duration of treatment with bedaquiline is 6 months. Extension of bedaquiline beyond 6 months may be considered in some people without other options (e.g. those with fluoroquinolone resistance or intolerance to linezolid), in consultation with a paediatric DR-TB expert and with strict baseline and follow-up monitoring.
- Linezolid is a Group A medicine associated with frequent hematological toxicity, depending on the dose and duration of use. Its use for the full duration of treatment may improve efficacy, but adverse events may limit the duration of use to the first few months.
    - If there are few options available, such as for TBM caused by an MDR/RR-TB strain or for MDR/ RR-TB with additional fluoroquinolone resistance but linezolid susceptibility, linezolid can be continued for longer durations, such as 6–9 months or longer as adverse effects allow.
- For children of all ages, delamanid is an option to add to MDR/RR-TB regimens if the child has (suspected) fluoroquinolone resistance or severe disease necessitating a fifth medicine.
    - The recommended standard duration of treatment with delamanid is 6 months but can be prolonged beyond 6 months depending on clinical response, adverse effects and availability of medicines with proper monitoring
- If the regimen cannot be composed with sufficient effective Group A or Group B medicines, addition of ethambutol and/or pyrazinamide (if DST of the child or source case confirms susceptibility) can be considered.

    - Due to difficulties in interpreting its DST, ethambutol should be considered only when it is likely to be effective.
    - P-aminosalicylic acid is another Group C medicine that can be used in children and adolescents if new medicines are not available or a four- or five-medicine regimen cannot be constructed.

- Ethionamide/prothionamide should be used as an additional medicine only if there is no known or suspected inhA mutation.
    - Ethionamide should be reserved for situations where more effective medicines (e.g. bedaquiline, linezolid, clofazimine) cannot be used.

- In children with fluoroquinolone resistance or with limited treatment options, extension of bedaquiline beyond 6 months and/or a combination of bedaquiline with delamanid may be considered. Careful monitoring of QT prolongation is strongly recommended when these medicines are used together.
- Injectable agents (amikacin, streptomycin) should not be used in children because of their risk of permanent hearing loss and their poor tolerability. Hearing loss is a frequent severe adverse effect of aminoglycosides, with a profound impact on language acquisition, ability to learn at school and further development.
- Duration of treatment using individualized regimens in children depends on the site and severity of disease and the extent of resistance (in addition to isoniazid and rifampicin resistance).
    - Children with non-severe disease can be treated for less than 18 months.
    - Children with extensive disease require longer treatment durations, depending on clinical progress, site of disease (e.g. bone or CNS), resistance pattern and number of types of medicines likely to be effective.

- Monitoring and management of adverse events are essential
- Severity of disease in children is defined as
    - In children <15 years, severe disease is usually defined by
        - Presence of cavities
        - Bilateral disease on chest radiography
        - Extra-pulmonary forms of TB other than TB lymphadenitis (Peripheral nodes of isolated mediastinal mass without compression)
    - In children, the following may also be considered when determining treatment duration
        - advanced malnutrition (defined by syndrome or by metrics)
        - advanced immunosuppression
        - positive TB bacteriology (smear, Xpert MTB/RIF, culture) may also be considered when determining treatment duration.

Table 37: Longer regimen use in other special populations

Special population	Consideration for the use of longer regimen
Severe forms of extra pulmonary TB and TB meningitis	• CNS, Osteoarticular and Miliary TB are treated with long regimens • Treatment of MDR/RR-TB meningitis is guided by ○ DST of the infecting strain ○ the ability of TB medicines to cross the blood–brain barrier. • Fluoroquinolones (Lfx/Mfx), linezolid, ethionamide (or prothionamide), cycloserine (or terizidone), and imipenem-cilastatin have good penetration across the blood–brain barrier. • Meropenem is preferred for cases of TB meningitis in children. Imipenem use is associated with seizures in children with TBM • High dose isoniazid and pyrazinamide are also useful in TBM if the strains are susceptible as they can reach therapeutic levels • Amikacin and streptomycin only penetrate the CNS in the presence of meningeal inflammation. • There are few data on the CNS penetration of clofazimine, bedaquiline or delamanid. • PAS and ethambutol do not penetrate the CNS well and should not be counted on as effective agents for MDR-TB meningitis.
Pregnancy	• Knowledge about the safety of bedaquiline and delamanid in pregnancy and during breastfeeding is sparse. • In pregnancy, a longer regimen should 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. • Amikacin, streptomycin, prothionamide and ethionamide are contraindicated during pregnancy.
HIV infection	• Knowledge about the safety of bedaquiline and delamanid in pregnancy and during breastfeeding is sparse. • In pregnancy, a longer regimen should 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. • Amikacin, streptomycin, prothionamide and ethionamide are contraindicated during pregnancy.
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. • No dose adjustment of clofazimine is required in patients with renal impairment.
Hepatitis B and C	• MDR-TB can be correlated with hepatitis B and C infection in many countries. • Active hepatitis B and C are risk factors for MDR-TB treatment failure. • Direct-acting antivirals (DAA) are well-tolerated when given with MDR-TB treatment. • It may be prudent to monitor closely for drug–drug interactions and hepatotoxicity among this patient group

10.7.7 Treatment monitoring

- Performance of MONTHLY sputum culture in addition to sputum smear microscopy is mandatory to monitor treatment response.
- 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.
- 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.
- Use culture to continue monitoring 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.

Table 38: Treatment monitoring schedule for longer regimens

	Month of treatment																				
Examination	Baseline	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Clinical symptoms & exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Toxicity symptoms & signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Educational & psychosocial	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height/BMI (wt/ht^2)	X																				
Xpert MTB/RIF	X																				
1st and 2nd Line drugs LPA	X																				
Sputum AFB	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Culture	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phenotypic DST	X																				
X-Ray	X						X						X						X		
Haematology (FBC, diff)[1]	X & week 2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Creatinine and potassium[2]	X	Repeat regularly if clinically indicated																			
LFTs (ALT/AST)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TSH[3]	X						X						X						X		
Fasting blood sugar	X																				
Serum Albumin[4]	X	Continue monthly if on Delamanid																			
Serum amylase/ Lypase[5]	X																				
ECG[6]	X & week 2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vision test charts[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Audiometry[2]								Recommended for patients on Injectables													
HIV test[8]	X																				
Hepatitis B, C	X																				
Pregnancy test[9]	X																				
CD4 count	X						X						X						X		
Viral load	X						X						X						X		

1. *If on Linezolid, FBC at baseline, week 2 and then monthly*
2. *Creatinine, potassium and audiometry should be requested monthly while on injectable. Continue monthly creatinine monitoring for patients at more risk of renal failure (HIV positive patients, diabetics patients receiving other nephrotoxic drugs). If any ECG abnormality check potassium (and Mg-Ca if available).*
3. *TSH: If on ethionamide, prothionamide, or PAS. If replacement with levothyroxine is required, repeat TSH every 30-45 days to adjust the dosage.*
4. *Serum albumin: If patient is on Dlm request serum Albumin at baseline: if low (<3,4 g/dl) monitor more frequent albumin and ECG. If serum albumin is <2.8g/dl, Dlm is contraindicated.*
5. *If patient is on Bdq and Lzd; request amylase and lipase at baseline. Then assess when clinically indicated*
6. ***ECG is mandatory for patients on Bdq, Dlm, Mfx and Cfz** at baseline, week 2 and then continue monthly ECG in patients receiving more than one QT prolongation drug (Bdq, Dlm, Mxf and Cfz). More frequent monitoring is required in patient with low albumin (<3.4 g/dl), low electrolytes, hypothyroidism or heart conditions.*
7. *If patient is on Linezolid, perform monthly visual acuity test (Snellen's chart) and color vision test (Ishihara's chart).*
8. *HIV test can be repeated if indicated (consider every 6 months).*
9. *Pregnancy test: at baseline, then offer effective contraceptives (barrier contraception or intra uterine device-IUD).*

10.8 Regimens for Pre XDR-TB

10.8.1 BPaL Regimen

This is an all-oral regimen composed of bedaquiline, pretomanid and linezolid (BPaL) used for Pre XDRTB (MDR/RR-TB patients with additional fluoroquinolone resistance).

All -oral shorter treatment regimen in case of Pre XDR (MDR-TB with FQ resistance).

Regimen	Composition	Duration
BPaL	bedaquiline (Bdq) + pretomanid (Pa) + linezolid	6-9 months

Dosing and duration of the BPaL regimen

Table 39: Dosing of BPaL component drugs for adults

Drug	Duration	Dosage
Bedaquiline	6-9 months	400 mg daily for 2 weeks, then 200 mg 3 times per week
Pretomanid	6-9 months	200 mg once daily
Linezolid	6-9 months	600 mg once daily

Note that:

- If the sputum culture taken after the patient has taken 4 months of treatment is still positive, the patient can receive an additional 3 months of treatment (total 9 months) as long as the patient is clinically well and /or improving.

Inclusion criteria for BPaL regimen

A patient, who is diagnosed with DR-TB in any of the following circumstances:

- Has a laboratory-confirmed resistance to at least rifampicin and fluoroquinolones; or
- Has strong clinical and radiological evidence of active TB and is a close household contact of a TB patient with a laboratory-confirmed resistance to at least rifampicin and fluoroquinolones; or
- Has been treated for MDR/RR-TB and has documented non-response to treatment, but DST suggests sensitivity to the drugs in the regimen; and a decision has been made by the Expert Committee to shift the patient to the BPaL regimen; or
- Has been treated for MDR-/RR-TB and has documented intolerance, but DST suggests sensitivity to the drugs in the regimen; and a decision has been made by the Expert Committee to shift the patient to the BPaL regimen.

Exclusion criteria for BPaL regimen

A patient who:

- Has a known severe allergy to any of the BPaL component drugs; or
- Has DST showing resistance to any of the component drugs; or

- Has a form of extrapulmonary TB that would require treatment longer than would be usual for pulmonary TB (e.g. CNS, Osteo-articular and Miliary TB); or
- Is pregnant or breastfeeding; or
- Children and Adolescents less than 14 years

BPaL regimen is not contra-indicated in PLHIV. There are some drug-drug interactions between antiretroviral drugs and bedaquiline:

- **Ritonavir:** inhibits metabolism of Bdq, increasing drug levels.

10.9 Treating mono and poly-drug resistant TB

If the patient has mono or polydrug resistant TB with resistance to rifampicin (susceptible to isoniazid), they should receive the same regimens as RR/MDRTB.

10.9.1 Isoniazid monoresistance:

In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, treatment with Rifampicin, Ethambutol, Pyrazinamide, and Levofloxacin is recommended for 6 months. It is foreseen that the Isoniazid resistance-TB treatment regimen would apply in the following situations:

Isoniazid resistance TB is confirmed before TB treatment is started:

- Treatment with the (H)REZ-Lfx is started immediately.
- If the diagnosis is strongly presumed (e.g. close contacts of a confirmed Isoniazid resistance - 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 to complete a 2HREZ/4HR regimen.

Isoniazid resistance TB is confirmed after the start of treatment with 2HREZ/4HR regimen:

- Rapid molecular testing for rifampicin resistance must be done (or repeated)
- Once rifampicin resistance is excluded, a full 6-month course of (H)REZ-Lfx is given.
- If rifampicin resistance is detected, the patient needs to be started on a recommended MDR-TB regimen.

Addition of isoniazid.

- There was no clear evidence showing that the addition of isoniazid adds benefit or harm to patients. For patient convenience and ease of administration, the 4-drug HREZ FDCs may be used to deliver the Isoniazid resistance TB treatment regimen alongside levofloxacin reference consolidated guideline. WHO

10.9.2 Adjuvant therapy

- Vitamin B6 (pyridoxine) preventive therapy at a dose of 100mg/day up to 200 mg/day should be given to all patients receiving isoniazid and linezolid to minimize peripheral neuropathy and neurological adverse event. For every 250mg of Cycloserine, 50mg of B6 should be given.
- Corticosteroids (Prednisolone 1 mg/kg and gradually decreasing by 10 mg per week when a long course is indicated) should be used in :
    - TB Meningitis (and other compromises of CNS) and maybe used in TB Pericarditis.
    - Severe forms of Immune Reconstitution Inflammatory Syndrome (IRIS).

10.10 Role of Surgery for patients on DR-TB treatment

- Generally, at least two months of therapy should be given prior to resection surgery to decrease the bacterial load in the surrounding lung tissue.
- In DR-TB patients, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended DR-TB regimen.
- Even with successful resection, an additional 12-18 months of chemotherapy should still be given.
- Treatment should be adjusted based on the DST results of the resected material
- Resection of cavitary lesions or destroyed lobes that harbor great numbers of tuberculosis organism improves patient outcomes.
- Partial lung resection for patients with DR-TB is to be considered only under conditions of good surgical facilities, trained and experienced surgeons, and with careful selection of candidates.

10.11 Current Structures set for the control of DR-TB in Sierra Leone

10.11.1 The drug-resistant TB treatment Center/DR-TB unit:

The drug-resistant TB treatment center is a healthcare facility where clinicians have been trained to initiate, treat, and manage DR-TB patients. Sierra Leone is currently implementing both the ambulatory and inpatient models of DR-TB care.

Key services at the DR-TB treatment centre

- Initiating treatment of all DR-TB cases after appropriate assessment and monitoring initial response to DR-TB treatment;
- Providing treatment supervision to DR-TB patients attending the unit
- Providing education and counselling to all patients at baseline and then on scheduled basis afterwards;
- Providing clinical and laboratory monitoring, and follow up
- Monitoring rational use of second-line drugs and ancillary drugs
- Management of side effects, monitoring adverse events and managing them accordingly
- Establishing and maintaining functional clinical management teams;
- Compiling monthly, quarterly, bi-annual, and annual reports on DR-TB patients; and
- Providing technical assistance and capacity building on management of DR-TB.
- Providing social support and welfare packages to DR-TB patients on treatment.
- Coordinate and provide DR-TB household contact tracing.

10.11.2 DR-TB Patient Review Committee

There should be a DR-TB patient review committee at each of the DR-TB treatment centers, comprised of professionals from various fields involved in the management of DR-TB patients. The committee should meet weekly and will be involved in the initiation, monitoring, and supervision of DR-TB patient treatment. The committee is responsible for making keys decisions on the management of patients while on treatment.

10.11.3 District TB Supervisor

The district TB supervisor is part of the district health management team and has administrative and management responsibilities to ensure effective DR-TB services in the district. The supervisor is

responsible for the following:

- Supervision of DOTS centers
- Compiling and analysing monthly, quarterly, bi-annual, and annual reports on DR-TB patients started on treatment, their culture conversion, and outcomes.
- Ensuring the availability and rational usage of second-line drugs and ancillary drugs for management of side effects
- Supporting the DOTS centers to conduct close contact tracing for DR-TB patients' homes and communities
- Serves as a member of the District Active Drug Safety Monitoring and Management aDSM Core Group.

10.11.4 DOTS site

The DOTS site has administrative and management responsibilities to ensure effective DR-TB services in the area. This will be integrated with the treatment of other TB and HIV patients.

The primary functions of the DOTS site are as follows:

1. Identify presumptive TB cases for screening
2. Arrange referral of sputum samples for testing
3. Trace patients with a confirmed diagnosis of DR-TB
4. Notify the district TB supervisor of presumptive and confirmed DR-TB cases
5. Test for HIV among presumptive and confirmed DR-TB cases
6. Conduct contact tracing, screening and investigation for all DR-TB contacts
7. Provide education on the DR-TB and monitor household infection control practices
8. Assess and implement infection control procedures in the facilities and promote their adoption in the household

10.11.5 Community level: DOTS Supporter

The DOTS supporter may be community caregivers, community health workers, or in some cases, a family member, although it is strongly recommended that family members do not serve as primary DOTS supporters. DR-TB treatment is long and often difficult for patients, and it can be hard for family members to insist on patients taking their medication when they do not want to.

Training is important for the DOTS supporters, they should be trained on the natural history of DR-TB and on basic infection control (e.g., cough hygiene), DR-TB medications, common side effects and symptoms of toxicity, and the role of HIV in TB infection.

10.12 Pre-management care at DOTS Centre

Ambulatory management is recommended for DR-TB patients. However, when that is not possible, patients can be referred to a health facility where health staff are trained. When such is to be done, the healthcare worker managing the patient (DOTS staff) must do the following, before sending the patient to the DR-TB treatment center:

1. Inform the district TB supervisor immediately;
2. Educate the patient and family member on the disease, its treatment (including duration and admission procedure), the importance of treatment adherence, and protection of other family members;
3. Address any concerns the patient might have;
4. Fill out the patient referral form;
5. Perform household screening and
6. Refer the patient to the DR-TB treatment Unit (use the form: Referral of presumptive RR/MDR patient for testing).

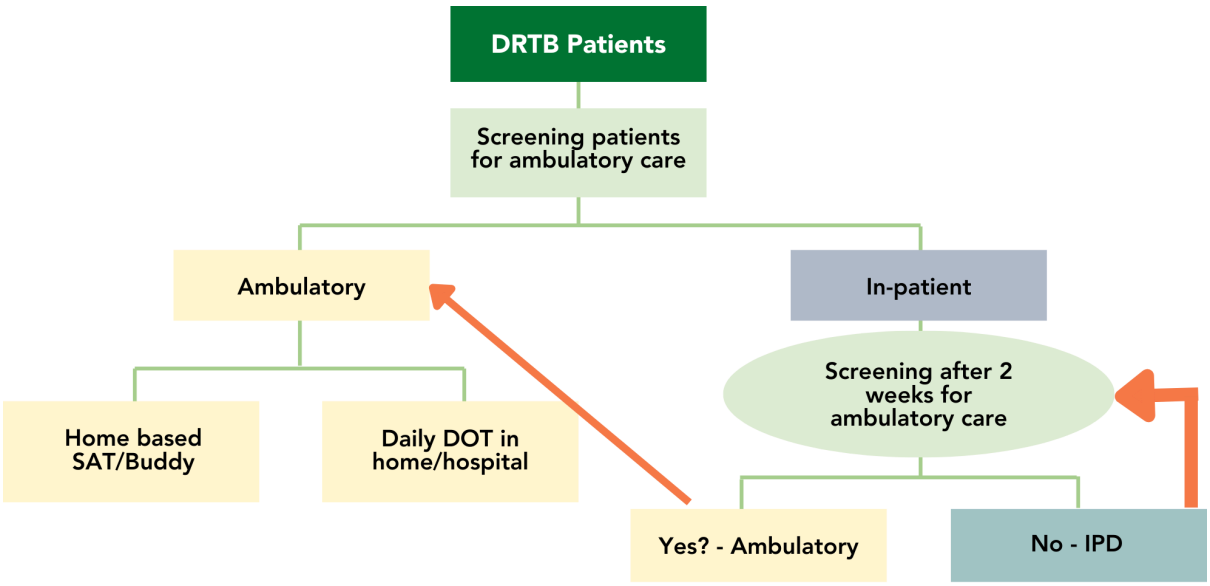
> The district supervisor/health centre staff must immediately inform the hospital about the DR-TB patient and arrange the referral to the nearest treatment facility.

10.13 Models of Care for DR-TB Patients

Provision of care for DR-TB patients should be in a person-centered manner, making it easier for all patients to access medications and treatment support and for TB treatment to be less disruptive to their lives. This includes the option of ambulatory care, accompanied by appropriate treatment supervision, patient education and social support, and infection control practices.

However, sometimes patients do require treatment in the hospital (inpatient), especially if with severe disease or treatment complications. The procedures below should guide the model of care modality.

Figure 13: Models of DR-TB care



10.13.1. Ambulatory care

Criteria for inclusion for ambulatory care

- Any patient on treatment of RR/MDR-TB, independent of age or HIV status, taking all oral medications.
- Able and willing to attend Bi weekly or monthly follow-up visits.
- Stable patient. No close monitoring is required, hospitalization is not recommended by treatment clinician.
- Patient has received psychosocial education and counselling, and was assessed for adherence and treatment readiness.
- Has a dedicated treatment buddy who has received training on psychosocial support and adherence and TB medications.
- Appropriate infection prevention and control conditions in the living place, whenever possible accompanied by home visits by treating team.

Exclusion criteria for ambulatory care

- Patient is very ill (e.g., bed bound, complications of TB like pneumothoraxes or pleural effusions that may require surgical intervention, , severe anemia)
- Has any of the following danger signs:
    - Respiratory rate > 30/min, Temperature > 39°C, Heart rate > 120/min, Systolic BP < 90mm Hg, Saturation < 90%, Moderate/severe dehydration, Unable to walk unaided, Altered mental state: confusion, strange behaviour, reduced level of consciousness, Any significant neurological problem.
- Has comorbidities (Severe liver disease, Uncontrolled DM, Hypertension, Advanced HIV disease with other opportunistic diseases, severe renal Insufficiency, Severe Anemia, and others) that required close observation and admission
- Patient does not meet other criteria for ambulatory care (eg, cannot attend for monthly follow up appointments, or no treatment buddy)
- Mentally unstable patients, psychosis, severe depression etc.
- Severe psychosocial condition, without family support, and living far away from the hospital.
- In the above scenarios patients will be treated as an in-patient until the criteria for ambulatory care are met.

10.13.2 Ambulatory Care Alternatives

The following are possible scenarios for ambulatory treatment of MDR TB patients:

1. Ambulatory DOT treatment in the TB Department of the hospital/ DOT sites
2. Home based Ambulatory care model with buddy support in the Home/community (after two weeks of Hospitalization)

Ambulatory DOT treatment at DRTB Clinic sites

In this model, patients may receive ambulatory treatment since day one of treatment.

Criteria for selection:

- Patient who can travel to the facility every day for directly observed therapy
- Patients who stay near the health care facility (< 5 Km)
- Patients who have no identified treatment buddy, or prefer to receive treatment from the DOTS centre

- Patients who had psychosocial and adherence assessment, without any issues identified

Home based ambulatory care model with buddy support (after two weeks of hospitalization)

Under this model patients receive full course of treatment under direct observation on ambulatory basis.

Criteria for selection:

- Patients who are tolerating treatment well, without adverse event needing constant monitoring
- Patients who live far distance (>5 kms) from the medical facility for DOT
- Patients whose community MDR TB supporter (treatment buddy) is trained and adheres to TB infection prevention and control
- Patients who can travel monthly for follow up appointments

In this scenario, patients receive DOT at home or in another venue chosen by the patient, being observed by DR-TB treatment supporter – treatment buddy. Patient and treatment buddy receive TB drugs supply for 1 month with 2 days buffer. Treatment buddy is responsible for providing DOT of DR TB patient, encouraging adherence, monitoring for adverse drug reactions, and contacting the treatment center if any problems arise.

For the home based care patients, counsellor organizes teleconsultation on weekly basis or home visit will be conducted on need basis.

10.14 Procedures for Patients on Ambulatory Care

For monthly follow up, examinations and laboratory testing, patient come to the hospital together with treatment buddy (as available). Transportation cost of patient and treatment buddy should be supported by the TB program and its partners.

When patient comes for their monthly follow up appointment at the hospital, two sputum samples and blood are collected. Clinical consultation and monitoring tests are performed. DR-TB treatment card should be checked by a nurse and pharmacist for the previous month. TB drugs for one month + 2 days buffer drugs should be given for patient and treatment buddy.

Weekly or Bi weekly home visit by CHW to identify any new adherence issues and continue to provide structured support. Any challenges identified are communicated to the clinical team for review.

10.15 Special Populations

Treatment buddy of children with DRTB, usually the mother or other guardian, receive detailed training and support on how to administer medications, and ways of supporting the children to adhere to treatment.

10.16. Management Of Adverse Effects And Pharmacovigilance

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.

10.16.1. 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 on the potential for adverse drug effects before starting treatment:
    - Review the common adverse effects associated with each prescribed medication 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.
    - Stress on early warning signs of important complications requiring immediate medical attention. Remember to reassure the patient that the majority of adverse effects are temporary and will improve over time.
    - Engage treatment supporter/family members on early identification and reporting.
- 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.

10.16.2. 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.

Table 40: 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 treatment hospital 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, 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 of the offending drug with regimen modification • Consult senior expert in the subsequent patient's management.

10.16.3 Being vigilant and detecting adverse drug events

Patients and health staff 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.

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.

10.16.4 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.

10.16.5 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 or
- 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.

10.16.6 Timelines of reporting (when to report)

Any suspected adverse drug reaction 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.

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

Adverse reactions are a sognificant 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.

- 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.
- 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.

Objectives of aDSM

- 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

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

All Serious Adverse Events (SAEs) detected should be reported to the national authority responsible for pharmacovigilance and should be regularly assessed for causality.

11 TB/HIV COLLABORATION AND OTHER COMORBIDITIES

11.1 TB/HIV Collaborative activities

This chapter describes protocols for:

- HIV testing and counselling for all patients known or presumed to have TB;
- HIV prevention for TB patients;
- ART for TB patients with HIV
- TB prevention for people with HIV
- Treatment of TB among people living with HIV;
- Infants, Children and adolescents
- Adults
- Providing co-trimoxazole preventive therapy to people with HIV and TB

HIV is a major risk factor for developing TB, and accounts for more than 25% of all TB deaths and causes one third of all HIV related deaths. In Sierra Leone, some hospitals in the country estimated 13.6% of deaths among PLHIV to be attributed to TB (Lakoh et al. 2019). Data from 2016-2023 estimated the TB/HIV coinfection rate at an average 14% per annum in the country. (Program Data).

People living with HIV are more likely to have TB and are at a greater risk of extrapulmonary and sputum smear-negative or Xpert MTB not detected TB, especially in advanced disease. This can result in under and misdiagnosis, and in turn, higher morbidity and mortality. Implementing HIV associated TB protocols and guidelines requires sound policy frameworks and the collaboration between TB and HIV programmes at all levels of health care delivery that will result in the reduction of the burden of TB among people living with HIV and vice versa.

The WHO TB/HIV policy guidelines provide for three main collaborative activities.

a. **Establish and Strengthen the mechanisms for delivering integrated TB and HIV services.**
b. **Reduce the burden of TB in people living with HIV and initiate early anti-retroviral therapy (the 3Is for HIV/TB).**
c. **Reduce the burden of HIV in people with presumptive and diagnosed TB.**

11.2 Collaboration and coordination between TB and HIV programmes

TB and HIV programme at all levels (National, Regional, District and Health Facility) should collaborate to address the dual epidemic of TB and HIV.

The Goal for the TB/HIV collaborative activities in Sierra Leone is to reduce the burden of TB and HIV in people at risk or affected by both diseases.

The objectives of TB/HIV collaboration are:

1. To establish and strengthen the mechanisms of collaboration and joint management between HIV and TB-control programmes for delivering integrated TB and HIV services preferably at the same time and location.
2. To reduce the burden of TB in people living with HIV, their families and communities by ensuring the delivery of the Three I's for HIV/TB and the early initiation of ART in line with the national guidelines.
3. To reduce the burden of HIV in people with presumed and confirmed TB, their families and communities by providing HIV prevention, diagnosis and treatment.

11.3 Integrated TB/HIV Services

Controlling TB/HIV requires collaboration and coordination between the TB and HIV programmes at all levels. Service integration should include full integration of the TB and HIV services in a clinic as much as possible.

In order to minimize the burden to the patient it is recommended that the patient receives both TB and ARV medicines from one health facility nearest to his/her home or workplace. Antiretroviral (ARV) drug collection should therefore be made accessible in health facilities that also offer TB therapy, or vice versa.

The package of services provided in any integrated TB/HIV service point will include:

- Provider-initiated HIV testing and counselling (PITC) for presumptive and confirmed TB patients.
- TB symptoms screening of all PLHIV for active TB at every visit.
- Diagnostic evaluation for all identified PLHIV with presumptive TB using Xpert MTB/Rif Ultra, X-ray, TB LAM, etc.
- Provision of TB preventive therapy (TPT) to all eligible PLHIV.
- Provision of co-trimoxazole preventive therapy (CPT) to co-infected patients.
- Early initiation of ART in all PLHIVs with TB.
- Immediate initiation of TB treatment in PLHIV infected with TB.

These services should be provided in a setting with optimal TB infection control measures.

11.4 Reducing the burden of TB in people living with HIV

At each contact with a HIV patient, heath service provider should screen for TB using Integrated Symptom-based screening and/or CXR, by asking and documenting the following among adults and adolescents:

1. Current cough (of any duration)
2. Fever of any duration
3. Weight loss
4. Excessive night sweats

For all populations (adults, adolescents, children and infants) PLHIV that answer yes to any of the above, should be investigated for TB disease using national diagnostic algorithm (Fig 9). PLHIV that answer no to all the parameters above are eligible for TB preventive treatment in the absence of contraindications (SEE ALGORITHM for TPT)

11.4.1 Intensified TB screening among PLHIVs

The screening for TB among PLHIV improves the patient-initiated pathway to TB diagnosis. This ensures identification of presumptive TB cases for further TB diagnostic evaluation, early detection of TB, prompt initiation of treatment to improve health outcome and reduce TB transmission.

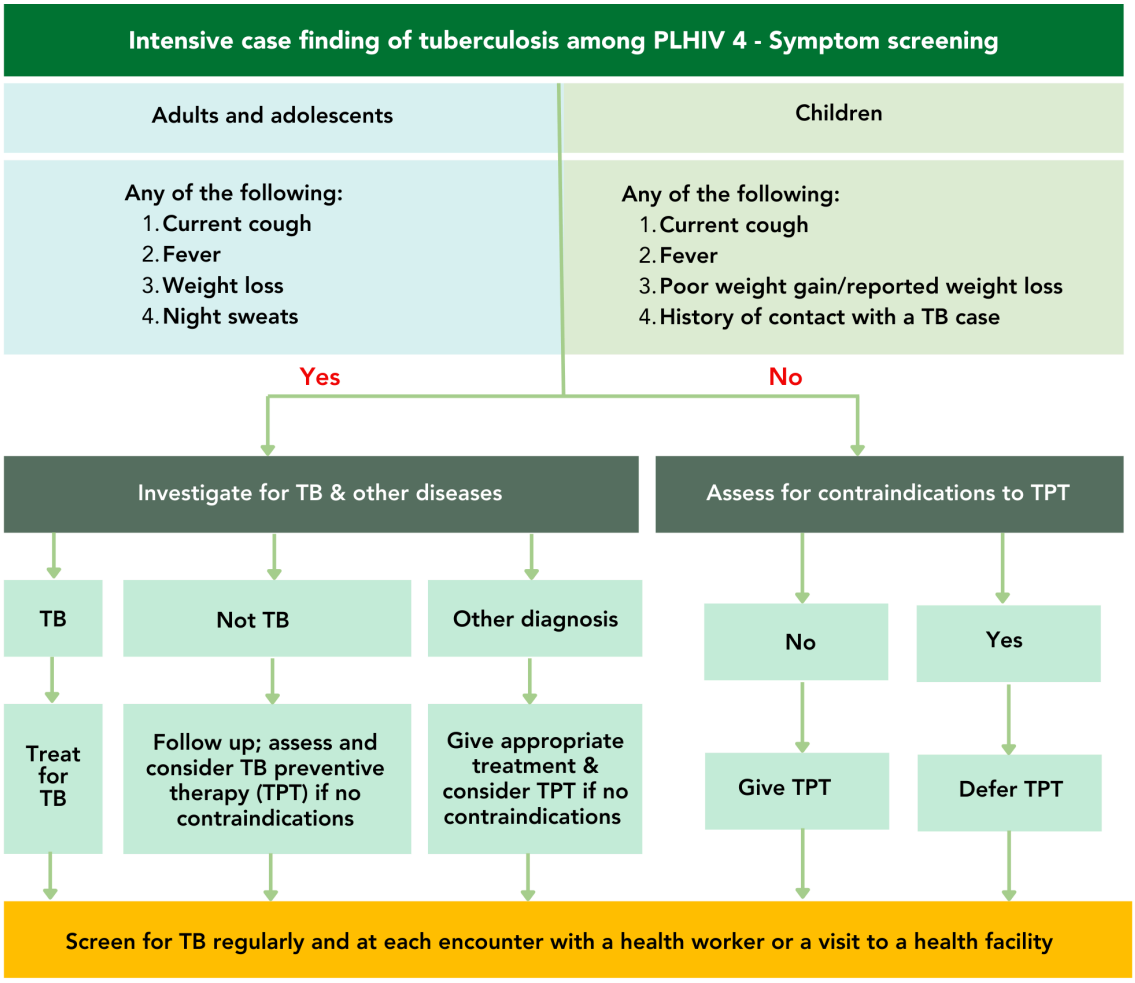
Chest X-ray (CXR) in combination with symptom screening has a highest sensitivity for detecting TB. Hence the need to strengthen effective TB screening among PLHIV at all visits and particularly at enrollment.

Recommendation for TB screening among PLHIV

- At point of enrollment into care: PLHIV should be screened for TB using both symptomatic checklist and chest X-ray.
- At every follow up visits: All PLHIV should be screened for TB using symptomatic checklist.

The algorithm for symptomatic screening among PLHIVs is shown in figure 8.

Figure 14: Algorithm for TB screening among adults, adolescents, children and infants living with HIV



Chest-Xray

Chest X-rays should be requested among people with HIV where available and feasible particularly for those that are symptomatic during routine follow up visits.

Computer aided detection of TB

According to 2021 WHO guidelines, computer aided detection software programs may be used in place of human readers for interpreting digital chest x-rays for screening and triage for TB disease.

11.4.2 Diagnosis of TB in PLHIVs

Diagnosis of TB in PLHIV is the same as in those without HIV infection. The primary diagnostic tool for TB in Sierra Leone is **Xpert MTB/Rif Ultra or Xpert MTB/Rif.** In situation where access to Xpert MTB/Rif Ultra or XpertMTB/Rif is still limited, all efforts must be made to ensure that samples from PLHIVs who have presumptive TB are transported to a site with **Xpert MTB/Rif Ultra or Xpert MTB/Rif** test as a priority.

Figure 15: Diagnostic pathway for TB in PLHIV

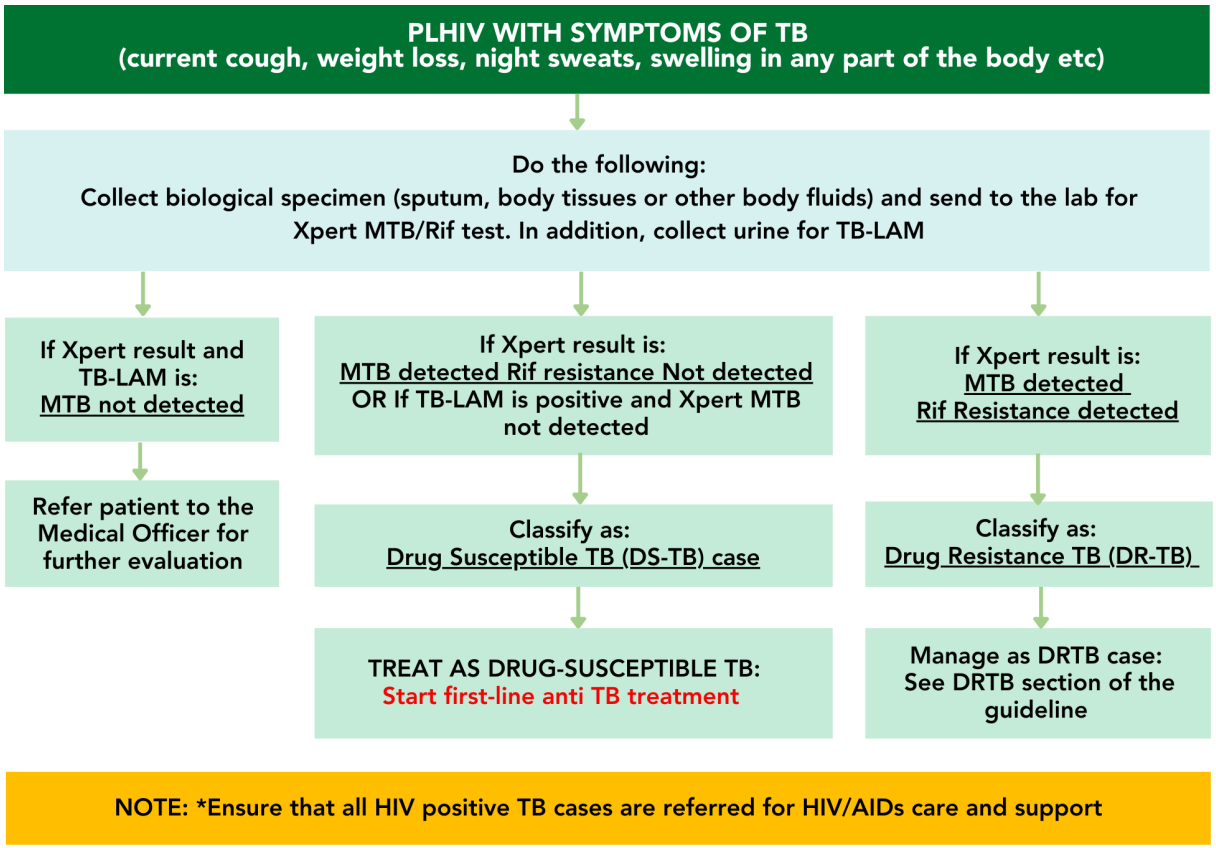


Table 41: Diagnosis of TB in PLHIVs

Diagnostic tests	Pulmonary TB sample	Extrapulmonary TB sample	Rifampicin resistance	Isoniazid resistance
Xpert®MTB/RIF	• Sputum • Gastric aspirate, • Nasopharyngeal aspirates, • Stool	• Meningitis; cerebrospinal fluid • Lymphadenopathy; lymph node aspirate, lymph node biopsy • Disseminated TB; blood • Other extrapulmonary: • Pleural fluid or • Peritoneal fluid or • Pericardial fluid or • Synovial fluid or • Urine	Yes	No
Xpert® MTB/RIF Ultra	• Sputum • Gastric aspirate • Nasopharyngeal aspirates, • Stool	• Meningitis; cerebrospinal fluid • Lymphadenopathy; lymph node aspirate, lymph node biopsy • Disseminated TB; blood • Other extra-pulmonary: • Pleural fluid or • Peritoneal fluid or • Pericardial fluid or • Synovial fluid o • Urine	Yes	No
Urine LF-LAM	• People living with HIV only (adults, adolescents and children) with • signs and symptoms of TB or • advanced HIV disease or • CD4 count<200 for inpatients • CD4 count <100 for asymptomatic outpatients • Urine sample	• People living with HIV only (adults, adolescents and children) with ○ signs and symptoms of TB or ○ advanced HIV disease or ○ CD4 count<200 for inpatients ○ CD4 count <100 for asymptomatic outpatients ○ Urine sample	No	No

In inpatient settings, LF-LAM can assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:

- with signs and symptoms of TB (pulmonary and/or extrapulmonary)
- with advanced HIV disease or who are seriously ill (respiratory rate of 30 and above, heart rate of 120 and above, temperature ≥ 390C and bed-ridden)
- irrespective of signs and symptoms of TB and with a CD4 cell count of less than 200 cells/mm3

In outpatient settings, LF-LAM is used in the diagnosis of active TB in adults, adolescents and children living with HIV.

- with signs and symptoms of TB (pulmonary and/or extrapulmonary) or seriously ill
- asymptomatic clients and with a CD4 cell count of less than 100 cells/mm3

Note:

LF-LAM should not be used as a replacement to mWRD tests such as Xpert MTB/RIF. mWRD should be used in all patients that are diagnosed using other modalities when feasible as it additionally detect rifampicin resistance. LF-LAM should not be relied upon to rule out TB disease (e.g. prior to TPT initiation) as it has very low sensitivity.

11.5 Diagnosis of Extra pulmonary TB (EPTB) in People with HIV

Extra pulmonary TB is TB outside the lungs. It accounts for about 15-25% of all cases of TB. HIV patients especially with low CD4 counts have higher rates of EPTB. Health care workers should have a high index of suspicion and comprehensively evaluate patients clinically. The symptoms and signs usually depend on the affected organ system as shown in Table 40.

Table 42: EPTB diagnostic approaches in people with HIV

Type of EPTB	Evidence strongly suggestive of EPTB	Investigations and recommendations
Lymph node TB	• 2cm or more in size, asymmetrical/ localized; painless swelling; firm/ fluctuant; may cause fistula, • Cervical location is more common • Patient presents with night sweats, weight loss, fever	• LN aspirate for Xpert MTB/RIF or FNAC • Start Anti-TB therapy
Pleural TB	• One of the most common forms of EPTB • Often asymptomatic especially if < 300 mls • Shortness of breath and chest pain (often unilateral) • Constitutional symptoms may be present. • Sputum production and cough are present in case of concurrent PTB • Effusion can progress to tuberculous empyema (purulent fluid with many bacilli)	• Chest X-ray • Pleural aspirate for GeneXpert • Start Anti-TB as soon as possible
Tuberculous Meningitis	• It is a serious form of TB that affects the meninges • Most common in children under 2 years and HIV infected patients • Any delay in diagnosis or treatment results in irreversible neurological sequelae or death • Typically has a sub-acute insidious course over days or weeks. • Symptoms include headache, irritability, fever, vomiting and altered mental status. • Meningeal syndrome (Stiff neck, hypotonia in infants, photophobia and headache) is usually present in most cases. • Cranial nerve palsy may occur eg. third nerve palsy	• Lumbar puncture for CSF Xpert MTB/RIF • CSF analysis (High protein, low glucose, Lymphocytes) • Exclude other causes of meningitis • MRI/CT scan (if available) • Chest X-ray may show a clue of miliary picture • Start Anti-TB immediately at any suspicion of TB meningitis • Delay ART for 4-6 weeks of anti-TB therapy if newly diagnosed with HIV. • High dose steroids as adjuvant therapy Prednisolone 1-2 mg/kg daily (maximum 60mg daily) for three weeks and then taper at 25% of the original dose per week for three weeks. Alternatively, dexamethasone at a dose of 8-16 mg/kg/day divided into three doses can be used when the patient is unable to take oral drugs.

Type of EPTB	Evidence strongly suggestive of EPTB	Investigations and recommendations
TB of joints and bones	• Up to 40% of patients with bone and/or joint TB have concurrent PTB • Spinal TB (Spondylodiscitis or Pott's) • Affects vertebra and intervertebral discs. • Thoracic spine is the most frequently affected • May present with localized back pain, paralysis may develop • Arthritis • **Most frequently** causes a chronic monoarthritis which starts insidiously • There may be little or no pain followed by joint destruction • Most affected are the hips, knees, elbows and wrists • Osteitis • **Least common** presentation of TB of the bones. • May be primary Osteitis or secondary to TB arthritis. • Typically, long bones are affected • Cold abscesses may occur occasionally	• Imaging of the affected bones or joints (X-ray, CT scan, MRI) • FNA of vertebral lesions and/ paraspinous abscesses when feasible. • Start Anti-TB • High dose steroids • Physiotherapy in case of neurological deficits • Confirmation of diagnosis should not delay initiation of treatment
Tuberculous Pericardial effusion	• Clinical signs include chest pain, shortness of breath, edema of the lower limbs, and sometimes ascites • Exam may reveal pericardial friction rub, raised jugular venous pressure, and tachycardia	• Chest X-ray • Cardiac ultrasound • Pericardiocentesis may be necessary in case of acute heart failure with hemodynamic compromise • Start Anti-TB IMMEDIATELY
Abdominal Tuberculosis	• Usually presents as ascites. • May present as an abdominal mass (Often right lower quadrant), pain and diarrhoea may be present. • Constitutional symptoms may be present.	• Abdominal USS • Paracentesis and analyze fluid with GeneXpert. • If no other possible causes start Anti-TBs
Urogenital TB	• Renal involvement is frequent and may be asymptomatic. • Signs and symptoms may develop slowly including • Dysuria, Urinary urgency and frequency, back/abdominal pain, tenderness/swelling of the testes, or epididymitis, or hematuria.	• Urinalysis may reveal pyuria (WBCs in urine) and micro or macroscopic hematuria which doesn't respond to antibiotics

Note:

LF-LAM can be used to diagnose all cases of EPTB where it is not feasible to use Genexpert. According to WHO recommended algorithms, a positive LF_LAM result can be used to initiate TB treatment, while other investigations are ongoing (with mWRDs or culture).

11.6. Treatment of TB among PLHIVs

Treatment of TB among PLHIV and those without HIV infection is essentially the same. However, the following will be taken into consideration when treating TB among PLHIVs.

a. TB treatment should be initiated first, followed by ART as soon as possible within the first 2 weeks of TB treatment. However, HIV-positive TB patients with profound immunosuppression (e.g. CD4 cell counts less than 50 cells/mm3) should receive ART preferably same-day but no later than seven days after initiating TB treatment with optimal regimens , after exclusion of TB meningitis.

b. For patients on rifampicin-based anti-TB combinations, avoid the use of most Protease Inhibitors (PIs) [eg., atazanavir/ritonavir (ATV/r)]. If DTG is to be used, the dose should be doubled, with the second dose administered separately (12 hours apart).

c. Patients on ART who develop TB should have the ARVs reviewed to accommodate the use of rifampicin in the anti-TB regimen.

d. Efavirenz cannot be used with Badaquiline (BDQ), as it decreases the concentration of BDQ.

e. Delamanid is generally considered safe to be administered with ART.

Refer to Table 41 below for different case scenarios involved in the management of TB/HIV co-infected patient.

Table 43: HIV-associated TB case scenarios and recommended management of TB

Scenario	TB management	Recommended ART
Pregnant, on ART and develops TB	Start anti-TB treatment immediately (ATT)	• If on EFV-based ART, continue with same regimen; If on DTG-based like TLD, the dose should be doubled, with the second dose administered separately (12 hours apart) Evaluate for failure.
Pregnant, on ATT, and diagnosed with HIV	Continue ATT	• Start ART immediately within 2 weeks TDF + 3TC + DTG* (add DTG 50mg to be given after 12 hours of TLD tablet daily if single DTG tablet is available)
Children 4 weeks to <10 years old with TB-HIV co-infection	Start ATT (RHEZ) immediately	• ABC + 3TC + DTG (DTG twice daily)
Newly diagnosed TB and HIV co-infection TB retreatment case and HIV co-infection	Start ATT immediately	• Start ART as soon as ATT is tolerated (usually within 2weeks) regardless of CD4 count or WHO Clinical Staging • TDF + 3TC + DTG* (DTG 50mg twice daily if single DTG tablet is available). ***If single tablet not available, give:*** • TDF + 3TC + EFV-400mg
On ART and develops TB	Start ATT immediately	• TDF + 3TC + DTG* (DTG 50mg twice daily if single DTG tablet is available). • TDF + 3TC + DTG(TLD)* (DTG 50mg 12 hours after the TLD fixed dose combination should be added if single DTG tablet is available). • If on ATV-r, switch ATV-r to DTG 50mg 12 hourly if DTG naïve. If DTG single tablet not available, give LPV-r and double the dose If on LPV-r, double dose of LPV-r • Evaluate for failure.

Scenario	TB management	Recommended ART
On ATT and diagnosed with HIV	Continue ATT	• Start ART as soon as ATT is tolerated (usually within 2 weeks), regardless of CD4 count or WHO clinical staging • TDF + 3TC + DTG (TLD) - DTG 50mg 12 hours after the TLD fixed dose combination if single DTG tablet is available).
On 2nd line ART with LPV-r and develops TB	Start ATT per guidelines immediately	• Switch LPV-r to DTG 50mg 12 hourly if DTG naive • ***If single DTG tablet not available*** increase LPV-r from 2 tabs BD to 4 tabs BD . If Rifabutin available (in place of Rifampicin), start at 150mg Monday/Wednesday/Friday

- *Patients on TB treatment should be initiated on TDF + 3TC + DTG. Take note that a 50mg DTG tablet in this case should be given 12 hours apart with the TDF + 3TC + DTG fixed dose combination*
- *REMEMBER to switch back to DTG 50mg once daily and LPV-r 2 tabs twice daily after TB treatment!*
- *Patients on ART on TAF who develop TB, the TAF should be switched to ABC. If there is normal renal function or above 30kg, switch to TDF*
- *People with HIV associated TB should receive ART within the first two weeks of initiating TB treatment*
- *If Rifabutin is available, use the same PI or DTG-based regimens as recommended for adults and adolescents.*
- *LPV-r and BDQ co-administration should be avoided*
- *Use LPV-r in First-Line or Second-Line ART if DTG not available or contraindicated*

11.7 TB Preventive Therapy (TPT)

TPT is the use of anti-TB medicines to prevent the development of active TB disease among PLHIV. TPT reduces HIV associated TB death and is therefore recommended as part of care package for PLHIVs without Active TB. Treatment can be:

- INH - daily dosage for 6months
- Rifapentine and INH (3HP) - weekly dosage for 3 months

Refer to section for detail on TPT Chapter 7.

11.8 Ensure control of TB Infection in health-care facilities and congregate settings

TB infection control is defined as a combination of measures aimed at minimizing the risk of TB transmission within populations. The foundation of infection control is early and rapid diagnosis, and proper management of TB patients. TB infection control requires and complements implementation of core activities in TB control, HIV control and health-systems strengthening. Details see chapter 7. TB infection control is growing in importance because of the association of TB with HIV and the emergence of multi drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB).

11.9 To reduce the burden of HIV in patients with presumptive and diagnosed TB, their families and communities by providing HIV prevention, diagnosis and treatment.

All patients who present with signs or symptoms that suggest TB or already confirmed should be tested for HIV. TB services are an important entry point to HIV prevention, treatment and care.

Detecting HIV infection in a TB patient is also critical for the TB patient's household members: HIV-

positive TB patients may have household members who are also living with HIV. Counselling and HIV testing should be done for immediate family members of all children and adults co-infected with TB/HIV.

For patients known or presumed to have TB, provider-initiated HIV testing should be done as a standard component of care. This is more efficient and more likely to result in patients learning of their HIV status, than referring them for HIV counselling and testing. A one-stop shop mechanism should be in all facilities providing both HIV and TB testing. If this is not possible, linkage and referral should be provided to achieve the goal of managing both HIV and TB. Presumptive TB cases who test positive for HIV but negative for TB should be linked to comprehensive HIV treatment and care services.

Appropriate prevention messages and methods should be provided to patients with confirmed or presumptive TB, according to their HIV status and local knowledge of the modes of transmission or assessment of risk. Education on abstinence, behavioral change and consistent and appropriate condom use should be provided. Among Key Population groups, transmission-based precautions should be applied in line with the consolidated national guidelines for the prevention, treatment and care of HIV.

11.10 Overlapping ARV and TB drug side effects

Concurrent use of ARVs and TB drugs has potential for added toxicity. The most common causes of skin rashes are pyrazinamide, isoniazid and rifampicin. ARVs such as Nevirapine and Efavirenz are also known to cause skin rashes. These overlapping side effects make it difficult to identify the causative drug when a patient is receiving treatment for both TB and HIV con-currently. Patients on both treatments need a thorough history and clinical assessment to establish which drug is responsible for the side effects.

11.11 Immune reconstitution inflammatory syndrome (IRIS)

A HIV-positive patient's condition could worsen within the first 6 months of starting ART because of IRIS. IRIS is as a result of recovery of the body's immune system. There are two common IRIS scenarios:

- An unmasking of an occult opportunistic infection,
- A paradoxical symptomatic relapse or worsening of a prior infection that was seemingly diagnosed and treated successfully.

Before starting ART, counsel TB patients about the possibility of a temporary worsening of symptoms. Occasionally a TB/HIV co-infected patient may experience a temporary worsening of TB symptoms soon after beginning ART and TB treatment. IRIS should be considered as a potential cause of such clinical worsening.

- Signs and symptoms include:
    - high fever;
    - lymphadenopathy; and
    - worsening CXR findings.
- Other causes of clinical worsening should be ruled out before making a diagnosis of IRIS; these include:
    - Undiagnosed TB disease;
    - Cryptococcal meningitis; and
    - Kaposi Sarcoma.
- Patients with advanced AIDS who start ART late are at the greatest risk of developing IRIS.

Any patient with symptoms of IRIS at primary health care facility should be referred to secondary or tertiary health facility for appropriate care.

- If a patient develops IRIS while on anti-TB treatment and ART:
    - Seek the advice of a senior ART provider or medical specialist.
    - There is no need to stop or change TB or ARV treatment.
    - Confirm that the patient adheres to his or her medication regimen as prescribed.
    - Admit severe cases to hospital.
- If treatment with steroids is indicated:
    - Give dexamethasone 8 – 16 mg/day (divided into twice daily dosing) or prednisolone 1 mg/kg body weight (once daily) for 14 – 21 days.
    - After 14 – 21 days, rapidly taper the steroids over a 10 – 14-day period while monitoring for recurrence and/or worsening of symptoms.
- Consider TB treatment failure or DR-TB if the patient's condition worsens despite having received one or more months of anti-TB treatment.

Note:

Immune Reconstitution Inflammatory Syndrome (IRIS) can occur in patients with very low CD4 cell count.

11.12 Provision of co-trimoxazole preventive therapy (CPT)

- All HIV-positive TB patients should be started on CPT to reduce the occurrence of opportunistic infections.
    - If possible, CPT should be started on the same day that the patient's HIV-positive status is determined.
    - The recommended dosage for trimethoprim-sulphamethoxazole (cotrimoxazole) is 960mg daily for adults and 60mg/kg for children not exceeding 960mg.
    - Contraindications to cotrimoxazole include:
        - Known severe drug reaction to sulphur-containing drugs,
        - Severe anaemia,
        - End-stage renal disease.
        - First trimester of pregnancy

Note:

1. HIV positive TB cases on CPT should be evaluated for continuum of care after TB treatment at the HIV services delivery site.
2. Refer to the national HIV treatment guidelines for further information.

11.13 Management of HIV associated TB in children

A comprehensive approach to diagnosis and integrated (family/household-centred) management of both TB and HIV is critical. Approach to diagnosis of TB in HIV-infected children is the same for HIV-uninfected children. Xpert MTB/RIF Ultra is the preferred diagnostic test for children presumed to have TB (PTB or EPTB), DR-TB and HIV-associated TB. However, AFB microscopy should be used where Xpert MTB/RIF Ultra is not immediately available or not accessible with short Turn-Around Time (TAT) and for treatment monitoring.

TB/HIV co-infection in children should be managed as follows:

- All children with presumed or confirmed TB should be tested for HIV

- All HIV-infected children should be screened for TB disease (including use of chest x-ray)
- Specimens from HIV-infected children should be sent for Xpert MTB/RIF Ultra onsite or by sample referral.
- TB/HIV co-infected children should be commenced on anti-TB treatment immediately before initiating anti-retroviral therapy (ART)
- ART should be started as soon as Anti TB Treatment is tolerated (usually within 2 weeks) regardless of CD4 count or WHO Clinical Staging.
- Children with HIV/TB co-infection should be followed up regularly and should be started on co-trimoxazole preventive therapy (CPT) if there is no contraindication.
- HCWs should counsel clients, caregivers and family members for optimal adherence as well as provide psychosocial and nutritional support
- If TB disease is excluded in the HIV-positive child, TPT should be given to the child irrespective of age.
- Counsel and test all family/household members for HIV and TB
- Patients should be weighed at regular intervals and dosages should be adjusted as appropriate for weight.

Table 44: Management of TB/HIV co-Infected children

Scenario	Action
Children diagnosed with TB/HIV co-infection at presentation	• Start TB treatment immediately • Commence ART immediately within 2 weeks of anti-TB treatment irrespective of CD4 count • The need to start ART preferably same-day but no later than seven days after initiating TB treatment with optimal regimens, after exclusion of TB Meningitis is much more imperative in those with CD4 <50cells/mm^3
Known HIV-positive children on ART, newly diagnosed with TB	• If on ART for more than 6 months, rule out ART treatment failure. • If ART treatment failure, manage as appropriate or refer • If no ART failure, continue on ART but with modification of regimen if necessary. • Start anti-TB treatment immediately
Children on LPV/r-based ART regimen diagnosed with TB	• If on ART for more than 6 months, rule out ART treatment failure. • If ART treatment failure, manage as appropriate or refer • If no ART failure, continue on ART but with modification of regimen if necessary. • Initiate TB treatment with Rifabutin-containing regimen as loose drugs
Children on TB treatment diagnosed with HIV infection	• Consider new recommendations from NACP

**Please consider the new WHO recommendations on dolutegravir containing regimen*

- Every HCW managing a child with presumed TB should make all efforts to ensure bacteriological confirmation of TB.
- If bacteriological confirmation (Xpert MTB/RIF Ultra, AFB smear microscopy or culture) is not possible, where the expertise is available HCWs should make clinical diagnosis supported by other evidences (e.g. chest x-ray or histology)

12. PATIENT-CENTERED CARE AND SUPPORT AND ADHERENCE TO TREATMENT

12.1 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, psychosocial, economic consequences but also from long-term sequela 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.

12.2 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 and address inequalities faced by TB/DR-TB patients and their families.

12.2.1 Directly Observed Treatment

Directly observed treatment (DOT) refers to any person observing the patient taking medications in real time to ensure a TB patient takes the right anti-tuberculosis medicines, in the right doses, at the right intervals for the sufficient period of treatment. Adherence in general was defined as taking > 90% of medications under conditions of direct observation by another person. 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.

12.2.2 TB Treatment Supporters

The National recommendation to be a treatment observer includes a trained health worker, trained community health worker or a trained TB treatment supporter.

- TB Treatment Supporter (TTS) is a person identified by the patient and trained to directly observe the optimal administration of TB treatment outside the health facility. The designated supporter could be identified either from community health worker, family member, neighbour, workmates, or community figures.
- The process of identification of a TB Treatment supporter should consider acceptance of the person by the patient; Living/working in close proximity; willingness to supervise treatment on daily basis; readiness to assist in identifying and handling adherence problems, and consent to maintain confidentiality.
- The designated TB treatment supporter should be trained by the TB focal person on how to daily supervise treatment administration and record information on provided TTS card; Assist care-provider and patient in identifying and communicating any adherence barriers; and, Retrieval of TB patients if interrupted treatment.

12.3 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 patients on treatment whenever feasible and resource allows. Patient care and adherence support interventions packages should be tailored to the needs of individual patient's (or 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 followings interventions:

12.3.1 Patient and care providers' education

Every TB/DR-TB patient, along with their family and designated treatment supporter, must receive verbal and written education by the 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, conducting contact investigation, optimization of adherence to treatment and care. This also helps TB focal person to identify key affected and vulnerable as well as marginalized populations, assess the need for additional adherence support interventions.

Care providers education: The TB program is expected to periodically assist the TB care providers', including TB laboratory personnel to build their competency on effective communication skills with their clients, in order to comprehensively assess and understand the patients' living perspectives, to identify potential barriers to adherence 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.

12.3.2 Emotional and Psychological support

TB care providers, community health 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 psychological support at the most marginalized populations also helps to maximize health equity.

Collaboration with Mental health program is also important for effectiveness of the support.

12.3.3 Peer-group support

Former TB patients should be encouraged to take part in provision of continuous adherence and emotional support to patients on treatment through peer-group support platforms organized by care-providers and local TB officers. They should also be engaged TB stigma reduction activities, in promoting contact tracing, preventive and other community level social mobilization activities with the help of community health workers. This approach is also believed beneficial to reach specific marginalized populations.

12.3.4 Patient food insecurity Support

Patient food insecurity support packages aims to enable TB/DR-TB patients to overcome socio-economic hardships that might force patients to become poorly adherent, and even interrupt treatment. Cognizant of the multi-faceted burden to DR-TB patients on treatment in the light of the scarcity of resource, the national program has developed nutritional and socio-economic support packages to be provided to the eligible DR-TB patients as integral part of the comprehensive treatment services delivered for DR-TB patients.

12.3.5 Economic Strengthening

Once patient starts to feel better and ready to resume productive life, linkage with locally available economic strengthening initiatives is required to secure patients' and their family income in long term and avert the catastrophic economic impact of the disease.

12.4 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 with limited effective treatment options, such as those with XDR-TB, 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 M/XDR TB 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 reaction assessment and management.
- Management of complications of M/XDR TB like lung fibrosis, cor pulmonale, bronchiectasis, pneumothorax.
- Psychosocial and economic support.
- 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.

12.5 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 populations at risk to progress to TB in high TB burden settings.

12.5.1 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.

12.5.2 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 that 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
- On documenting unintentional loss of weight during TB treatment.

12.5.3 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 43 below is classification for adult patients using Body Mass Index (BMI).

Table 45: Malnutrition classification by body mass index (BMI) - for adults

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	

12.5.4 Nutritional Support

Nutritional 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 44).

Table 46: 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. #Plumpy 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.		

12.6 TB and Diabetes Mellitus

As the global prevalence of diabetes mellitus (DM) increases, especially in low-to-middle income countries where tuberculosis (TB) remains endemic, there is a growing number of TB patients with DM. This is a major concern for TB control programs, clinicians and patients alike because DM patients are at an increased risk of TB and are more likely to face poor TB treatment outcomes, including treatment failure, relapse and even death. 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 case detection before advanced progression of TB and the prevention of transmission through infection control.

Despite the increased risk of TB among those with poorly controlled diabetes and the benefit of TB preventive therapy, there is no current national policy on preventive therapy of latent TB infection (LTBI) in people diagnosed with DM. Standard course of TB treatment is recommended in patients with Diabetes Mellitus who develop Tuberculosis.

13. IMPLEMENTING TB INFECTION PREVENTION AND CONTROL MEASURES

TB infection control is defined as a combination of measures aimed at minimizing the risk of TB transmission within populations. The foundation of infection control is early and rapid diagnosis, and proper management of TB patients.

TB infection control requires and complements implementation of core activities in TB control, HIV control and health-systems strengthening.

TB infection control is growing in importance because of the association of TB with HIV and the emergence of Multi Drug Resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB).

13.1 Rationale for TB infection control:

- Persons with undiagnosed, untreated and potentially contagious TB are often seen in HIV care service points and other units in health care settings.
- Globally, up to 10% of persons with HIV infection may have previously undiagnosed TB at the time of HTS
- 30-40% of PLHIV living in high burden TB settings will develop TB in their lifetime, in the absence of TB preventive or ARV therapy.
- PLHIV-associated immunosuppressed may become infected or re-infected with TB if they are exposed to patient with infectious TB disease
- Health care workers and other staff are also at particularly high risk of infection with TB because of frequent exposure to patients with infectious TB disease.
- Current work environment especially ART and DOTs clinics are congested and poorly constructed.

13.5 Components of TB Infection Control

There are three main components of Tuberculosis infection control. They are:

- Work practice and administrative control measures.
- Environmental control measures.
- Personal protective measures.

In all, work practice and administration control measures have the greatest impact on preventing TB transmission. Environmental control measures provide further steps to reduce/eliminate risk of exposure. Personal protective measures should be used at high risk areas or during procedures e.g Lab personnel in MDR Labs, HCWs providing MDR services.

Work practice and administrative control measures

These serve as the first line of defense for preventing the spread of TB in health care settings. The aims are:

- To prevent TB exposure to staff, patients and visitors
- To reduce the spread of infection by ensuring rapid and recommended diagnostic investigation and treatment for patients and staff known to have TB.

These can best be accomplished through the prompt recognition, separation, provision of services, and referral of persons with potentially infectious TB disease (Find, Actively, Separate and Treat promptly – FAST Strategy).

Hand hygiene

Hand hygiene is the single most effective way to reduce the risk of spreading or acquiring infections in general, and a crucial procedure, even if not preventing air-borne diseases as TB. Hands are involved during handshakes, opening/closing of doors, touching of surfaces and our main tool for work. They are the key link in the chain of transmission. Hand hygiene reduces the spread of infectious agents, terminate outbreak and prevention of disease spread from person to person contact. There are five moments of hand hygiene, which includes

i. Before patient contact
ii. Before aseptic task
iii. After body fluid exposure task
iv. After patient contact
v. After contact with patient surroundings

Respiratory hygiene and cough etiquette

This measure helps

- To prevent transmission of respiratory infections in healthcare settings, including influenza, TB, COVID-19
- To reduce risk to unprotected persons at the first point of contact in facilities

Respiratory hygiene and cough etiquette applies to healthcare workers, patients and visitors and it involves

- Covering of nose and mouth when coughing or sneezing
- Coughing into flexed elbow.
- Contain respiratory secretions with disposable tissue and dispose appropriately
- Perform hand hygiene after contact with respiratory secretions and contaminated objects
- Encourage coughing persons to be seated away from others in common waiting areas (ideally, at least 3 feet/1meter from others), or ask them to wait outside

13.6 Recommended TB-IPC interventions at different service points:

13.6.1 General Out Patient Department (GOPD)

- Provide health education on TB and Infection Control (cough etiquette) daily
- Display appropriate IEC materials on IPC
- Ensure patient triage based on the facility setting and prompt services
- Separation of TB and HIV clinics where possible
- Ensure adequate ventilation in patients waiting area and consulting rooms.
- Provide adequate signage for patient's navigation within the facility.
- When examining TB patients or Presumptive TB case, ask them to turn their head away, to avoid coughing directly at the health worker.
- All staff should be encouraged to know their HIV status and those positive should be assigned to work in less risk areas.

13.6.2 DOTS clinic / Medical Wards

- Emphasize ambulatory treatment, where possible
- Minimize time in hospital ward, discharge patients as soon as their stable for ambulatory DOT
- Utilize community treatment models (treatment supporters) to decongest the facility
- Provide information on TB IPC (especially cough hygiene and ventilation) at home and within the community to patients/relatives during discharge
- Ensuring adherence to cough etiquette among patients
- Ensuring windows are always open for cross ventilation
- Ensure appropriate disposals of waste
- Children less than 6 years should not be allowed to visit patients in the wards
- Ensure restricted visit hours by relations, and relations should not be allowed to sleep overnight in the wards
- If possible, admit TB patients in separate ward from other patients.
- Avoid admission of HIV/AIDS case in same wards with TB patients

13.6.3 Laboratory

- Adherence to SOPs in the lab
- Sputum collection should be in an open space outside the laboratory
- Ensure adequate ventilation
- Ensure appropriate disposals of laboratory waste
- Reduction of turnaround time for sputum results to at most 48hours
- Use of appropriate personal protection especially in high risk units, e.g N95 respirator

13.6.4 Other service points: Records unit, pharmacy, X-Ray, other GOPDs

- Ensure availability and appropriate display of IEC materials on IPC
- Provision of health education on IPC
- Ensure adequate ventilation
- Ensure early identification of Presumptive TB case and prompt provision of services

Note: All health facilities should have:

- Infection prevention and control team
- Infection prevention and control plan
- M&E system for infection prevention and control

13.7 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 prevention and control behavior-change campaigns should be part of any community sensitization and education. The infection prevention control messages need to promote the importance of early identification of cases, cough etiquette and adherence to treatment.

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

To reduce exposure in households:

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

14. COMMUNITY BASED TB CARE, ACSM AND ENGAGING ALL CARE PROVIDER

14.1 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 TB control aims at empowering the community to improve its own health through community health program package services.

TB control is a complex undertaking and requires the collaborative efforts of a broad range of persons, organizations, and institutions both in and outside the public health sector. Key to improving the detection of TB cases is the community. This includes;

- Community members
- Non-Governmental Organizations (NGOs)
- Civil Society Organizations (CSOs) of all kinds, including community health programs, development organizations, religious groups, patient advocates, traditional healers, midwives, neighborhood associations, informal care providers and many more.

Decentralizing tuberculosis control measures beyond health facilities by harnessing the contribution of the community could;

- Increase access to effective tuberculosis care.
- Reduce barriers to success in tuberculosis control.
- Increase community awareness of tuberculosis and the benefits of treatment.
- Reduce stigma.
- Facilitate easy access to case-finding, diagnosis and treatment.
- Reduce the level of defaulting by tracing daily follow up.
- Help to achieve a high treatment success rate.

14.2 Community Structures for TB Control.

14.2.1 The role of the community

Communities can perform the following as shown below;

- Raising community awareness of TB and TB treatment
- TB Case detection, referral and contact/absentee/defaulter tracing
- Addressing stigma: direct and indirect approach
- Raising awareness to encourage compliance
- General support and education for treatment
- Direct observation of treatment in special circumstances and a strong supervision system

Table 47: Summary of potential for community involvement in tuberculosis control

Purpose of community involvement	Type of community involvement	Activity	Comments
Raising community awareness of TB and TB treatment.	Formal/informal	Delivery of messages to promote knowledge of TB symptoms and need for treatment completion.	Peer educators have limited usefulness
Case detection and referrals for diagnosis.	Formal	CHW surveillance	Combining diseases or activities make surveillance more cost-effective.
Providing access to drugs	Formal	CHWs as providers of TB drugs	Combining with a non-stigmatized disease or integrated with PHC programme increases social acceptability.
Addressing stigma: direct approach.	Formal/informal	Disseminating information through home care volunteers or through communication and discussion groups.	Patients, providers and the communities are involved in communication and discussions
Addressing stigma: Indirect approach	Formal	Integrating community-based TB control programmes with non-stigmatized health care programmes or PHC	
Raising awareness to encourage compliance	Formal/informal	Disseminating information and encourage compliance	Messages should address individual benefits of treatment completion and known side effects of treatment should explained.
General support	Formal/informal	Family support, peer groups and community volunteers to support patients throughout treatment.	Psychological support and assistance to delivery and collection of biological specimens, results and drugs
Direct observation of treatment.	Formal/informal	CHW, family members or other community members to observe patients taking medication.	The majority of innovative approaches are in the area of community-based TB control.
Recognition of adverse effects and tracing of patients who interrupt treatment.	Formal	CHW to identify and refer patients with adverse drug reactions. Community Volunteers to keep in contact with patients over the entire treatment period.	Early identification and referral improves compliance to treatment.
Documentation of progress and outcomes.	Formal/informal	Formation of HCW associations, use of manual and the contribution of school children or family members to read instructions.	Local community volunteers to provide services to favour disadvantaged communities.

14.2.2 Addressing stigma in TB Control

Stigma is a barrier that presents a serious obstacle to successful TB control. Health-seeking behavior is made up of a balance of costs and benefits to the patient. The benefits of getting well are unlikely to out-weigh the costs of social and family rejection and loss of employment and accommodation at the early stages of the disease.

Direct approach

A direct approach to address stigma in a society involves understanding and addressing the beliefs and attitudes of the community towards the disease through qualitative research and awareness campaigns.

Three strategies have been identified which could be applied to TB programmes:

- Involvement of patients, providers and the community in communication and discussion of TB
- The use of 'health care volunteers' to disseminate information about TB in communities
- The use of TB focused IEC/BCC messages based on qualitative research

The employment of these strategies should be considered to increase coverage of TB cases in areas where stigma is marked and treatment coverage low.

Indirect approach

An indirect method aims to lessen the effect of stigma on health services utilization and to improve treatment adherence without directly addressing community attitudes but by creating more socially accessible services. Examples from selected programmes have shown that, by associating the stigmatized disease with a non-stigmatized disease, treatment is found to be more acceptable.

14.3 Support and motivation of patients

TB treatment has a long duration, symptoms can subside before course completion, and the drugs prescribed can give side-effects. Patients who are aware of their diagnosis and have come forward for treatment require support and motivation to continue.

Community members are most conveniently placed to help support and motivate patients during their treatment regimens. Three ways of motivating patients to adhere to medication are :

- Raising awareness of the benefits of completing treatment.
- Providing general support.
- Directly observing patients taking their medication.

General support

As they are familiar with their patients and in close proximity to them, community members are well suited to the role of supporter. In TB control, home visits by community members and self-help groups are two strategies used to support patients treated in the community.

Volunteers from local community groups may be willing to support patients in the community without financial remuneration and only limited benefits. Peer groups are beneficial in TB control. Sharing fears, beliefs and experiences with other members of the group will be very beneficial.

In addition to enlisting family support, community members can be approached to volunteer as house-to house supporters for TB patients, and the patients themselves encouraged to establish self-help groups.

Direct observation of treatment

Organized community groups, peer groups, chosen members of the community and family members all have the potential to act as supervisors to ensure completion of treatment and cure by directly observing the patients in their communities.

Recognizing adverse effects and tracing patients who interrupt treatment

Patients suffering severe side-effects are likely to interrupt their treatment. The use of CHWs to recognize adverse drug reactions will be very helpful in TB treatment and care. Recognition and referral will enable the patients to continue treatment using alternative drug regimens.

Tracing patients who interrupt treatment in developing countries remains problematic. Community based TB supervisors maintaining close contact with patients can be more efficient than health services staff in tracing TB patients who interrupt treatment.

Documentation of progress and outcome

Information collection and recording are a vital component of TB control programmes. Involving communities in TB control will inevitably mean transferring some of this to community members. In many primary health care and disease control programmes, accurate and timely record keeping has been problematic. Nevertheless, some examples of innovative solutions may be applied to TB control:

- The use of manuals with pictures and symbols to replace word and numbers; for record keeping to enable illiterate or semi-literate community members to keep records accurately.
- The use of school children or literate family members or neighbors to read instructions and fill in records.

15. ENGAGING ALL HEALTH CARE PROVIDERS IN TB CONTROL

15.1 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 (PPM) for TB Care and Control represents a comprehensive approach for systematic involvement of all relevant healthcare providers in TB control activities. PPM 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 also implies engaging relevant care providers in prevention and management of TB/HIV co-infection and Drug Resistant-TB.

Public Private Mix is the involvement of all health care providers (public and private) as well as formal and informal health care in the provision of TB care. This should be in line with International Standards for TB Care. The NLTCP is aware that the private sector is most often the first point of contact for health services so it prioritizes the engagement of all care providers in the provision of TB services to ensure access to improved quality of care and strengthen TB case notification in the country. In addition, the TB programme is engaging the private sector in order to ensure all health care providers provide TB care and control according to the NLTCP guidelines. The programme will strive to:

- Establish/maintain a mechanism for collaboration between the NLTCP and all health care providers (private and public) for TB care and control.
- Institutionalize standard TB case detection and treatment across private and public health care providers.
- Reduce diagnostic delays by involving all non NLTCP care providers (private and public).
- Improve access to TB care by engaging all health care providers.
- Improve notification of TB cases by non NLTCP care providers (private and public).
- Reduce significantly/eliminate catastrophic costs to TB patients.
- Build the capacity of health care providers in TB control.

15.2 Implementation approaches

PPM models

The NLTCP - PPM encompasses two models of collaboration which are:

- Public-private: collaboration between the NLTCP and the private health care providers. These facilities can be:
    - Private-for-profit
    - Private non-profit
- Public-public: collaboration between the NLTCP and the public health care providers that are not formally engaged by the TB program.

15.2.1 Public-private mix model

This describes the collaboration between NLTCP and the private sector providers. These care providers include but are not limited to:

- Faith-based health facilities
- Private hospitals and clinics
- Private tertiary health institutions
- Nursing/convalescent homes
- Community pharmacies
- Stand-alone medical laboratories
- Health facilities of corporate organizations and industries
- Proprietary and Patent Medicine Vendors
- Traditional/alternative medicine practitioners

15.2.2 Public-public mix model

- This describes the collaboration between NTBLP and the public health care providers that are not formally engaged by the TB program. Such public care providers include but are not limited to:
    - Public tertiary health institutions (University Teaching hospitals)
    - Military hospitals and clinics (Army, Navy, Air Force)
    - Para-military hospitals and clinics (Prison, Immigration, Customs, etc.)
    - Police Medical Services (hospitals and clinics)
    - National Government Research Institutions.
    - The medical centers of tertiary academic institutions

15.3 Schemes for collaboration

A scheme is the categorization of the level of service that private health providers can offer under the TB program. The eligibility for any of the schemes depends on availability of appropriate human and material/infrastructural resources and willingness of the provider to participate. Four schemes for collaboration have been identified and they are as follows:

- **Scheme 1**: Identification and referral of presumptive TB.
- **Scheme 2**: Identification of presumptive TB, diagnostic services, and referral for treatment initiation.
- **Scheme 3**: Identification of presumptive TB and treatment of diagnosed TB cases.

15.3.1 Scheme 1: Identification and referral of presumptive TB

This scheme involves the identification of presumptive TB (a person who has one or more of the following symptoms: cough of 2 weeks or more or cough of any duration in HIV infected patients, fever, drenching night sweats and weight loss) and referral of the presumptive TB to a health facility for diagnostic evaluation. Preferably, samples should be collected from the presumptive TB case and transported to the diagnostic facility. The following care providers may opt to participate in this scheme:

- Community providers like traditional birth attendants and traditional medicine practitioners among others
- Community pharmacies.
- Private stand-alone laboratories (without Xpert MTB/RIF).
- Workplace clinics.
- Private for-profit hospitals and clinics.

- Faith-based hospitals and clinics.

Requirements/eligibility criteria for engagement

- Willingness to collaborate with NLTCP
- Willingness to refer patients to approved diagnostic centers
- Undergo training in line with the national guidelines
- Sign a memorandum of understanding (MOU) with the NLTCP

Roles and responsibilities

The provider will:

- Identify and refer presumptive TB (pulmonary and extra-pulmonary) to the nearest health facility providing TB diagnostic and/or treatment services.
- Identify presumptive TB and collect specimen for diagnosis.
- Document all identified presumptive TB in the Presumptive TB register.

15.3.2 Scheme 2: Identification of presumptive TB, diagnostic services, and referral for treatment initiation

This scheme involves the identification of presumptive TB (a person who has one or more of the following symptoms: cough of 2 weeks or more or cough of any duration in HIV infected patients, fever, drenching night sweats and weight loss), provision of Xpert MTB/RIF test and/or radiological diagnostic services, and subsequent referral to health facility providing TB treatment.

The following providers may opt to participate in this scheme:

- Stand-alone medical laboratories and diagnostic centers.
- Health facilities with in-house laboratories that do not provide TB treatment.

Requirements/eligibility criteria

- Willingness of facility to collaborate with NLTCP
- Availability of qualified medical laboratory personnel.
- Willingness to be trained.
- Availability of adequate infrastructure for infection control and safety
- Availability of GeneXpert machine or other rapid diagnostic test for TB.
- Sign an MOU with the NLTCP.

Roles and responsibilities

The provider will:

- Adhere to NLTCP policies on TB diagnosis.
- Conduct symptomatic screening for walk-in clients and perform laboratory diagnosis for those eligible.
- Inform clients that are diagnosed with TB of the availability of TB drugs and refer to collaborating health facilities for treatment.
- Provide prompt feedback on result to the referring institution/health worker/doctor.
- Inform all stakeholders (without delay) in the event of an abrupt disruption of diagnostic services.
- Store slides in line with national SOP for laboratory quality assurance (follow up test).
- Participate in the external quality assurance program.
- Complete appropriate recording and reporting tools.

- Collate, analyze, use and report data to NLTCP.

15.3.3 Scheme 3: Identification of presumptive TB and treatment of diagnosed TB cases

This scheme involves the identification of presumptive TB (a person who has one or more of the following symptoms: cough of two weeks or more or cough of any duration in HIV infected patients, fever, drenching night sweats and weight loss), linkage to Xpert MTB/RIF services and/or radiological TB diagnosis, and provision of TB treatment in line with the national guideline.

The following providers may opt to participate in this scheme:

- Faith-based hospitals and clinics
- Private for-profit hospitals and clinics
- Private for non-profit hospitals and clinics.
- Workplace clinics
- Community pharmacies

Requirements/eligibility criteria

- Willingness to collaborate with NLTCP
- Availability of qualified health personnel
- Trained on the NLTCP standards of TB treatment and care
- Strictly adhere to national guidelines
- Sign an MOU with the NLTCP

Roles and responsibilities

The provider will:

- Identify a TB focal person for the facility.
- Ensure that screening, diagnosis, and treatment of TB are done in accordance with the NLTCP guidelines.
- Ensure that patient-centered care approach is implemented.
- Ensure follow-up clinical and laboratory evaluation in line with the NLTCP guidelines.
- Complete all paper-based and electronic recording and reporting tools used by the NLTCP
- Ensure that all diagnosed TB patients have documented reachable contact information (physical address and phone numbers).
- Ensure appropriate and continuous health education to the patients.
- Support patient to identify treatment supporter if he/she cannot come daily to the facility for supervised treatment.
- Ensure that all household contacts of infectious TB patients are investigated in line with the NLTCP guidelines.
- Manage treatment interruption with support from the District Supervisor.
- Conduct community outreach to generate demand for TB services in their area as necessary.

15.4 Steps to engage all healthcare providers for PPM in TB control

The NLTCP should:

1. Engage the umbrella bodies (when available)
2. Line-list and map all private and non-government health facilities in the District.

3. Conduct rapid assessment of each listed facilities using a standard checklist.
4. Approach facilities that meet the minimum requirement for PPM for possible engagement into any of the schemes.
5. Discuss the conditions and benefits for collaborating with the NLTCP and seek consent to collaborate.
6. Discuss the schemes and allow the facility to make a choice using the PPM task mix.
7. Sign a Memorandum of Understanding between the facility and the NLTCP
8. Identify a TB focal person for the facility
9. Organize appropriate orientation/training according to the scheme selected.
10. Provide essential programme materials (drugs, recording and reporting tools, reagent, consumables) appropriate for the scheme selected as soon as the orientation/training is completed
11. Provide directory of TB diagnostic and treatment centers in the District to all PPM facilities.
12. Provide IEC materials.
13. Conduct regular follow-up mentoring visits to facilities to reinforce skills after training

15.7 Contextual issues with implementing PPM

User Fees

The NLTCP desires that services for TB should be free. However, private facilities may choose to charge minimal fees for services such as registration, consultation, fees for ailments other than TB and other charges as agreed with providers and captured in the MOU.

Incentives And Enablers

To ensure effective engagement of the private sector, the NLTCP can recommend the following incentives and/or enablers:

- Performance based incentives for processes required for TB case finding (including specific incentive per TB case detected)
- Provision of free anti-TB medicines and laboratory consumables and equipment.
- Training/retraining of the service providers
- Platform to serve as role models for other care providers in the community.
- Formal recognition through giving awards to deserving health care providers.
- Sponsorship to participate in national review meetings, conferences and any other capacity building programs.

16. TUBERCULOSIS AND LEPROSY LOGISTICS SUPPLY MANAGEMENT SYSTEM

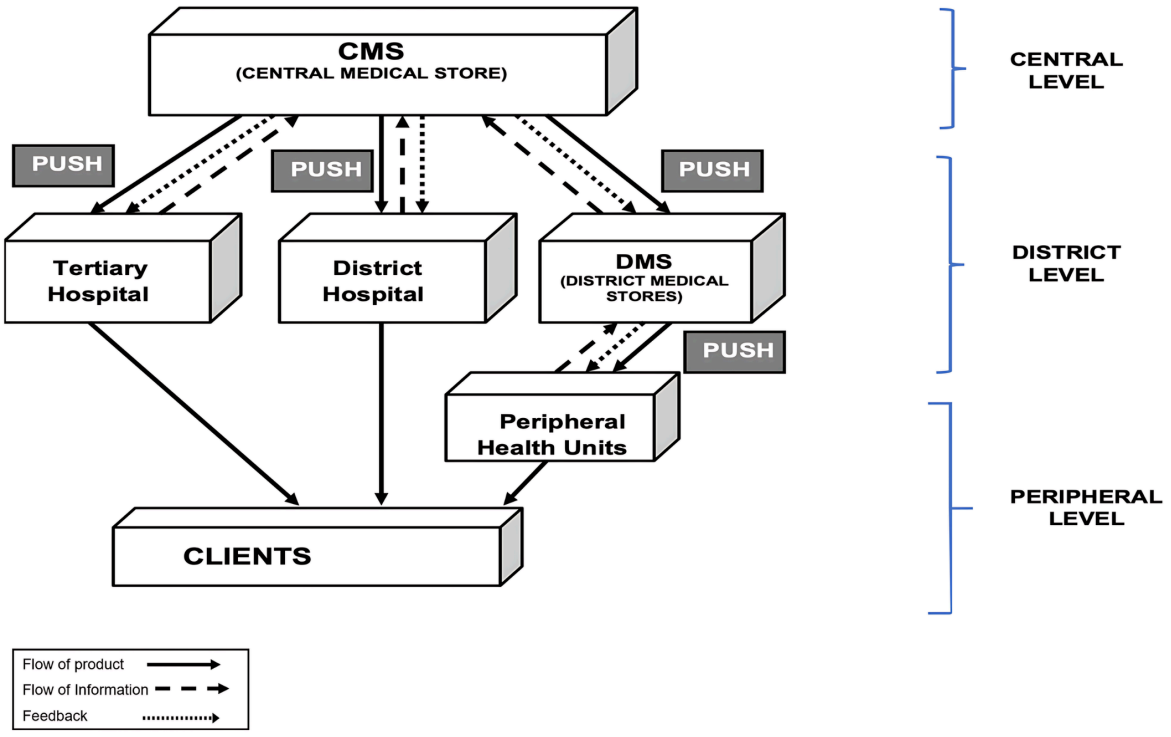
The purpose of TB health product supply chain management is to make available effective, affordable, safe, and good quality Pharmaceuticals and Health commodities to all TB patients /suspects always. It is important that all staff involved in the Programme know how to manage these commodities for rationale use and avoid wastage.

The major objectives of health product supply chain management Include:

- Always maintaining an adequate stock of medicines in the pipeline i.e., within the minimum and maximum, stock levels for all TB commodities.
- Prevention of Stock out and wastages due to expiry
- Ensuring rationale dispensing of TB medicines.
- Ensuring patient safety.

The NLTCP flow of commodities can be seen in the chart below:

Figure 16: Flow of TB commodity and logistic information within Sierra Leone



16.1 Logistics Management Information System (LMIS)

Logistics is the flow of material, information and money between consumers and suppliers. (Frazelle, 2002). It is the science and arts of getting the right amounts of the right things to the right places at the right time. (Foster, 1990). This is very important in a TB Control Programme. Logistics Management Information System (LMIS) is a system of records and reports- whether paper-based or electronics – used to aggregate, analyze, validate, and display data from all levels of the logistics system that can be used to make logistic decisions and manage the supply chain.

Six Rights of a Logistic System

- Right product
- Right quantities
- Right condition
- Right place
- Right time
- Right cost

16.2 TB logistics supply management system arrangement

Timely and uninterrupted supply of medicines and other consumables is one of the important requirements for the successful implementation and sustainability of the Programme. Procurement, storage, maintenance of stock and timely distribution of anti-TB drugs together with consumables and diagnostics are essential for quality services under National TB Control Programme. One of the most important tasks is to make sure that all DOT facilities have the adequate stock of drugs and consumables. Monitoring of TB/Leprosy commodity supplies from central to districts and DOT facilities is through a web-based real time software i.e., M-supply to avoid any shortage and expiry of medicines.

In Sierra Leone NLTCP provides quality drugs to all the diagnosed TB patients without any interruption. First line drugs are being provided for Drug Sensitive TB patients depending upon their weight. An efficient drug supply chain system should ensure:

- Continuous availability of quality anti-TB drugs
- Maintenance of adequate drug stocks at all levels
- Prevention of expiry of drugs at all levels
- Effective timely transportation of drugs
- Proper maintenance of drug records
- Quality of drugs throughout its shelf life
- Safeguarding against pilferage

A Procurement and Supply Chain Management (PSM) Unit is established at National Leprosy and Tuberculosis Control Programme (NLTCP) for coordinating the Procurement and management of Supply Chain of all types of anti TB/Leprosy drugs, ancillary drugs, diagnostics and consumables. This unit is headed and supervised by a Programme Pharmacist, who is the PSM Officer of the NLTCP. The procurement of TB commodities is done based on the policies and funding provided by Global Fund through the Global Drug Facility (GDF) of the Stop TB Partnership, and the procurement of leprosy drugs is done through WHO.

The procurement is done based on Technical Specifications formulated by the NLTCP quantification committee and approved by National quantification committee of MoH – Sierra Leone. The finalized quantification file is shared with the Country Team at Global Fund.

Annual/periodic requirements of the drugs and diagnostics are finalized at National Level based on the inputs on the TB/Leprosy case notifications, stock levels and consumption pattern.

Currently all procurement of First line and Second Line TB drugs, ancillary drugs, diagnostics, and consumables which are funded by The Global Fund are procured through the Global Drug Facility (GDF). The First Line and Second Line Drugs should be pre-Qualified for the eligibility of procurement for any funding sources under any Procurement Agencies.

In addition to Anti TB drugs and other diagnostics, Binocular Microscopes, LED-Florescence Microscope, GeneXpert Machines, MTB/RIF ULTRA and XDR Cartridges, LPA, Solid and Liquid Culture laboratory equipment & consumables are also procured at NLTCP level through GDF and WAMBO platforms.

16.2.1 Distribution of TB/ Leprosy commodities

Distribution of drugs is to be carefully monitored, to ensure uninterrupted availability of quality drugs. Requirements at drug stocking points (National, District and PHU Stores) are based on current utilization patterns and expected stocks at the time of delivery.

16.2.2 First Line Drugs distribution

Distribution of first line drug supplies is primarily supplied from the manufacturer to National Government Medical Stores Depots at Fawaz, by Ferry Junction in Freetown. In addition to National Government Medical Stores Depots, drugs are supplied through 16 District Medical Stores (DMSs) operating across the country by National Medicines and Supply Agency (NMSA). Quarterly, NLTCP PSM team issue drugs and other commodity matrix based upon consumption, closing stocks and stocking norms. The commodities are issued from the National warehouse during the First Mile distribution to the District Medical Stores (DMSs) for onward Last Mile distribution to the hospital/PHU facility Stores. In case of any emergency, drugs are issued directly to the districts with strong collaboration between National PSM team, NMSA and Logistics Team at the district that made the emergency request. The districts should follow up with NLTCP/NMSA in case of delay in receipt of drugs after distribution schedule date provided by NMSA. The commodities are transported through a well-defined transportation mechanism/ Third-party Logistics (3PL).

16.2.3 Second Line Drugs distribution

Distribution system of Second Line drug supplies is primarily supplied from the manufacturer to National Government Medical Stores Depots at Fawaz, by Ferry Junction in Freetown., In addition to National Government Medical Stores Depots, the drugs are supplied to MDR-TB treatment centers operating across the country (currently at Koidu in Kono district, Makeni in Bombali district and Lakka Hospital in Western Area Rural) by National Medicines and Supply Agency (NMSA). The commodities are issued from the National warehouse to the MDR-TB facility stores. In case of any emergency, commodities are issued directly to the districts with strong collaboration between National PSM team, NMSA and Logistics Team at the district that made the emergency request. The Pharmacist/Logistics team at the treatment centers should follow up with the NLTCP/NMSA in case of delay in receipt of drugs after the emergency request is made and after distribution schedule date provided by NMSA. The commodities are transported through a well-defined transportation mechanism/ Third-party Logistics (3PL).

16.3 Anti – TB commodities inventory management at facility level

16.3.1 Recording, Reporting and Monitoring Tools

Inventory control card / or Stock card is maintained at the National, district & PHU stores in the prescribed format recommended by the country. A Stock card / or Inventory control card is maintained to record receipt, issue, and balance stock of drugs. The status of stock along with their expiry details can be ascertained at any point of time through this card. All receipts should be entered neatly including transfers from other districts. Before making any issue of drugs, the Store and Inventory Management Assistant (SIMA) should always look at expiry columns of the stock card to check as to which drugs are due to expire first. The drugs, which are due to expire first, are to be issued first so that all the drugs issued will follow the FEFO principles.

However, while the SIMA shall strictly follow FEFO principles, it is also expected of him to ensure that all short-expiry TB/Leprosy drugs do not get issued to districts, hospitals and PHUs. Instead, distribution shall be based on the utilization pattern of each district, hospital and PHU facilities.

16.3.2 Daily Dispensing Register (DDR) and monthly Health Facility Reporting Form

The DDR should be used to capture the daily consumption of all TB/Leprosy commodities in all DOT facilities in the country. The consumption receive from DDR will then inform the monthly Health Facility Reporting Form that records the monthly commodity consumption from each DOT facility to the district for onward uploading of the consumption data into the DHIS2 platform that is under the control of Directorate of Planning Policy and Information (DPPI) of the Ministry of Health of Sierra Leone.

16.3.3 Claim & Return Form

This tool is use for:

- Reverse logistics activities
- Retrieval of commodities
- Returning of expired/damaged commodities to higher level

i. **Inventory Control Card/or Stock Card:** The stock card is a stock keeping record that keeps information about the movement and quantity of a product in the facility's storage area.

ii. **Waybill:** The delivery voucher is a transaction record used to accompany supplies being moved from a higher level to a lower level. Like the returning and claimed forms above, the Waybill, is in triplicate copies. Distributed as follows: , 1st copy at the receiving facility, the 2nd copy is returned to the Central level as a proof of delivery and the 3rd which is also known as the tickler copy retained by the carrier or 3 PL to facilitate payment for services.

iii. **Daily Commodity Register:** For the recording daily commodity consumption data.

iv. **Monthly Health Commodity Reporting Form:** For recording and reporting of health commodities consumed by health facilities to districts or National monthly.

v. **GeneXpert cartridge consumption tracking form:** Used in the collation and documentation of Logistic data of cartridges.

vi. **Pharmacovigilance Forms:** These forms are used for reporting adverse drug reactions, to all TB medicines in the program.

vii. **ADSM forms:** These forms are used for reporting adverse events or adverse drug reactions, to new TB medicines and regimens.

16.4 Responsibilities of health facility staff in the management of TB commodities

In always ensuring the availability of all medicines the designated service provider in the facility (Pharmacist, GHW, and Laboratory Personnel) must perform the following functions:

Receive TB commodities

- Ensure that all TB commodities are accompanied by a Delivery Voucher.
- The person responsible must inspect items physically for wholesomeness (ensuring the commodities are not damaged, soaked or broken).
- Check for completeness as listed in the delivery voucher.
- Physical counting of all items delivered should be conducted to ensure that they match numbers written in the delivery vouchers.
- Check the batch numbers listed and ensure they match batches listed in the delivery voucher.
- Check expiry dates to ensure items can be reasonably consumed before expiry.

- Endorse the delivery voucher after ensuring items received reflect what is written in the delivery voucher.
- If there are discrepancies this should be noted in the remark column.
- A copy of the delivery voucher must be kept in the facility.

Entering received items in the Stock Cards

- All items received in the facility must be entered into appropriate stock cards.
- Select stock card for individual item received.
- Enter the date, batch number, quantity of items received in the appropriate column.
- Endorse the stock card.
- This must be done for all items received.

16.5 Making an emergency order

Emergency ordering is initiated to prevent stock out of a particular item. This is initiated when the stock level is one month and below before the end of the quarter (normal distribution cycle).

- The need for emergency supply should be communicated to the National Procurement and Supply Chain officer by the District Pharmacist or Hospital Pharmacist.
- A neighboring District Medical Sore or hospital facility may also be contacted (for any possible transfer of commodities).
- Communication of emergency order should be by email from the responsible logistics head of the district or hospital.

16.6 Calculating the Months of Stock (MOS)

- Determine the Stock on Hand (SOH) by conducting a physical inventory.
- Divide the SOH by the last quarter average monthly consumption (AMC).

$$\text{MOS} = \frac{\text{Stock on Hand}}{\text{Average Monthly Consumption.}}$$

Actions to take after calculating MOS. If:

- 1 MOS or less = (Emergency) place emergency order immediately
- 2 MOS or less= (Below Minimum) monitor stock more frequently.
- 3-5 MOS = (Ok) No action necessary
- Above 5 MOS = (Over stock) Determine your Month of Stock Cover. If the Month of Stock Cover is less than the MOS return or transfer the difference.

16.7 Quality monitoring of commodity consumption (10 patient index and 10 smear index)

Continuous monitoring of commodity consumption is needed to minimize wastage of TB medicines and lab reagents. This is to measure the average number of kits used to treat 10 patients in a specified period (patient index) as well as the quantity of reagents used to prepare 10 smears (smear index)

- Patient index is determined by the quantity of kits/ used in a specified period divided by number of patients reported within the period multiplied by 10.

- Smear index is determined by the number of tests(reagents) used to prepare every 10 slides in a facility.

$$\text{10 patient index} = \frac{\text{Quantity of kits used X 10}}{\text{Number of patients reported}}$$

$$\text{10 smear index} = \frac{\text{Number of tests used X 10}}{\text{Number of smears (workload)}}$$

Acceptable range for patient index is 9 -11 kits and for smear index 8 -12 tests.

16.8 Management of the supply box

The patient kit used for the treatment of patients is designed for patients within the standard weight band of **38-54kg (DSTB)**. However, there are situations when patient weight falls outside this weight bands necessitating the need to create a supply box to provide the extra medicines where needed, especially for DSTB medicines.

How to create a supply box

In the event of a patient with weight outside the standard weight band (as stated above), an adjustment to the patient kit is required and the following steps are to be taken:

1. Take a full (complete) TB kit from the facility store.
2. Write supply box on the outside of the kit.
3. Separate the content of the kits (Adult, pediatric, DRTB) into individual medicines contained in the kit e.g. RHZE, RHZ, RH (75+150) RH (50+75) for DSTB; and Cm (Igm), Am(500mg),Pto/Eto 250mg , Z 400mg, Cs 250mg , Lfx 250mg , Mfx 400mg, Cfz100mg , E 400mg , H 300mg , Bdq 100mg, Dlm 50mg , Lzd 600mg and PAS 4g for DRTB.
4. Medicines remaining from the kits of patient who were lost to follow-up, died, or were transferred out should be emptied into the supply boxes.
5. Any extra blisters you removed when adjusting a patient kit (for patients below the standard weight band) should be emptied in the supply boxes.
6. Open a stock card for the medicine in each of the supply box.
7. Excess components of the respective kit should be noted and returned to the shelf with appropriate adjustment of the stock card.
8. Additional blisters needed for adjusting the kits (for patient above the standard weight band), can be taken from the supply box.

16.9 Storage of Drugs and Supplies

Health facility drugs and supplies are kept in the health facility's drug store room, which should be well kept and managed by a designated responsible staff member. Good storage and management procedures are important for anti-TB drugs (and all drugs) and supplies kept in the store room or cabinet.

It is important to:

Keep drugs safe.

- Stocks of anti-TB drugs are kept safe in the main storeroom, which should be locked when not in use.
- Drugs and other commodities should not be kept directly on the floor
- Ensure that fire prevention measures are implemented.

Keep the storeroom in good condition

- The temperature, light and humidity in the main store room should be kept moderate by increasing ventilation, creating drainage areas, and repairing any roof leaks quickly.
- Storage conditions can be improved by some simple measures using fans, air vents or windows to increase ventilation, direct light can be prevented from entering the room by hanging curtains or painting the window glass.
- No one should eat, drink or smoke in the store room. Do not keep food or drinks in the store room. This will help to keep the store room clean and free of pests and rodents.

Organize drugs and supplies

- Stocks of anti-TB drugs in the storeroom (in individual patient drug boxes or stocked by type of drug) should be placed on shelves by expiry date: the drugs that expire soonest should be in front and those that expire later should be behind.
- When taking drugs off the shelf, use those expiring first (First-to-expire, First-out (FEFO)
- Return expired drugs to the TBL Supervisor using the record for returning and transferring of commodities.
- Maintain a stock card for each drug and each drug strength and this should be kept with that drug on the shelf.
- Routinely inspect drugs and other supplies. Whenever tablets begin to change color or solutions have unusual deposits of solids, stop issuing such and report to TBL supervisor or district pharmacist.

16.10 Treatment Regimen and Drug strengths and dosages

Table 48: Daily dosages of first-line anti-TB medicines for adults

Essential TB drug (abbreviation)	Recommended daily dose mg/kg	Dose range in mg/kg	Maximum dose (mg)
Rifampicin (R)	10	8-12	600
Isoniazid (H)	5	4-6	300
Pyrazinamide (Z)	25	20-30	-
Ethambutol (E)	15	15-20	-

Table 49: Daily dosages of first-line anti-TB medicines for children

Essential TB drug (abbreviation)	Dose mg/kg	Dose range in mg/kg
Rifampicin (R)	15	10-20
Isoniazid (H)	10	7-15
Pyrazinamide (Z)	35	30-40
Ethambutol (E)	20	15-25

Table 50: Fixed dose combination for adults and children above 14 years (weighing 25 Kg or more)

Drug	Dosage form	Strength
Rifampicin + Isoniazid (RH)	Tablet	150mg +75mg
Rifampicin + Isoniazid + Ethambutol (RHE)	Tablet	150mg +75mg +275mg
Rifampicin + Isoniazid + Pyrazinamide + Ethambutol (RHZE)	Tablet	150mg +75mg +400mg +275mg

Table 51: Fixed dose combination for children < 14 years

Drug	Dosage form	Strength
Rifampicin + Isoniazid (RH)	Tablet	75mg + 50mg
*Rifampicin + Isoniazid + Pyrazinamide (RHZ)	Tablet	75mg +50mg + 150mg

**Ethambutol is in a loose form, 100 mg, and added to RHZ for the intensive phase of treatment.*

Table 52: Number of daily tablets needed to reach the proper dosing, based on weight band for adults

Regimen	Pre-treatment weight			
	>25-37 kg	38-54 kg	55-70 kg	> 70 kg
Intensive phase (2 months): Combined tablet of RHZE (150mg+75mg+400mg+ 275mg)	2	3	4	5
Continuation phase (4 months): Combined tablet of RH (150mg + 75mg)	2	3	4	5

Table 53: Number of daily tablets needed to reach the proper dosing, based on the child's weight.

Daily Regimen	Pre-treatment weight (Kg)					
	<4	4- 7	>7-11	>11-15	>15- <25	≥ 25
Intensive phase (2 months) • Combined tablets: RHZ (75mg+50mg+150mg) • Ethambutol tablet (100mg)	½ ½	1 1	2 2	3 3	4 4	Adult tablets
Continuation phase (4 months) Combined tablets of RH (75 mg + 50 mg)	½	1	2	3	4	

Table 54: Dosing for isoniazid preventive therapy for children.

Weight band	Number of tablets daily
	Isoniazid 100 mg
< 6 kg	½
6 - 9 kg	1
10 - 13 kg	1 ½
14 - 19 kg	2
20 - 24 kg	2 ½
25+ kg	Adult dosages recommended

Table 55: Drug dosage of DR TB drugs for adult patients.

Drugs	16-29 kg	30-45 kg	46-70 kg	>70 kg
Rifampicin(R)	300mg	450mg	600mg	600mg
Isoniazid (H)	300mg	600 mg	900 mg	900 mg
Ethambutol(E)	400 mg	800 mg	1200 mg	1600 mg
Pyrazinamide(Z)	750 mg	1250 mg	1750 mg	2000 mg
Levofloxacin (Lfx)	250 mg	750 mg	1000 mg	1000 mg
Moxifloxacin (Mfx)	200 mg	400 mg	400 mg	400 mg
High dose Mfx (Mfxh)	400mg	600mg	800mg	800mg
Bedaquiline (Bdq)	**Week 0–2:** Bdq 400 mg daily **Week 3–24:** Bdq 200 mg 3 times per week			
Linezolid (Lzd)	300 mg	600mg	600mg	600mg
Clofazimine (Cfz)	50 mg	100 mg	100 mg	200 mg
Cycloserine (Cs)	250 mg	500 mg	750 mg	1000 mg
Delamanid (Dlm)	50 mg twice daily (100 mg) for 24 weeks in 6-11 years of age 100 mg twice daily (200 mg) for 24 weeks for >11 years of age 13			
Amikacin (Am)	500 mg	750 mg	750 mg g	1000 mg
Ethionamide (Eto)	375 mg	500 mg	750 mg	1000mg
Pyridoxine (Pdx)	50 mg	100 mg	100 mg	100 mg

17. MONITORING AND EVALUATION

This chapter describes the monitoring and evaluation of the TB programme. A monitoring and evaluation system are essential for programme management since it provides the basis for assessing progress made towards achieving programme goals. In addition, it provides information about the size of the TB problem and its evolution over time. A key element of the End TB strategy is the establishment and maintenance of a system to monitor case detection and treatment outcomes.

The objective of this chapter is to track NLTCP performance in providing quality services to all tuberculosis cases in the country. It should be able to provide information among others:

- Availability of TB services in the country
- Routine monitoring and supportive supervision
- Routine data collection and analysis

In addition to providing indicators of how well objectives have been achieved, it also helps in knowing whether activities have been undertaken as intended and whether services are effective in reaching programme goals. It can be used to address weaknesses in programme design and implementation. Using information in decision making can help to ensure accountability of staff and managers. A good M&E system is required at every level in the health system, characterized by the following:

- Clear goals, objectives and targets (that are cumulative, with facility targets leading to district targets leading national targets)
- The selection of indicators which are valid, reliable, specific, operationally feasible and comparable over time and in different districts and the country.
- Quality assurance procedures to ensure that quality data is collected.
- The timely submissions and processing of data.
- The ability to process and analyze data.
- Data dissemination in both directions.
- Both monitoring and evaluation are done on a "cohort" basis. This ensures that all patients recorded in the register within a specified calendar quarter are accounted for within the analysis.

17.1 Monitoring

Monitoring is the routine tracking of key elements of program performance through careful record keeping and regular reporting. Monitoring is used to assess whether or not activities are carried out as planned. It focuses on the activities implemented and results achieved. It provides continuous information on the progress being made to achieve goal and alerts staff and manager to problems, providing an opportunity for these to be resolved early.

Effective monitoring relies on accurate records being maintained for all patients and periodic, regular reporting of activities. The tools that have been developed by the TB Programme help standardize the way in which information is collected.

17.2 Evaluation

Evaluation is an episodic, in-depth analysis of programme performance. It assesses progress towards operational targets and epidemiological objectives. It relies on data generated through routine information as well as from other sources such as research studies. There are various types of evaluation:

- Process evaluation measures the quality of programme implementation and assesses coverage.
- Outcome and impact evaluations measure programme results and the effect on the target population.
- Outcome evaluations also measure the extent to which stated objectives are achieved with respect to the program's goal.

Evaluation is an essential management tool, not only for the analysis of results, but also for the management of the TB programme, particularly for guiding implementation, ordering drugs and laboratory reagents, training of health staff, identifying problems in service delivery and eventually the expansion of the health structures involved in the TB programme. Regular evaluation is required not simply for surveillance purposes but is necessary for efficient management of the programme. An evaluation of the extent to which targets set by the TB programme are reached helps identify parts of the programme that are not functioning well. Regular collation of essential information is an integral part of the routine operations of the TB programme and should not be compromised or minimized due to other pressures.

17.3 Surveillance

Surveillance is the systematic ongoing collection of epidemiological data (i.e. disease outcomes) to track trends in disease incidence or prevalence over time. Data may be collected through sero prevalence surveys or through the routine reporting of cases seen by health facilities. Although surveillance data is an important source for M&E, surveillance should not be confused with, or substituted for, actual programme monitoring.

17.4 Standard tools used in the TB Programme

The following tools are used by the TB programme:

Table 56: Tools used in TB program

Tool	Uses
District TB Register	Used to track number of patients on treatment for the district. Used to report periodically for the district. Quarterly, annually report of new and old cases. Used to report on cohort analysis periodically
Presumptive TB Register	Used at facility level to record symptomatic patients reporting to that facility, to assist the follow-up of results and initiation of treatment.
Health facility Tuberculosis Register	Used at the facility to track the number of patients on treatment in a particular health facility.
Request form for Microscopy, GeneXpert, Culture and DST	A specific TB laboratory request form used by all facilities. Correct completion can help assess case-finding.
Laboratory Register for Microscopy and Xpert MTR/RIF	Used to record the number of presumptive screened and cases on follow up.
Laboratory Register for DR-TB	Used to record the number of presumptive MDR-TB screened and cases on follow up

Tool	Uses
Tuberculosis Treatment Card	This is used to record details of treatment including daily doses taken for all TB cases. Used in all facilities to collect information about the patient, treatment and outcomes (demographic, disease classification, treatment regimen, monitoring and outcomes). This is the source document used to complete the health facility TB register.
DR-TB treatment Card	This is used to record details of treatment including daily doses taken for all DRTB cases. Used in all DRTB facilities to collect all the information about the patient, treatment and outcomes (demographic, disease classification, treatment regimen, monitoring and outcomes). This is the source document used to complete the DRTB register.
Patient Referral Transfer Form	Used to refer a patient to another TB site
Patient ID Card	Issued at the beginning of intensive phase to the patient to monitor treatment.
District Monthly Report on TB Notification	Used by the health facility to report on the monthly case load.
District Quarterly Report on TB Notification	Used by the health facility to report on the quarterly case load.
Health Facility Quarterly Report on TB Notification	Used by the health facility to report on the quarterly case load.
Health Facility Monthly Report on TB Notification	Used by the health facility to report on the monthly case load.
District Monthly Report on TB Outcome	Used by district supervisors to collate facility TB outcome reports within the district.
District Quarterly Report on TB Outcome	Used by district supervisors to collate facility TB outcome reports within the district.
Health Facility Quarterly Report on TB Outcome	Used by health staff to collate facility TB outcome reports within the district
Health Facility Monthly Report on TB Outcome	Used by health staff to collate facility TB outcome reports within the district
NLTCP Tuberculosis Preventive Treatment Register	Used to indicate the number of anti-tuberculosis medicines given to prevent the development of TB disease
Transfer form	Used in all facilities to report on the key patient information from the register when the patient is transferred/moved from one district/facility to another.
National Supervision checklist	Used by National supervisors to evaluate and monitor DOTS facility performance.
Suspected Adverse Drug Reaction/ Medical Error Reporting Form	Form filled in by the health staff for all patients on treatment with anti-TB medication experiencing any unwarranted effect either mild or adverse.
Baseline assessment Form	Form filled for baseline investigation of all patients commencing second line anti-TB medication.
X-ray & Radiology Form	A form that is filled for all patients going for radiological examination. It provided basic information about person

** Excludes some tools used at facility level for patient management.*

17.5 Standard reports

Accurate recording and reporting of TB (and HIV) in adult and children are critically important for improved epidemiological surveillance, measuring the impact of interventions and facilitating the planning and organization of services. Recording and reporting are also relevant for defining the need for technical assistance and drug procurement and to determine staff requirements. Patients with TB should therefore always be included in the routine NLTCP recording and reporting system.

It is essential to notify the NLTCP of all identified TB cases, register them for treatment and record their treatment outcome. Evaluation of treatment outcome by cohort analysis is a valuable indicator of program quality for TB patients.

In addition to recording in the TB treatment register, it is important to maintain facility medical records and to include information on TB screening, results and treatment (preventive or curative) health documents. This will improve continuity of care and communication between health services. Children should also be included in integrated TB/HIV activities. It is important to establish and maintain linkages between TB and HIV care, recording and reporting in HIV care and treatment settings; ART registers should include records of TB screening and TPT as well as CPT.

The following reports should be analyzed regularly (monthly, quarterly, biannually and annually):

1. Quarterly report on All TB patients registered/ notified: Completed at district level and reports on the completed quarters cohort.
2. Quarterly report on smear conversion: Completed at district level and reports on the previous quarter's cohort.
3. Quarterly report on treatment outcomes for new and retreatment smear positive pulmonary TB and All TB patients: Completed at district for the cohort registered 9 months earlier.
4. Quarterly report on TB-HIV indicators: Completed at district for the cohort registered 9 months earlier.
5. Quarterly report on programme management: Compiled at national level, and is mainly a narrative report.
6. Half yearly and annually: national level.

17.6 Information flow

Information is collected at community and facility levels in the TB presumptive register, laboratory register and used to update the facility and district register. This should be done on a regular (daily) basis. Good data is dependent on the quality of information in the paper-based TB register. These need to be reviewed throughout the month for completeness and correctness. As soon as a TB register sheet is completed, it needs to be sent to the district office for data capturing. TB register sheets must be sent to the district office and data captured through out the month to allow sufficient time for data validation and analysis at the end of a cohort period.

Recommended timelines for data collation:

- Data from facility to district must be collated by the 5th of the new month.
- By the 15th of the new month, data from the district must have reached national office.
- National compile and analyze quarterly and submit to Ministry of Health and partners.

17.7 TB Programme Indicators

The following key TB indicators will be reported by the programme.

Table 57: Programme indicators

Indicator	Description	Data source	Frequency of reporting
Impact			
TB incidence rate per 100,000 population.	*Numerator:* Number of new and relapse cases during the year *Denominator:* Number of people in the population X 100,000	TB recording and reporting system national.	Annually
TB mortality rate per 100,000 population.	*Numerator:* Number of deaths from all forms of TB and deaths from TB in PLHIV in a year. *Denominator:* Number of people in the population x 100,000	TB recording and reporting system national.	Annually
RR-TB and/or MDR-TB prevalence among new TB patients: The proportion of new TB patients with RR-TB and/or MDR-TB	*Numerator:* The number of new TB cases with RR-TB and/or MDR-TB X 100. *Denominator:* Total number of new TB patients with DST results/Expert results.	Drug Resistant Survey.	Every 5 years.
TB/HIV mortality rate per 100,000 population.	*Numerator:* Number of HIV positive people who die of HIV with TB as a contributory cause of death. *Denominator:* Number of people in the population X 100,000.	Modelling	Annually
Outcome			
Treatment coverage: Percentage of patients new and relapse TB that were notified and treated among the estimated incidence in the same year.	*Numerator:* Number patients with new and relapse TB that were notified and treatment. *Denominator:* Estimated number of incident people with TB in the same year (all forms of TB bacteriological and clinically diagnosed).	Programme data	Annually.
Treatment success among all forms of TB: Bacteriologically confirmed plus clinically new and relapse	*Numerator:* Number of patients with all forms of TB (bacteriologically confirmed and clinically diagnosed) in the specify reporting period who subsequently were successfully treated *Denominator:* Total number of people with all forms of TB (bacteriological and clinically diagnosed) notified in the same period.	District register	Quarterly/ Annually
Treatment coverage for RR-TB and/or MDR-TB: Percentage of notify people with bacteriologically confirmed TB, drug resistant RR-TB and/or MDR-TB as a proportion of all estimated people with RR-TB and/or MDR-TB.	*Numerator:* Total number of people with bacteriologically confirmed RR-TB and/or MDT-TB. *Denominator:* Estimated number of people with RR-TB and/or MDR-TB	District register	Annually

Indicator	Description	Data source	Frequency of reporting
Treatment success rate of RR-TB and/or MDR-TB: Percentage of patients with RR-TB and/or MDR-TB successfully treated.	***Numerator:*** The number of patients with bacteriologically confirmed RR-TB and/or MDR-TB enrolled on second line regiment during a specify period who are successfully treated (cure + treatment completed). ***Denominator:*** Total number of people with bacteriologically confirmed RR-TB and/or MDR-TB who were registered during same the period.	District register	Quarterly/ Annually
Percentage of notified TB patients of all forms (bacteriologically confirmed and clinically diagnosed) that are contributed by non NTP providers (private, NGOs) includes new and relapse.	***Numerator:*** Number of patients with all forms of TB (bacteriologically confirmed and clinically diagnosed) diagnosed, managed and/or refereed by non-NTP providers. ***Denominator:*** Total number of TB all forms notified by the national TB Programme.	District register	Quarterly/ Annually
Percentage of notified TB patients of all forms (bacteriologically confirmed and clinically diagnosed) that are contributed by community referrals includes new and relapse.	***Numerator:*** Number of patients with all forms of TB (bacteriologically confirmed and clinically diagnosed) diagnosed, managed and/or refereed by community to the health facilities for diagnosis. ***Denominator:*** Total number of TB all forms notified by the national TB Programme.	District register	Quarterly/ Annually
Percentage of new and relapse cases tested using the WHO rapid diagnostic test at time of diagnosis.	***Numerator:*** The number of new and relapse TB cases tested using the WHO Rapid Test at the time of diagnosis. ***Denominator:*** Total number of new and relapse cases.	HF/District register	Quarterly
Treatment success rate all forms: Percentage of patients with all forms of TB, bacteriologically confirmed plus clinically diagnosed successfully treated (cure plus treatment completed) among all TB patients notify during a specific period. Includes new and relapse cases.	***Numerator:*** Number of patients with all forms of TB, bacteriologically confirmed plus clinically diagnosed successfully treated in a specific reporting period who subsequently were successfully treated (cure plus treatment completed) ***Denominator:*** Total number of people will all forms of TB (bacteriologically confirmed and clinically diagnosed in the same period.	District register	Quarterly/ Annually
Percentage of people who completed TPT out of those who initiated TB Preventive Therapy.	***Numerator:*** Total number of people who completed TPT during a specify reporting period. ***Denominator:*** Total number of people who initiated TPT during a specify reporting period.	TPT register	Quarterly/ Annually

Indicator	Description	Data source	Frequency of reporting
Contact investigation coverage: Proportion of contacts of people who are bacteriologically confirmed cases evaluated for TB among those eligible.	***Numerator:*** Number of household contacts (and/or close contacts) of the people with bacteriologically confirmed TB who were evaluated for TB disease or infection in the specify reporting period. ***Denominator:*** Total number of illegible contacts of people with bacteriologically confirmed TB in the same reporting period.	Contact register	Quarterly
Percentage of new and relapse TB cases who have documented HIV status.	***Numerator:*** Number of new and relapse cases registered during a specific reporting period who have HIV result test (whether positive or negative) recorded in the TB register. ***Denominator:*** Number of new and relapse cases registered during a specific reporting period.	District register	Quarterly
Percentage of HIV positive new and relapse TB cases on ART during treatment.	***Numerator:*** Number of HIV positive new and relapse TB patients started on TB treatment during the reporting period who are already on ART or who start on ART during TB treatment. ***Denominator:*** Number of positive new and relapse TB patients registered during the reporting period.	District register/ART register	Quarterly/ Annually
Treatment success rate for HIV positive TB patients: Percentage of HIV positive TB patients all forms (bacteriologically confirmed or clinically diagnosed) successfully treated among HIV positive TB patients notify during a specific period* Includes new and relapse TB cases.	***Numerator:*** Number of HIV positive patients (bacteriologically confirmed plus clinically diagnosed) notified in a specific period who were successfully treated. ***Denominator:*** Total number of HIV positive patients (bacteriologically confirmed plus clinically diagnosed) notified during the same period.	District register and annual data	Annually
Percentage of people with confirmed RR-TB and/or MDR-TB that that second line treatment	***Numerator:*** Number of people with bacteriology confirmed RR-TB and/or MDR-TB notified and started second line treatment regimen during a specify period. ***Denominator:*** Number of people with bacteriology confirmed RR-TB and/or MDR-TB during the same period of time.	DR-TB register	Quarterly
Treatment success rate of RR-TB and /or MDR-TB: Percentage of RR-TB and/or MDR-TB successfully treated.	***Numerator:*** Number of patients with bacteriologically confirmed RR-TB and/or MDR-TB enrolled on second line treatment during a specified period who are successfully treated (Cure and treatment completed). ***Denominator:*** Total number of people with bacteriologically conform RR-TB and/or MDR-TB notified during the same period.	DRTB register	Quarterly/ Annually

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ANNEXES

Annex 1: Engaging Treatment Supporter for DOT

Steps

1. Describe to the patient the following criteria for selecting a treatment supporter:
   a. Preferably a close relation to the patient (family/non family)
   b. Living within same household or at walking distance of less than 500 meters from patient's home
   c. Physically able to visit the facility
   d. Willingness of the individual to provide support to the patient
2. Place the patient on daily DOT while waiting for the treatment supporter
3. Ask the patient to invite the treatment supporter to the health facility immediately or within a period of 2 days
4. Provide health education to both patient and treatment supporter on the following:
   a. Basic information on TB and TB Infection Control (especially cough etiquette)
   b. Treatment duration and number of tablets to take daily
   c. Sputum follow-up examination (2, 5 and 6 months)
   d. Possible side effects of anti TB drugs and the need to report back to health facility in case of any complaints.
5. Discuss the roles and responsibilities of the treatment supporter:
   a. Ensuring daily DOT
   b. Support the patient to come to the health facility for drugs collection every 2-4 weeks
   c. The patient and treatment supporter should return used (empty) blisters
   d. Support the patient to come to the health facility for follow-up sputum examinations and management of side effects or complications if any.
   e. Inform the health care worker in case of unavailability of the treatment supporter
6. Reconfirm the willingness of the treatment supporter
7. Document the name, address and phone number of the treatment supporter as the contact of the patient on the Patient TB Treatment Card.
8. Ensure that the patient and treatment supporter agree on timing of drug intake and drug storage.
9. Provide the treatment supporter with drugs (two to four weeks)
10. Health care worker to complete all appropriate section of the patient treatment card and block dates not applicable for the months on treatment.
11. The treatment supporter and patient should discuss any challenges with health care worker . Where available a community health worker should be used for supervision and defaulter tracing.

Annex 2: Roles and Responsibilities of key staff of NLTCP

Programme Manager

1. Manage and co-ordinating all TB control activities in the country.
2. Provide managerial and technical support for the Regional and District management teams, and District Supervisors.
3. Mobilization of resources from government and partners for the implementation of the TB Programme activities.
4. Ensure procurement and distribution of the NLTCP commodities or supplies.
5. Ensure adequate Human Resources for the Programme.
6. Maintain active collaboration with National and International NGOs /voluntary agencies including private health providers.
7. Coordinate all Partners supporting TB control in Sierra Leone.
8. Collate, analyse and use data generated to improve programme performance and share with Government, partners and WHO.
9. Organization of periodic review and evaluation of the NLTCP.
10. Develop an annual operational plan for the control of TB.
11. Perform any other duty that may be assigned.

District Coordinators/Supervisors

1. Management, coordination and supervision of all TB control activities at District levels.
2. Ensure requisition, adequate supplies and distribution of TB medicines and commodities to all providers in the Districts.
3. Collect, collate, analyse and use data generated to improve programme performance.
4. Disseminate reports to the National, Regional and District Governments, as well as other organizations and institutions as appropriate.
5. Co-ordinate partners involved in programme implementation within the district.
6. Assist HCW in the diagnosis and management of difficult TB patients.
7. Maintain active co-operation with NGOs supporting the TB programme at District levels.
8. Perform any other duties that may be assigned.

Laboratory Lead (National level)

1. Set up Quality Assurance system for the National TB Programme.
2. Carry out regular supervision to each of the laboratories aimed at ensuring that Standard Operating Procedures (SOP) are adhered to and carry out on-the-job training
3. Assist the national TB programme manager in the quantification and distribution of all laboratory commodities

4. Maintain adequate stock of laboratory supplies and consumables to eliminate stockout at the National, Regional, District and Health Facility levels
5. Ensure effective utilization and management of consumables, equipment and laboratory materials.
6. Coordinate all sputum logistics in the District by working closely with the District Supervisors.
7. Ensure the submission of quarterly/annual reports, the request for commodities for all laboratories in the country.
8. Facilitate laboratory feedback and information dissemination of quarterly QA activities at all levels
9. Organize regular training for laboratory staff.
10. Keep records of work and collate statistical data on workload every quarter
11. Perform any other duties that may be assigned

Procurement and Supply Management Officer(s)

1. Coordinate National quantification and order of medicines, laboratory reagents and other commodities for the TB control in collaboration with partners.
2. Support the programme in appropriate use of the medicines and commodities.
3. Coordinate and support commodities management at service delivery points (DOTS sites, GeneXpert, and microscopic centre).
4. Monitor overall stock level of all commodities at all levels.
5. Support and strengthen capacities of the HCW for TB commodity management
6. Provide PSM quarterly report to the Programme Manager.
7. Maintain TB commodities logistic data and tools
8. Perform any other duty as assigned

Monitoring and Evaluation Officer(s)

1. Routine collation, validation and analysis of National data (paper-based and electronic)
2. Provide feedback to National, Regional Districts, health facilities and communities on statistical data through the Programme manager.
3. Quarterly monitoring of National activity implementation and tracking to advice the Programme Manager on level of implementation.
4. Support the capacity building of District and TB health facility staff and community TB workers on the use of programme Recording and Reporting tools
5. Periodic review of programme information and strategic change
6. Support evaluation of programme interventions at all levels
7. Support the conduct of operational research.
8. Perform other functions as assigned by the National Programme manager.

TB care and prevention focal person

1. Oversee the expansion of TB services to all health facilities (public and private) in the country.
2. Facilitate collaboration with the private health providers and engage them in TB control.
3. Support the TB programme manager in ensuring all elements of the End TB strategy are implemented.

MDR-TB Focal Person

1. Oversee the implementation of PMDT in the field to ensure implementation according to National Guidelines.
2. Work closely with the DR-TB treatment centers to ensure all management of all patients are in line with the national guidelines.
3. Liaise with the field to promote ambulatory management of DR-TB patients.

Childhood and adolescent TB Focal Person

1. Oversee and provide leadership in the implementation of all activities related to the management of Child and Adolescent TB all over the country with emphasis and focus on the three targets set in the NSP for 2025:
   - To increase the proportion of children 0-14 years of age among all TB nationwide to 15%
   - To successfully treat 85% of children with TB (all forms)
   - To initiate 90% of eligible children <5 in contact with TB patients on IPT
2. Liaise with the Maternal and Child Health and other Programs to ensure screening of all children for TB
3. Strengthen contact investigation and ensure Tuberculosis Preventive Treatment for all children and adolescents is high on the agenda.
4. Set up (or revive) and conduct regular meetings of the Child and Adolescent TB TWG, which should serve as a strong advocacy group for Child and Adolescent TB
5. Improve the Monitoring and Evaluation of child and Adolescent TB activities by ensuring that key indicators on childhood TB are available on the supervision schemes/questionnaires and the DHIS2
6. Set up and constitute a team of Child and Adolescent TB Focal Persons with representatives in each district

Laboratory worker at the health facility level

1. Observe all standard operating procedures and basic safely measures for efficient and effective biological specimen examination, in all cases, as designed by the programme.
2. Advise patients and other health workers on correct and safe sputum collection.
3. Prepare specimen for Xpert MTB/RIF for diagnosis, staining and examining sputum for follow up cases.
4. Ensure prompt dispatch of results to the clinic within 72hrs from the receipt of specimen
5. Record findings and reports using the NLTCP Information System.
6. Store slides neatly inside the slide box for Quality Control.

7. Create and facilitate the practice of Internal Quality Control as an integral part of standard laboratory practices.
8. Maintain effective communication with reference laboratory for the purpose of Quality Control and cooperate with them by preserving serially, all read Z.N. smears.
9. Maintain adequate stock of reagents and supplies to eliminate stockouts.
10. Ensure effective utilization and care of reagents, equipment and materials meant for the programme

National Reference laboratory

1. Carrying out culture and DST of all biological specimens from the field and provide feedback.
2. Shift all specimens for External Quality Assurance to the Supranational Reference laboratory and ensure feedback.
3. Together with the national TB Programme organise training for laboratory staff.
4. Support the National TB Programme in carrying out quality assurance of the district and peripheral laboratories.
5. Develop panels for quality assurance.
6. Provide quarterly report to the National TB programme manager on performance of the laboratory.
7. Perform any other duties assigned.

Annex 3: Adverse Event Form

Healthcare professionals can also report safety issues spontaneously using the adverse drug reaction reporting form.

Adverse Event Form **AE ID #: _____**

Surname: _____ Given name: _____ Facility patient ID#: _____	
Date of onset of event: __ __ /__ __ __ /__ __ __ __ (DD/MM/YYYY)	
Date of reporting the event (today's date): __ __ /__ __ __ /__ __ __ __	
Were all anti-TB drugs suspended due to this AE?	☐ Yes ☐ No

Use one AE form per event. Tick the box in the right column that applies to the AE being reported.

Organ system	**Common Adverse Events (check ONE)**
Cardiovascular disorders	☐ Cardiac arrhythmia ☐ **Prolonged (corrected) QT interval**
Chemistry	☐ **Hypokalemia (K ≤ 3.4 mEq/L)** ☐ Hypomagnesemia (Mg ≤ 1.4 mmol/L) ☐ Lactate (serum lactate greater than ULN)
Ear disorders	☐ **Hearing impairment (hearing loss)** ☐ Tinnitus ☐ Vestibular disorder
Endocrine disorders	☐ **Hypothyroidism**
Enzymes	☐ **Increased liver enzymes (ALT increased, or AST increased (≥ 1.1 x ULN))**
Eye disorders	☐ **Optic nerve disorder (optic neuritis)**
Gastrointestinal disorders	☐ Diarrhea ☐ Dyspepsia ☐ Nausea ☐ Oral discomfort/dysphagia
	☐ Pancreatitis ☐ Vomiting
Hematology	☐ **Absolute neutrophil count low (ANC ≤ 1500/mm^3)** ☐ **Anemia (Hb < 10.5 g/dL)** ☐ **Platelets decreased (< 75,000/mm^3)**
Immune disorders	☐ Allergic reaction
Musculoskeletal disorders	☐ Arthralgia ☐ Arthritis

	☐ Myalgia ☐ Tendinopathy
Neurological disorders	☐ Dysgeusia ☐ Headache ☐ Peripheral neuropathy (neurosensory disorder or paresthesia) ☐ Seizure
Reproductive system and breast disorders	☐ Gynecomastia
Psychiatric disorders	☐ Anxiety ☐ Depression ☐ Psychosis ☐ Suicidal ideation
Renal and urinary disorders	☐ **Acute kidney injury (acute renal failure)**
Skin disorders	☐ Mucocutaneous symptoms (includes rash) ☐ Pruritus ☐ Skin hypo- or hyper-pigmentation
Other adverse events	
Other (enter one adverse event) if not listed in the most common list:	_____

Severity

Grade	☐ 1 ☐ 2 ☐ 3 ☐ 4

Related test results

Test	**Lab ID number**	**Date**	**Value**
		__ __ /__ __ __ /__ __ __ __	
		__ __ /__ __ __ /__ __ __ __	
		__ __ /__ __ __ /__ __ __ __	

Form filled by: _____ Date: __ __ /__ __ __ /__ __ __ __
Form entered by: _____ Date: __ __ /__ __ __ /__ __ __ __

Ministry of Health and Sanitation

☐ **Adverse Drug Reaction** ☐ **Initial report**
☐ **Products Quality Defect** ☐ **Follow –up report**
☐ **Medication Error**

Suspected Adverse Drug Reaction/Medication Error Reporting Form

PATIENT *DETAILS*

*Patient's name:		Address:	
*Sex:	*Age(months/years):	Height:(cm)	Weight:(kg)
Health Facility:			

1. DETAILS OF DRUGS

*Name:		*Strength:
*Daily Dose:	*Start date:	End date:
Therapeutic indication:	Route of administration:	
Name and Address of Manufacturer:		

DETAILS OF ADVERSE EVENTS

*Description of reaction experienced by patient:

*Date/time reaction started	Date/time reaction stopped	Was patient admitted ☐ Yes ☐ No	Duration of admission (hours/days)

4. DRUGS TAKEN CONCOMITANTLY /IN THE LAST 3 MONTHS PRIOR TO THE REACTION.
All concomitant drugs including self- medication and herbal preparations

Brand or Generic Name:	Daily dose	Route of Administration	Date started	Date Stopped	Reasons for Use

Action taken	Outcome	Treatment of reaction
☐ *Drug withdrawn* ☐ *Dose increased* ☐ *Dose reduced* ☐ *Dose not changed* ☐ *Unknown*	☐ *Recovering/resolving* ☐ *Recovered/resolved* ☐ *Recovered with sequelae* ☐ *Not recovered*	

REPORTER DETAILS

Name:	
*Designation:	
Date:	Telephone No:

Note: Fields marked (*.) are mandatory

Annex 4:

Laboratory Sputum Request Form:

DOCUMENT No. MOH NTRL/ALS/F5.4-002

Sierra Leone-Ministry of Health

National TB Reference Laboratory Lakka Government Hospital

P.O. Box: Tel. email:

TB Culture & Drug Susceptibility Testing Request& Report Form

PATIENT ADDRESS: Patient Full Name: _____

Age (Yrs): _____ Sex: M _____ F _____

Region: _____ District: _____ Community: _____

Address: _____ _____Tel.: _____

Referring Health Facility: _____ _____Co-infection: _____

TB registration No:_____MDR TB No:_____

Lab No [for NTRL use only]_____

TB DISEASE TYPE & TREATMENT HISTORY:

Site: Pulmonary _____ History:☐New (Never treated before for ≥ _1 month)

☐ Extrapulmonary (specify): _____☐Failure ☐Relapse ☐ Return after default

☐MDR contact ☐Uncertain Previous Treatment:

☐ New ☐1st line ☐ 2nd line ☐ Other _____

Description _____

REQUEST FOR TESTING AT REFERENCE LABORATORY:

Diagnosis: Specimen Type: Sputum

Follow up: at _____ months of 1st line treatment Other (Specify):_____

_MDR follow up: at _____ months of treatment Presumptive XDR suspect: _____

Date specimen collected: ____/____/____ (European Calendar)

Date specimen received: ____/___/____ (European Calendar)

Requested tests: Microscopy Culture DST phenotypic

[☐1st line ☐_2nd line] LPA [☐1st line ☐2nd line] ☐GeneXpert

Requesting physician: Name: _____ Profession: _____Tel:_____

LABORATORY RESULT [for NTRL / NTRL use only] :Laboratory Number: _____

Microscopic examination:

Method used: ☐ Direct Smear ☐ Concentrated Smear ☐Ziehl-Neelsen (ZN) ☐Fluorescence
☐ GeneXpert Result: result

Positive Result Detected Indeterminate Not detected Remark Negative

Actual No 1 + 2 + 3+ M.Tuberculosis Rifampicin Resistance

Table 58: Dosing of medicines used in second-line MDR-TB regimens by weight band (patients 15 years or older)

	Medicine	Weight-based daily dose	Formulation	Weight bands for patients 15 years or older[a]					Usual upper daily dose[b]	Comments
				30-35 kg	36-45 kg	46-55 kg	56-70 kg	>70 kg		
A	Levofloxacin	–[c]	250 mg tab	3	3	4	4	4	1.5 g	
			500 mg tab	1.5	1.5	2	2	2		
			750 mg tab	1	1	1.5	1.5	1.5		
	Moxifloxacin	Standard dose[c,d]	400 mg tab	1	1	1	1	1	400 mg	
		High dose[c,d]	400 mg tab	1 or 1.5	1.5	1.5 or 2	2	2	800 mg	
	Bedaquiline	–[c]	100 mg tab	4 tabs od for first 2 weeks; then 2 tabs od M/W/F for 22 weeks					400 mg	
	Linezolid	–[c]	600 mg tab	(<15 y)	(<15 y)	1	1	1	1.2 g	For dosing of linezolid for the BPaL regimen, refer to Section 7, Table 7.2.
B	Clofazimine	–[c]	50 mg cap or tab[e]	2	2	2	2	2	100 mg	
			100 mg cap or tab[e]	1	1	1	1	1	100 mg	
	Cycloserine or terizidone	10–15 mg/kg	250 mg cap	2	2	3	3	3	1 g	

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients 15 years or older[a]					Usual upper daily dose[b]	Comments
				30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg		
C	Ethambutol	15–25 mg/kg	400 mg tab	2	2	3	3	3	–	
	Delamanid	–[c]	50 mg tab	2 bd	2 bd	2 bd	2 bd	2 bd	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	–[c]	500 mg + 500 mg powder for injection, vial (10 mL)	2 vials (1 g + 1 g) bd					–	To be used with clavulanic acid.
	Meropenem	–[c]	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, ampoule[f]	2.5 mL	3 mL	3–4 mL	4 mL	4 mL	1 g	
	Streptomycin	12–18 mg/kg	1 g powder for injection, vial[f]	Calculate according to the dilution used					1 g	
	Ethionamide or prothionamide	15–20 mg/kg	250 mg tab	2	2	3	3	4	1 g	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 bd	1 bd	1 bd	1 bd	1 to 1.5 bd	12 g	
			PAS acid (4 g) sachet	1 bd	1 bd	1 bd	1 bd	1 to 1.5 bd		

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients 15 years or older[a]					Usual upper daily dose[b]	Comments
				30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg		
Other medicines[g]	Isoniazid	4–6 mg/kg (standard dose)[d]	300 mg tab	2/3	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[h]	–[c]	125 mg clavulanic acid as amoxicillin/ clavulanate, 500 mg/ 125 mg tab[h]	1 bd	1 bd	1 bd	1 bd	1 bd	–	Only to be used with carbapenems.
	Gatifloxacin	–[c]	400 mg tab	2	2	2	2	2	800 mg	Currently, there is no availability of gatifloxacin on the market. Gatifloxacin is not used in persons <18 years.
	Pretomanid[i]	–[c]	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.

(<15 y): follow the separate dose schedule for patients younger than 15 years of age; bd: two times a day; BPaL: regimen of bedaquiline, pretomanid and linezolid for 6–9 months; cap: capsule; HIV: human immunodeficiency virus; im: intramuscular; iv: intravenous; g: gram; kg: kilogram; mL: millilitre; mg: milligram; M/W/F: Monday, Wednesday, Friday; soln: solution; susp: suspension; MDR-TB: multidrug-resistant TB: MDR/RR-TB: multidrug- and rifampicin resistant tuberculosis; tab: tablet; WHO: World Health Organization.

a Dosages were established by the guideline development groups for the WHO guidelines on drug-resistant tuberculosis treatment (2018 and 2020 updates) and the WHO Global Task Force on the Pharmacokinetics and Pharmacodynamics (PK/PD) of TB medicines and other experts. They are based on the most recent reviews and best practices in the treatment of MDR/RR-TB. For certain agents the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008;48:303–32). Owing to the pharmacokinetic properties of certain medicines, the doses proposed may exceed the mg/kg per day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient. In patients <30 kg, the schedule for those aged <15 years should be followed, unless otherwise indicated. If multiple dose options are given for one weight band, the lower or

higher option should be selected, depending on whether the patient is at the lower or higher limit of the body weight range. Dosing more closely to the target mg/kg per day should be aimed for, and is more feasible with oral or parenteral fluids, and when solid forms of different dosages are available. Fractioning of tablets into halves or less should be avoided, if possible. Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range, to minimize the adverse therapeutic consequences of over- and under-exposure, respectively (especially for injectable agents, linezolid and fluoroquinolones).

b Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.

c No weight-based dosing is proposed.

d The higher dose may be used except when: there is risk of toxicity; levels are expected to be lowered because of pharmacokinetic interactions, malabsorption or other reasons; or the strain has low-level drug resistance.

e Tablets are expected to become available in the near future.

f The weight-based daily dose is for 6 or 7 days per week administration (M/W/F scheduling may permit higher dosing). Volumes shown may differ by preparation. Streptomycin may be diluted in three different ways. For iv use, the volume may be increased.

g Amoxicillin/clavulanic acid is only recommended as a companion agent. Because of a lack of data from the latest analysis on longer MDR-TB regimens in adults, gatifloxacin, isoniazid and thioacetazone are not included in the grouping table of medicines used for longer regimens. Pretomanid is recommended to be used only as part of the package of the BPaL regimen.

h Only available in combination with amoxicillin as co-amoxyclav (e.g. 500 mg amoxicillin/125 mg clavulanic acid fixed-dose combination). It is given with each dose of carbapenem, either as 125 mg bd or 125 mg 3 times daily.

i Use for age 14 years or older.

See the text of the handbook for more details on the use of medicines.

Table 59: Dosing of medicines used in second-line MDR-TB regimens by weight band (patients under 15 years)[a]

	Medicine	Weight-based daily dose[b]	Formulation	Weight bands among patients under 15 years old[a]							Usual upper daily dose[b]	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 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[c]	2 mL[c]	3 mL[c]	5 mL[c]	0.5 or 0.75	1	(>14 y)	(>14 y)	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 1–15 kg	20 mg /mL susp	4 mL	6 mL	8 mL	11 mL	14 mL	15 mL	20 mL[d]	600 mg	
		10–12 mg/kg od in >15 kg	600 mg tab[c]	0.25	0.25	0.25	0.5	0.5	0.5	0.75[d]		
B	Clofazimine	2–5 mg/kg	50 mg cap or tab[e]	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[e]	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)	1 g	
			250 mg cap[c]	4–5 mL[c]	5–6 mL[c]	7–10 mL[c]	2	2	2	(>14 y)	1 g	

Group	Medicine	Weight-based daily dose[b]	Formulation	Weight bands among patients under 15 years old[a]							Usual upper daily dose[b]	Comments
				5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg		
C	Ethambutol	15–25 mg/kg	100 mg dt	1	2	3	4	–	–	(>14 y)	–	
			400 mg tab[c]	3 mL[c]	4 mL[c]	6 mL[c]	1	1 or 1.5	2	(>14 y)		
	Delamanid	–	50 mg tab	–	–[f]	–[f]	–[f]	1 bd	1 bd	2 bd	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, ampoule[g]	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[g]	Calculate according to the dilution used					(>14 y)	(>14 y)	1 g	
	Ethionamide or prothionamide	15–20 mg/kg	125 mg dt (ethionamide)	1	1	2	3	4	4	(>14 y)	1 g	
			250 mg tab	0.5	0.5	1	2	2	2	(>14 y)	1 g	

Group	Medicine	Weight-based daily dose[b]	Formulation	Weight bands among patients under 15 years old[a]							Usual upper daily dose[b]	Comments
				5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg		
C	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)		
			PAS sodium salt 60% w/w (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[h]	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[i]	–	62.5 mg clavulanic acid as amoxicillin/ clavulanate, 250 mg/62.5 mg, powder for oral solution, 5 mL	2 mL bd[i]	3 mL bd[i]	5 mL bd[i]	8 mL bd[i]	10 mL bd[i]	(>14 y)	(>14 y)	–	Only to be used with carbapenems.

(>14 y): follow the separate dose schedule for patients older than 14 years of age; alt: alternate; bd: two times a day; cap: capsule; dt: dispersible tablet; g: gram; im: intramuscular; iv: intravenous; kg: kilogram; mL: millilitre; mg: milligram; M/W/F: Monday, Wednesday, Friday; soln: solution; susp: suspension; tab: tablet.

a Dosages were established by the guideline development groups for the WHO guidelines on drug-resistant tuberculosis treatment (2018 and 2020 updates) and the WHO Global Task Force on the Pharmacokinetics and Pharmacodynamics (PK/PD) of TB medicines and other experts. They are based on the most recent reviews and best practices in the treatment of MDR/RR-TB. For certain agents the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008;48:303–32). Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the mg/kg/day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient. In patients >30 kg, follow the schedule for >14 years old unless otherwise indicated. If multiple dose options are given for one weight band select the lower or higher option depending on whether the patient is at the lower or higher limit of the body weight range. Dosing more closely to the target mg/kg/d+B48ay should be aimed for, and is more feasible with oral or parenteral fluids and when solid forms of different dosage are available. Fractioning of tablets into halves or less should be avoided if possible. Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range to minimize the adverse therapeutic consequences of over- and under-exposure respectively (especially for injectable agents, linezolid and fluoroquinolones).

b Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.

c Dissolving in 10 mL of water may facilitate administration in patients in lower weight bands and avoids fractioning solid formulations, although bioavailability is uncertain (use of dispersible tablets is preferred if available).

d In individuals >44 kg a dose of 600 mg od is proposed.

e Tablets are expected to become available in the near future.

f May be used in children 3–5 years of age. Giving half a 50 mg adult tablet in these children does not result in the same blood levels observed in trials using the special 25 mg paediatric tablet. Bioavailability may further be altered when the 50 mg tablet is split, crushed or dissolved.

g Weight-based daily dose is for 6 or 7 days/week administration (M/W/F scheduling may permit higher dosing). Volumes shown may differ by preparation. Streptomycin may be diluted in three different ways. Dosing closer to the upper limit of the mg/kg/day is more desirable. For iv use, the volume may be increased.

h These agents are only recommended as a companion agent (amoxicillin/clavulanic acid) or not included because of a lack of data from the latest analysis on longer MDR-TB regimens in adults (isoniazid).

i Only available in combination with amoxicillin as co-amoxyclav. Only to be used with carbapenems, in which case they are given together, e.g. 125 mg bd or 125 mg 3 times daily in the 24–30 kg weight band.

See the text of the handbook for more details on the use of medicines.

MINISTRY OF HEALTH
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