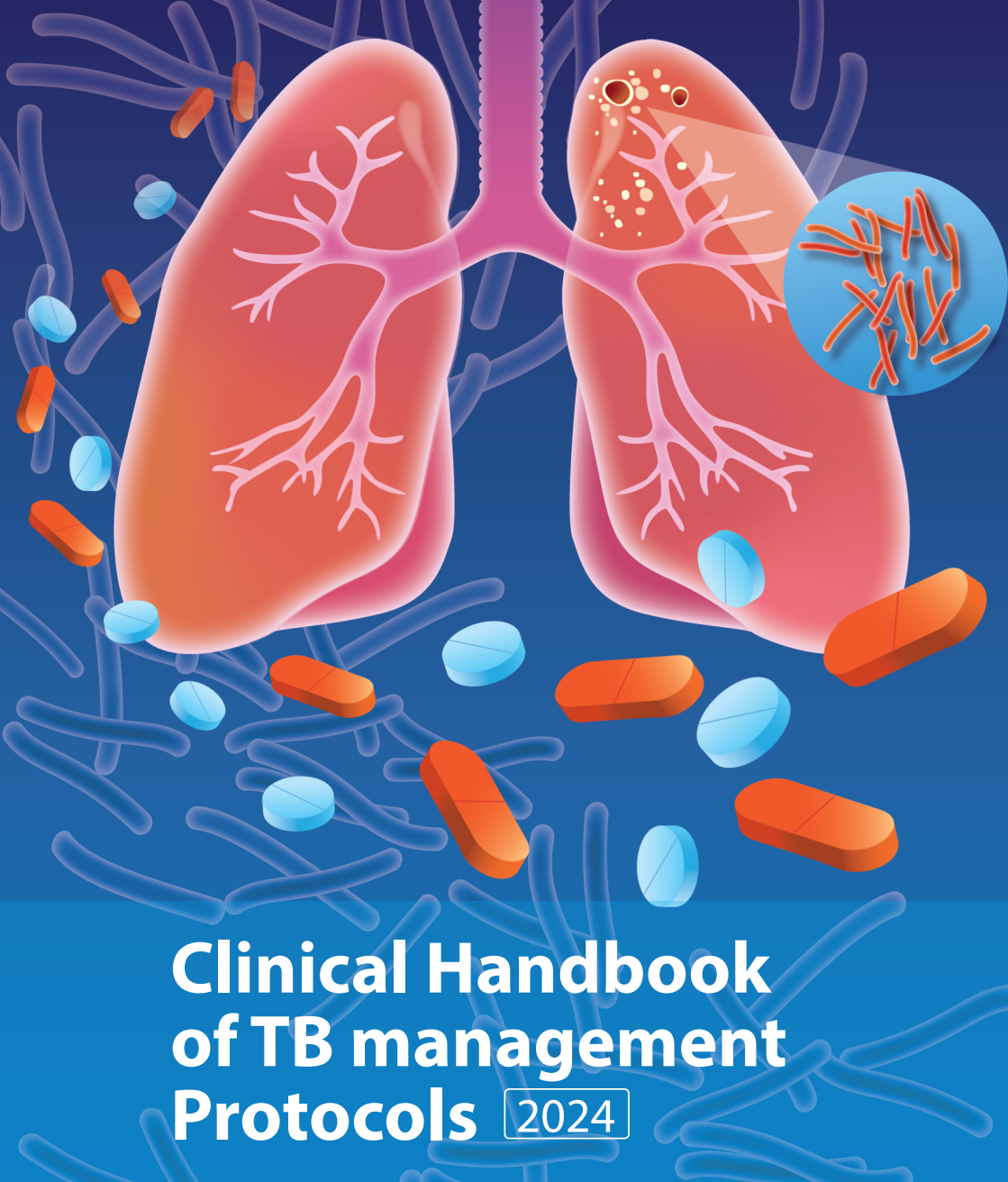




Clinical Handbook of TB management Protocols 2024



Government of Nepal
Ministry of Health and Population
Department of Health Services
National Tuberculosis Control Center

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Foreword



Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB), an acid-fast bacillus, mostly affecting the lungs. In Nepal, it remains as a major public health problem. In 2021, Nepal was listed among 30 high burden countries for drug-resistant TB (DR-TB) in the World. According to the National TB Prevalence Survey (NTPS) conducted in 2018/19 AD, 69000 people develop TB and 17000 TB deaths are accounted annually in Nepal. In an era of evolving clinical practices, emerging drug-resistant strains, and the complex interplay with other diseases such as HIV and AIDS, Diabetes and so on, it is imperative that healthcare professionals are equipped with practical, concise, and up-to-date knowledge on national protocols of TB treatment to manage TB effectively.

This brief, clinically focused handbook shares an overview of tuberculosis, provide insights on the national diagnostic and treatment protocols including the recent advancements, particularly in the management of drug-resistant TB (DR-TB) treatment with shorter and all oral treatment regimens. This handbook is a valuable resource for practitioners on the front lines of TB care. It emphasizes the importance of patient-centered care and multi-disciplinary approach in TB management too. Most importantly, this has been developed for the first time in Nepal to assist the practitioners for the uniform, evidence informed and nationally adopted treatment guidelines and protocols for TB management.

Hereby, I would like to express my sincere appreciation to all the colleagues from National Tuberculosis Control Center (NTCC), World Health Organization (WHO), Save the Children and other TB partners who devoted their valuable time, expertise, and effort to the development of this handbook. I believe that this handbook will empower each health care professional to provide the highest quality of care to those affected by TB, ultimately contributing to the fight against this preventable as well as curable disease in Nepal.

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Abbreviations

AFB	Acid-Fast Bacillus
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral treatment
BAL	Bronchoalveolar Lavage
BCG	Bacillus Calmette-Guérin
BPaL	Bedaquiline, Pretomanid and Linezolid
BPaLM	Bedaquiline, Pretomanid, Linezolid and Moxifloxacin
CAD	Computer-Aided Detection
CDC	United States Centers for Disease Control and Prevention
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CXR	Chest X-Ray
DOT	Directly Observed Treatment
DS	Drug Susceptible
DST	Drug susceptibility testing
EP	Extrapulmonary
FDC	Fixed-dose combination
FNA	Fine Needle Aspiration
FNAC	Fine Needle Aspiration Cytology
GDG	Guideline Development Group
GTB	Global TB Programme
GUV	Germicidal Ultraviolet
HEPA	High-Efficiency Particulate Air
HIV	Human immunodeficiency virus
HR	Isoniazid and Rifampicin
HRE	Isoniazid, and Rifampicin, with Ethambutol
HRZE	Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol
IDP	Internally Displaced People
IPC	Infection Prevention and Control
INH	Isoniazid

IGRA	Interferon-Gamma Release Assays
LPA	Line Probe Assay
LNTB	Lymph Node Tuberculosis
LR	Longer Regimen
MDR-TB	Multidrug-resistant tuberculosis
MTB	Mycobacterium tuberculosis
MTBC	Mycobacterium tuberculosis complex
mWRD	molecular WHO- recommended Rapid Diagnostics
NAAT	Nucleic Acid Amplification Test
PBC	Pulmonary Bacteriologically Confirmed
PLHIV	People Living with HIV
PTB	Pulmonary Tuberculosis
RR	Rifampicin resistance
SAM	Severe Acute Malnutrition
TB	Tuberculosis
TBST	TB antigen-based skin test
TST	Tuberculin Skin Test
WHO	World Health Organization
WRD	WHO- Recommended Rapid Diagnostics
XDR	Extensively Drug-Resistant

TB Medicines

Am	Amikacin
Amx-Clv	Amoxicillin-clavulanic acid
Bdq	Bedaquiline
Cfz	Clofazimine
Cm	Capreomycin
Cs	Cycloserine
Dlm	Delamanid
E/Eth	Ethambutol
Eto	Ethionamide
H/INH	Isoniazid
H ^h	High-dose isoniazid
lpm-Cln	Imipenem-cilastatin
Km	Kanamycin
Lfx	Levofloxacin
Lzd	Linezolid
Mfx	Moxifloxacin
Mpm	Meropenem
PAS	P-aminosalicylic acid
Pa	Pretomanid
Pto	Prothionamide
R/RIF	Rifampicin
S	Streptomycin
T	Thioacetazone
Trd	Terizidone
Z/PZA	Pyrazinamide

Definitions of TB

WHO Definitions of TB, Revised 2022

1. Presumptive TB	Refers to a patient who presents with symptoms or signs suggestive of TB (previously known as a TB suspect).
2. Bacteriologically confirmed TB	When a biological specimen is positive by smear microscopy, culture or a rapid diagnostic test for TB recommended by WHO.
3. Clinically diagnosed TB	When a person who does not fulfil the criteria for bacteriological confirmation has been diagnosed with TB disease by a medical practitioner who has decided to give the person a full course of TB treatment.
4. New patient	A person with TB disease who has never been treated for TB or has only previously ever taken TB drugs for less than 1 month.
5. Serious adverse event	An adverse event that leads to death or a life-threatening experience, to hospitalization or prolongation of hospitalization, to persistent or significant disability, or to a congenital anomaly. Adverse events that do not immediately result in one of these outcomes but that require an intervention to prevent such an outcome from happening are included. Serious adverse events may require a drastic intervention, such as termination of the drug suspected of having caused the event.
6. Severe extrapulmonary TB	Presence of miliary TB, TB meningitis, osteoarticular TB or pericardial TB. In children aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered severe.
7. TB disease	A disease in humans caused by the <i>M. tuberculosis</i> complex, which comprises eight distinct but closely related organisms – <i>M. bovis</i> , <i>M. caprae</i> , <i>M. africanum</i> , <i>M. microti</i> , <i>M. pinnipedii</i> , <i>M. mungi</i> , <i>M. orygis</i> and <i>M. canetti</i> . The most common and important agent of human disease is <i>M. tuberculosis</i> .
8. TB patient	A person who is in care for TB disease.

Classification of TB

A. Based on Method of Diagnosis

1. Presumptive TB
2. Bacteriologically confirmed TB case
3. Clinically diagnosed TB case

B. Based on anatomical site

1. Pulmonary tuberculosis (PTB)
2. Extrapulmonary tuberculosis (EPTB)

C. Based on history of previous TB treatment

1. New patients
2. Previously treated patient
 - a. Relapse patient
 - b. Treatment after failure patient
 - c. Treatment after loss to follow-up patient
 - d. Other previously treated patient
3. Patients with unknown previous TB treatment history

D. Based on drug resistance

1. Rifampicin resistance
2. Monoresistance
3. Polydrug resistance
4. Multidrug resistance
5. Pre Extensively drug resistance
6. Extensively drug resistance

E. Based on HIV Status

1. HIV- positive TB patient
2. HIV-negative TB patient
3. HIV status unknown TB patient

Introduction

Tuberculosis (TB) is a communicable disease which is a major public health problem in Nepal. It is one of the top 10 causes of death in Nepal, and the leading cause of death from a single infectious agent (ranking above HIV/AIDS). TB is caused by the *Bacillus Mycobacterium Tuberculosis* (*M. Tuberculosis*), which is spread when people who are sick with TB expel bacteria into the air; for example, by coughing. The disease typically affects the lungs (pulmonary TB) but can also affect other sites (extra pulmonary TB). About a quarter of the world's population is infected with *M. tuberculosis* which is similar for Nepal. TB can affect anyone anywhere, but most people who develop the disease are adults. There are nearly twice as more cases among men than women, and 30 high TB burden countries account for almost 90.0% of those who fall sick with TB each year. TB is a disease of poverty, and economic distress, vulnerability, marginalization, stigma and discrimination are often faced by people with TB. TB is curable with medicine nearly 90.0% cure rates and preventable with specific measures that reduce risk of transmission. With access still falling short of universal health coverage (UHC) for all forms of TB, many still have also missed out (nearly 50.0% in Nepal) on diagnosis and care.

This handbook is an abridged version of the updated guidelines for the diagnosis and treatment of tuberculosis including drug-resistant tuberculosis (DR-TB) in Nepal. It has been developed for the first time to meet the objectives so that all the practitioners including private and public sectors can get guidance on up-to-date, uniform, evidence-informed practices for suspecting, diagnosing and managing various forms of TB including all levels of healthcare delivery. They can then contribute to the National Program to improve the detection, care and outcomes in TB; to help the program with initiation of treatment, adherence and completion whilst minimizing drug toxicity and overtreatment; and contribute to practices that minimize the development of DR TB. However, the materials of this handbook should be carefully interpreted and the full version of the TB guidelines as well as experts should be consulted in case of questions.

In line with the International Standards of TB Care (ISTC), 2021, the NTP as a whole agreed on a set of principles about what each TB patient in Nepal needs as a basic standard of care. These principles are a complementary set to the standards for TB care in Nepal.

The provider should adopt a patient-centered approach to managing TB, to promote well-being and adherence to treatment and to relieve suffering. Patients have the right to be fully informed about their care at every stage, to be able to make decisions about their treatment and to be treated with dignity and respect.

TB Situation in Nepal, 2022/23 (FY 2079/80)

The reported case notification rate (CNR) of all forms of TB is 126 per 100,000 (37447) whereas CNR for bacteriologically confirmed (new and relapse) pulmonary TB is 71 per 100,000 population. There were 98.4% incident (new and relapse) TB cases registered. Among all forms of total notified TB cases, 73.0% were pulmonary and among total pulmonary, 79.0% were bacteriologically confirmed pulmonary (PBC) TB.

Majority of the TB notifications (25716, 68.7%) were from Madhesh (9161), Bagmati (8849) and Lumbini (7706) Province. The highest case notification was in Lumbini (148 per 100,000) followed by Madhesh (147 per 100,000) and Bagmati (143 per 100,000) Provinces. Most (71.0%) cases were reported in the age group (15-64) years while there was a significant proportion (21.0%) of TB cases in the older age (Above 65 years). Childhood TB was around 8.0% while men were nearly 2 times more than women among the reported TB cases. The treatment success rate for drug-susceptible tuberculosis (DS-TB) was 92.0% and death rate was around 3.0% .

Likewise, a total of 693 DR-TB were notified, among which 546 DR-TB patients were enrolled in the treatment; with nearly half (265) of them in shorter regimen (SSTR). The treatment success rate for DR TB was 82.0% and the death rate was 9.0%.

Screening and Diagnosis

1.1 Methods of screening and diagnosis

- Complete medical evaluation of a patient for TB disease includes medical history, physical examination, radiograph, and laboratory/bacteriologic examination.
- TB screening is important to test and detect the presumptive TB cases early through standard TB testing algorithm.
- Early systematic TB screening would be the first and foremost stage of TB case detection and management.
- The key objectives of TB screening are:
 - To detect presumptive TB cases
 - To test them for TB with appropriate diagnostic tool
- Systematic screening for TB disease is defined as the systematic identification of people at risk for TB disease, in a predetermined target group, by assessing symptoms and using tests, examinations or other procedures that can be applied rapidly & efficiently.
- The screening tests, examinations and other procedures should efficiently distinguish people with a high probability of having TB disease from those who are unlikely to have TB disease.
- Among those whose screening is positive, the diagnosis needs to be established by diagnostic evaluation, consisting of one or more diagnostic tests, and clinical assessment, which together have high accuracy.
- If TB is diagnosed, the patient should be put on TB treatment as early as possible

Presumptive TB

Presumptive TB (previously known as a TB suspect) refers to a patient who presents with the following signs and symptoms of TB. Persons with the following findings should be screened for TB:

1. Signs and symptoms of TB
 - a. Cough for 2 weeks or more
 - b. Coughing sputum with or without blood
 - c. Fever (evening rise/low grade) and night sweat
 - d. Loss of appetite and unintentional weight loss
2. Household or other close contacts of bacteriologically confirmed pulmonary TB
3. Chest X-ray suggestive of any unexplained lung field abnormality (including TB)

Presumptive Pediatric TB refers to children with persistent fever and/ or cough for more than 2 weeks, weight loss* or no weight gain, and/ or history of contact with infectious TB cases**.

Notes:

* History of unexplained weight loss or no weight gain in past 3 months; weight loss is defined as loss of more than 5% body weight as compared to highest weight recorded in last 3 months.

** In a symptomatic child, contact with a person with any form of active TB within last 2 years may be significant.

1.2 Suggested screening strategies for presumptive TB cases

S.n.	Location	Priority groups for screening	Possible screening strategies
1	Out-patient and in-patient department	• TB symptomatics • Contacts of TB patients • People living with HIV & AIDS • Diabetics, Cancer • Prolonged steroid therapy • Immunosuppressive therapy • History of TB; incomplete TB therapy • Pregnant women • Structural lung disease	1. Symptomatic Screening of TB symptoms 2. Chest X-ray
2	Community* (KAP)	• Malnourished children • Mining communities; occupational lung diseases • Substance or alcohol abuse • Healthcare workers • PLHIV • Refugees • Internally displaced people • People living or working in congregate settings (such as prison)	1. Door-to-door active case finding and screening for TB symptoms 2. Sputum collection & transportation of suspected TB cases (symptomatic and suggestive on X-ray) for TB testing 3. Screening with portable Chest X-ray

* Community screening is done when prevalence is at least 0.5%, or should be a known risk group

1.3 WHO recommended tools for TB screening

Group	Symptom screen	Radiology	Laboratory test	Remarks
Age group over 15 years old	Cough, fever, weight loss or night sweats	Chest X-ray (CAD* can be used as an alternative to human reports)	mWRD**	Alone or in combination
Adults & adolescents with HIV	4 symptoms-cough, fever, weight loss or night sweats	Chest X-ray	mWRD**	
Children under 15 years, close contacts of TB	Cough, fever or poor weight gain	Chest X-ray		Alone or in combination
Children <10 years, living with HIV	Cough, fever, poor weight gain, or close contact	If possible, Chest X-ray		

*Computer-aided Detection; **molecular WHO-recommended Rapid Diagnostics

1.4 Laboratory tests of tuberculosis

Below are the available laboratory tests for tuberculosis. In Nepal, wherever accessible, the initial test for the diagnosis of the tuberculosis are WHO-approved rapid diagnostic tests (WRDs); these are defined as diagnostic tests that employ molecular or biomarker based technique for the diagnosis. The newer, rapid and sensitive molecular tests recommended for the initial detection of MTBC and drug resistance are designated as mWRDs.

1. Molecular WHO-recommended Rapid Diagnostics (mWRDs)
 - Nucleic Acid Amplification Test (NAAT) such as Xpert MTB/Rif, Xpert MTB/Rif Ultra, Truenat, etc. for detection of MTB and RR*
 - Multicolor NAAT (Xpert MTB/XDR) for detection of first and second-line drug resistance including INH, fluoroquinolones, ethionamide, second-line injectable drugs (amikacin, kanamycin**, capreomycin**)
 - Line Probe Assay (LPA) for drug resistance detection
2. Mycobacterial culture and susceptibility
3. Sputum smear microscopy

* Rifampicin Resistance ** No longer recommended for DRTB treatment

Tools to detect TB infection

1. Tuberculin Skin Test (TST) or Mantoux Test
2. Interferon-gamma release assays (IGRA)
3. TB antigen-based skin tests (TBST)

1.5 Methods of obtaining a respiratory specimen

Sample collection methods for TB

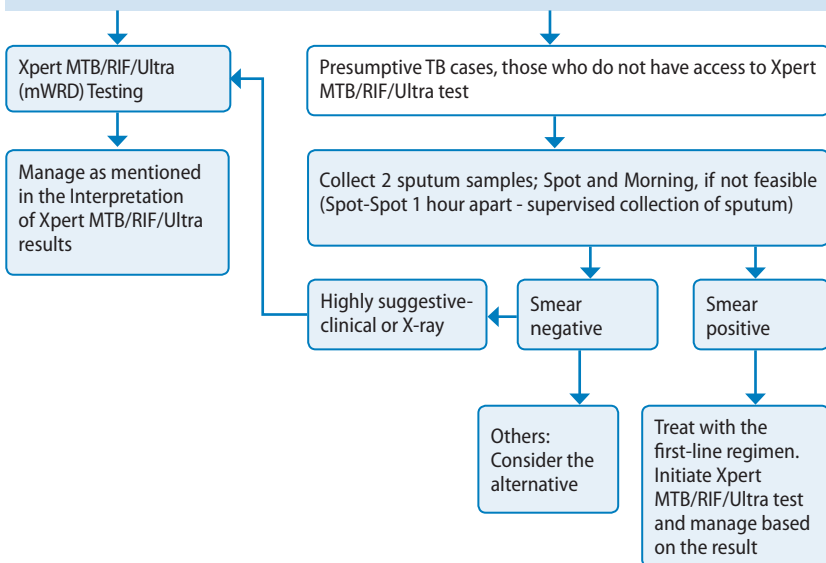
Method	Description	Advantages	Disadvantages
Spontaneous Sputum Sample	Patient coughs up sputum into a sterile container	• Inexpensive • Easy to do	• Patient may not be able to cough up sputum without assistance or may spit up saliva instead of sputum • Health care provider must coach and supervise the patient when collecting sputum
Sputum Induction	Patient inhales a saline mist which can cause a deep cough	• Easy to do • Used to obtain sputum when coughing sputum is not productive	• Specimens may be watery and may be confused with saliva (should be labeled "induced specimen") • Requires special equipment • May cause bronchospasm
Bronchoscopy with Lavage	Bronchoscope is passed through the mouth or nose directly into the diseased portion of the lung, which is lavaged (bronchoalveolar lavage [BAL]) to obtain specimen.	• Easy to do • Used to obtain sputum when coughing sputum is not productive	• Specimens may be watery and may be confused with saliva (should be labeled "induced specimen") • Requires special equipment • May cause bronchospasm
Gastric Aspiration	Tube is inserted through the patient's mouth or nose and passed into the stomach to get a sample of gastric secretions that contain sputum that has been coughed into the throat and then swallowed.	• Used to obtain samples in children who are not able to produce sputum when they cough	• Must be performed as soon as the patient wakes up in the morning • Patient may be required to stay in the hospital • Can cause discomfort for the patient

Source: Core Curriculum on Tuberculosis: What the Clinicians should know, CDC, 2021

1.6 Diagnostic algorithm and treatment initiation for new presumptive TB patients

Persons to be evaluated for TB (adults) with:

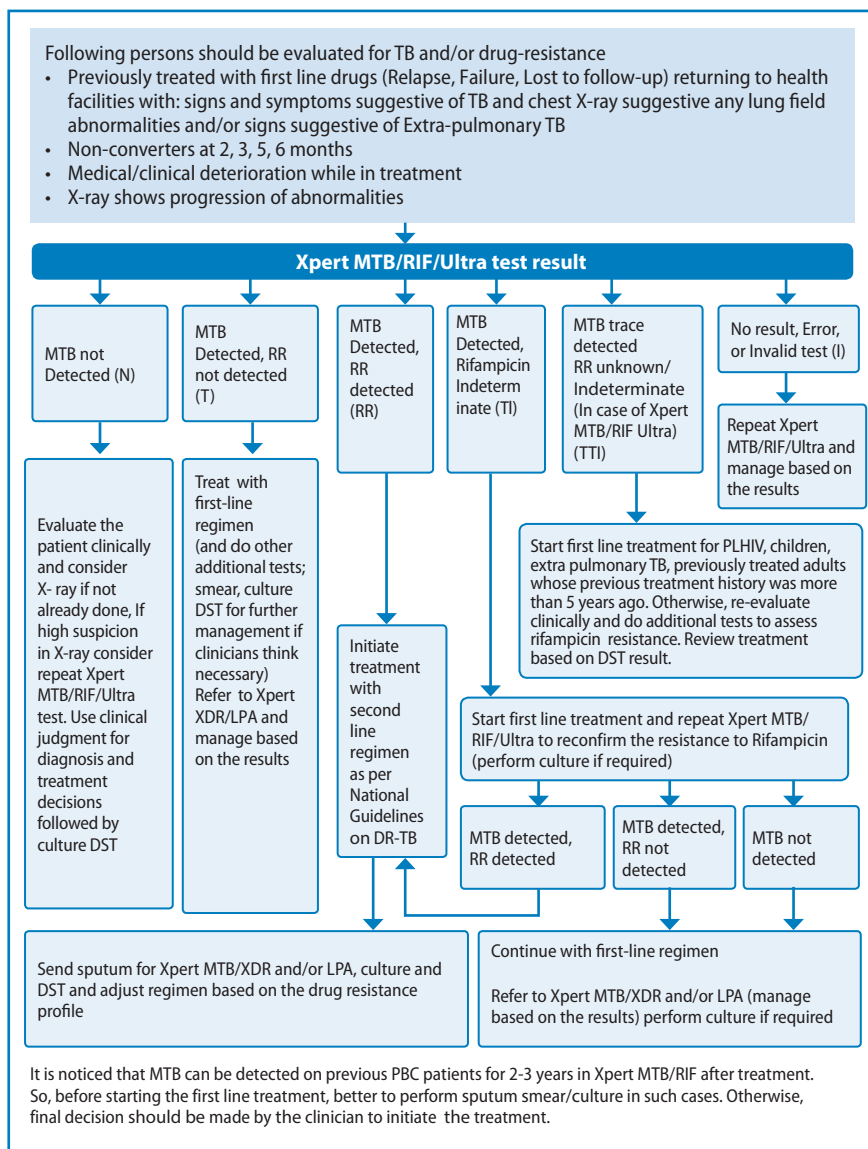
- Signs and symptoms suggestive of TB:
 - Cough for 2 weeks or more
 - Coughing sputum with or without blood
 - Fever (evening rise/low grade) and night sweats
 - Loss of appetite and unintentional weight loss
- Household contact (symptomatic) of bacteriologically confirmed TB
- Chest X-ray suggestive of any lung field abnormality
- Persons being evaluated for extrapulmonary TB



Notes:

1. Priority for diagnosis and rapid DST among new cases: PLHIV, Children, Symptomatic contacts of PBC and DR case, EP samples (CSF, lymph node and another tissue specimen), health care workers, people living in enclosed space (lum, prison, IDP etc.), immuno-compromised (patient under long term steroid therapy, Cancer, Diabetic).
2. All Priority cases and other presumptive cases who have access to Xpert will receive Xpert testing as an initial diagnostic test.
3. Sputum microscopy should be done for all diagnosed TB cases for monitoring purpose and where there is no access to Xpert MTB/RIF/Ultra test for diagnostic purpose.
4. For those new presumptive TB case with MTB detected, Rifampicin Resistance detected result from Xpert MTB/RIF/Ultra testing, if considered low risk of DR TB, the clinician can decide to repeat the test in case required.

1.7 Diagnostic algorithm and treatment initiation for previously treated TB patients and Interpretation of Xpert MTB/RIF/Ultra results



Note: DST (Drug susceptibility testing): In vitro testing using either: 1) molecular, genotypic techniques to detect resistance-conferring mutations (such as Xpert MTB/XDR) ; or 2) phenotypic methods (culture and susceptibility) to determine susceptibility to a medicine

1.8 Interpretation of Xpert MTB/RIF and/or Xpert MTB/RIF/Ultra results

Label	Result and Interpretation	Action to be taken
T	MTB detected; rifampicin resistance not detected	Diagnosis of TB confirmed. Treat with first-line TB regimen in new patients.
RR	MTB detected; rifampicin resistance detected	Refer to DR-TB treatment Center for the start of second-line TB treatment.
TI	MTB detected; rifampicin resistance indeterminate	Diagnosis of TB is confirmed. Start treatment with first-line regimen and send new sputum specimen to repeat the test to reconfirm the resistance to rifampicin. Pay special attention to quality of sputum sample, conditions of storage, transportation and speed of shipment. If the result is RR, refer to DR-TB treatment Center.
N	MTB not detected	Additional investigations are required to exclude TB.
I	Invalid/no result/error	Send a new sputum specimen to repeat the test. Pay special attention to quality of sputum sample, conditions of storage, transportation and speed of shipment
TTI	MTB trace detected; rifampicin resistance unknown/indeterminate (In Xpert MTB/RIF Ultra)	Start first-line treatment: • PLHIV • Children • Extrapulmonary TB • Adults being evaluated for pulmonary TB who - are not at risk of HIV and - who do not have a history of prior TB or TB treatment within the past 5 years Otherwise, reevaluate clinically, need to do additional tests* to assess rifampicin resistance. Review the treatment based on DST result.

Once RR is detected, the first thing is to inform and refer the patient to the DR-TB treatment center for treatment enrollment.

* In patients with a prior history of TB within the past 5 years or whose TB treatment was completed less than 5 years ago, Xpert Ultra trace results (and occasionally Xpert MTB/RIF " MTBC detected low or very low") may be positive, not because of active TB but because of the presence of non-viable bacilli. Clinical decisions must be made based on all available information and clinical judgement.

1.9 Interpretation of drug susceptibility test by LPA result and treatment decision

LPA is a rapid technique based on polymerase chain reaction (PCR) that is used to detect *Mycobacterium tuberculosis* (MTB) complex as well as drug susceptibility to rifampicin, isoniazid, ethambutol, fluoroquinolone and second line injectables (SLIs).

First Line LPA (FL-LPA): First Line LPA showed a sensitivity of 95.8% and a specificity of 98.4% for detection of rifampicin resistance by direct testing and a sensitivity of 94.5% and a specificity of 99.3% for detection of Isoniazid resistance. In Nepal, all previously treated patients with rifampicin susceptible result go for FL-LPA along with non-converters at 2/3, 5 and 6 months of treatment, medical/clinical deterioration while in treatment and X-ray shows progression of abnormalities.

Second Line LPA (SL LPA): Second Line LPA detects the resistance of second line anti-TB drugs such as fluoroquinolones and SLIs. It also detects the resistance of ethambutol. SL-LPA is done to all MDR/RR-TB cases.

	Mutation*	Meaning and resistance caused	Treatment regimen
First-line LPA result	<i>InhA</i>	Low level H resistance and confers resistance to Eto	Treat with the regimen for H-resistant TB
	<i>KatG</i>	High level H resistance and confers resistance to Hh	Treat with the regimen for H-resistant TB
	<i>Dual (InhA and KatG)</i>	High level H resistance and confers resistance to both Hh and Eto	Avoid Eto containing regimen
	<i>RpoB</i>	Rifampicin resistance with and without H resistance	Treat with MDR/RR-TB regimen
Second line LPA result (all RR-TB casepatients)	<i>GyrA, GyrB</i>	FQ resistance (Ofx, Lfx, Mfx)	Treat with FQ Resistant MDR/RR-TB Regimen (BPaL or longer regimen).
	<i>rrs, eis</i>	Resistance to Second-line injectables	Any regimen (Shorter/Longer Regimen)

Note: This is not provided in the official result but can be requested to the laboratory that will assist physicians in designing individualized regimens for DR-TB when standard regimen can't be used.

1.10 Diagnosis of extrapulmonary TB in adults

Common Symptoms

- Fever (found in up to 80% of all patients)
- Weight loss
- Night sweats
- Loss of appetite

Essential tests for presumptive EPTB

- Chest X-ray
- HIV test

Clinical approach to the diagnosis of EPTB

Site of EPTB	Typical Clinical Presentation	Investigations	Findings
Peripheral LNTB	Asymmetrical, painless, non-tender enlargement of lymph node (over 1 cm across) in the neck, armpit or groin.	Microscopy for AFB or culture of MTB or Xpert MTB/RIF or cytology from lymph node fluid or tissue, cytology in FNAC specimens.	Giant multinucleated cells (Langhans cells), surrounded by epithelioid cells aggregates, T lymphocytes and few fibroblasts.
Mediastinal LNTB	Patients with cough, fever, shortness of breath, weight loss or night sweats	Hilar widening on chest X-ray and/or mediastinal lymphadenopathy on chest CT	Granulomatous tubercles evolve to central caseous necrosis and tend to become confluent, replacing the lymphoid tissue.
Abdominal	Patients with dull or colicky abdominal pain, abdominal distension, weight loss, night sweats or fever	Evidence of abdominal lymphadenopathy on abdominal ultrasound scan, CT or MRI, cytology in FNAC specimens.	MTB detection from FNAC specimen in Xpert MTB/RIF
TB Meningitis	Any patient with clinical features of meningitis in the form of fever, headache, neck rigidity and vomiting, with or without altered sensorium and associated focal neurological deficits for a period of 5 days or more	CSF findings typical of TBM: lymphocytic (more rarely neutrophilic) pleocytosis with low serum:CSF glucose ratio and high protein.	Xpert MTB/RIF used as an essential test for TBM. A negative Xpert result does not rule out TBM. The decision to give ATT should be based on clinical features and CSF profile.

Site of EPTB	Typical Clinical Presentation	Investigations	Findings
Pleural TB	A patient with cough, chest pain or shortness of breath, with or without fever and weight loss, with evidence of a pleural effusion on examination or CXR	Collect pleural fluid for: a) glucose, protein, ADA and lactate dehydrogenase (LDH) levels (send concurrent blood sample for serum protein and LDH); b) differential cell count; c) microscopy and culture for MTB; and d) cytology, e) pleural biopsy	Pleural TB usually causes an exudative effusion, defined on the basis of Light's criteria (pleural fluid/ serum protein >0.5; pleural fluid/serum LDH >0.6; pleural fluid LDH > two- thirds the upper limit of serum LDH) Test for adenosine deaminase activity (ADA-2) level performed on pleural fluid can help support a diagnosis of pleural TB
Intestinal TB	Recurrent intestinal colic, partial or complete intestinal obstruction, chronic diarrhoea, unexplained weight loss, palpable mass in lower abdomen, lower GI bleeding	Suspects of TB affecting the lower and upper GI tract should be offered endoscopic examination with appropriate biopsy sampling. Biopsy specimens should be sent for: a) histology and staining for AFBs; b) culture for MTB; c) ultra sound	Assessment of the small intestine TB may require specialist imaging to identify and characterize lesions. Common findings include short segment strictures and ileocecal wall thickening with enlarged necrotic lymph nodes.
Peritoneal TB	Abdominal distension, abdominal swelling with ascites, abdominal pain, fever	Test of ascitic fluid can aid in the diagnosis of peritoneal TB. Specimens should be sent for: a) cytology; b) albumin and protein; c) adenosine deaminase (ADA); d) microscopy for AFB; e) culture for MTB; f) ultra sound	A serum albumin:ascitic fluid albumin ratio (SAAG) of 2.5 g/mL). ADA >39 IU/mL in ascitic fluid is suggestive of abdominal TB. intraabdominal fluid (free or loculated), inter-loop ascites, mesenteric lymphadenopathy, bowel wall thickening, enlarged lymph nodes with central necrosis and peripheral enhancement and peritoneal and omental thickening.

Site of EPTB	Typical Clinical Presentation	Investigations	Findings
Miliary TB	Symptoms of miliary tuberculosis can be vague and difficult to identify. They include weight loss, fever, chills, weakness, general discomfort, and difficulty breathing. Usually seen in immunocompromised people.	Samples of infected fluids may be examined under a microscope, culture, Xpert (MTB/RIF) and tested. Samples may be: CSF, obtained by lumbar puncture; urine; fluid from the space between the lungs pleura; fluid from the pericardium; joint fluid; bone marrow.	A chest x-ray may show the thousands of small spots that are typical in miliary tuberculosis. Other imaging tests are done depending on which areas of the body are affected. They may include computed tomography (CT), ultrasonography, and magnetic resonance imaging (MRI).
Spinal TB	Localized back pain for more than 6 weeks with tenderness, fever and weight loss, with or without signs of spinal cord compression. Patients with advanced disease may have severe pain, spinal deformity, paraspinal muscle wasting and neurological deficit.	MRI is useful in making a diagnosis in the early stages of disease. CTguided or open biopsy must be considered. Specimens should be sent for: a) Microscopy and culture for pyogenic bacteria; b) Microscopy and culture for MTB; c) histopathology/ cytology; d) GeneXpert	Diagnosis of Spinal TB made with the result of MRI (with or without neurological involvement); cytological and hisyopathological findings; AFB on Microscopy; growth of MTB in culture. Decision to initiate ATT made by Specialist.
TB of bone and joint	Affected part becomes painful and/or swollen with joint effusions and synovial thickening, causing boggy swelling with restricted range of motion. Systemic symptoms such as fever, weight loss, anorexia and regional lymphadenopathy may be present.	X-ray of affected part; USG may useful in the cases; biopsy mass or fluid sent for: a) Microscopy and culture for pyogenic bacteria; b) Microscopy, culture and Xpert (MTB/RIF) for MTB; c) histopathology/ cytology	Diagnosis of TB of bone and joint made with the result of xray; cytological and hisyopathological findings; AFB on Microscopy; growth of MTB in culture; MTB detection on Xpert (MTB/RIF). Decision to initiate ATT made by Specialist.

Site of EPTB	Typical Clinical Presentation	Investigations	Findings
TB pericarditis	Chest pain, shortness of breath, with or without fever and weight loss, distant heart sounds, apex beat difficult to palpate or haemodynamic abnormalities, who has evidence of pericardial effusion or constriction on chest X-ray, ECG or echocardiogram	All patients presenting with symptoms consistent with TB should have a chest X-ray. Echocardiogram (transthoracic) to confirm pericardial effusion and/or constriction. If pericardial fluid is obtained, it should be sent for cytology, GeneXpert and for ADA level may support the diagnosis.	Appearance of hilar widening, and a globular or “water bottle” heart shadow on chest X-ray; pericardial effusion and/or constriction, and can detect signs of impending tamponade in Echocardiogram; differential cell count and raised ADA level may support the diagnosis from pericardial fluid.
Urinary TB	Lower urinary tract symptoms (frequency, urgency and nocturia) associated with dysuria and/or haematuria for at least 2 weeks, which has not responded to a 5–7 day course of antibiotics. Some patients have systemic symptoms of fever, weight loss and night sweats.	Three to five early morning urine samples collected for staining and microscopy for AFBs and culture for MTB. To identify sterile pyuria, this may suggest urinary TB by routine culture. Cytology and histopathology may confirm the diagnosis of TB.	Histopathological result remains same as other EP TB: Smear AFB may be positive; culture and Xpert detects MTB in three to five early morning urine samples sediments.
Female genital TB	A premenopausal woman presenting with infertility, menstrual problems, unexplained abdominal pain or pelvic mass. A postmenopausal woman presenting with vaginal bleeding.	Aspirate or biopsy mass specimens should be examine for: a) staining and microscopy for AFBs; b) culture; and c) histopathology; d) GeneXpert	Laparoscopic appearance typical for FG TB; any gynaecological specimen positive for AFBs on microscopy or positive for MTB on culture; any gynaecological specimen with findings consistent with FG TB on histopathological examination.
Male genital TB	Scrotal pain or swelling for 2 weeks or more not responding to a 7–14 day course of antibiotics, or with discharging sinuses in the scrotum. Rarely systemic symptoms occur.	Biopsy specimens should be examine for: a) staining and microscopy for AFBs; b) culture and drug susceptibility testing; c) histopathology; d) GeneXpert	Specimen positive for AFBs on microscopy or positive for MTB on culture; any specimen with findings consistent with MG TB on histopathological examination.

1.11 Identifying presumptive TB in children

Pulmonary TB in children

Persistent, non-remitting cough for >2 weeks not responding to conventional antibiotics (amoxicillin, co-trimoxazole or cephalosporin) and/or bronchodilators

and/or

Persistent documented fever ($>38^{\circ}\text{C}/100.4^{\circ}\text{F}$) >2 weeks after common causes such as pneumonia, typhoid, malaria have been excluded

and/or

Documented weight loss or not gaining weight during the past 3 months (especially if not responding to de-worming together with food and/or micronutrient supplementation) OR severe malnutrition

and/or

Fatigue, reduced playfulness, decreased activity

Note: In a child (<15 years) in close contact with a known bacteriologically confirmed TB or clinically confirmed TB should be regarded as presumptive TB case and referred to for evaluation.

Extra pulmonary TB in children

- Extra pulmonary TB is common in children and presentation varies with age.
- Symptoms vary depending on site of disease and characteristically are persistent, progressive and may be associated with weight loss or poor weight gain.
- Clinical assessment in all cases should consider: History of contact, sputum/other relevant samples for smear microscopy/Xpert MTB/RIF and HIV test.

Identification of presumptive TB among <5 year children using TB score chart

At facility level, the TB score chart is a screening tool and does not exclusively include or exclude TB in a child. It is however very helpful in the diagnosis of TB and should be interpreted with the history, examination, and the results of investigations.

Feature	0	1	2	3	4	Score
Length of Illness (in weeks)	< 2	2-4		> 4		
Nutritional status (weight for age)	Above the -2 SD line	Between the -2 and -3 SD line		Less than the -3 SD line		
Recent close contact with an infectious TB case (adult PTB or bacteriologically confirmed)	None	Verbal history of TB contact		Proven bacteriologically confirmed contact		

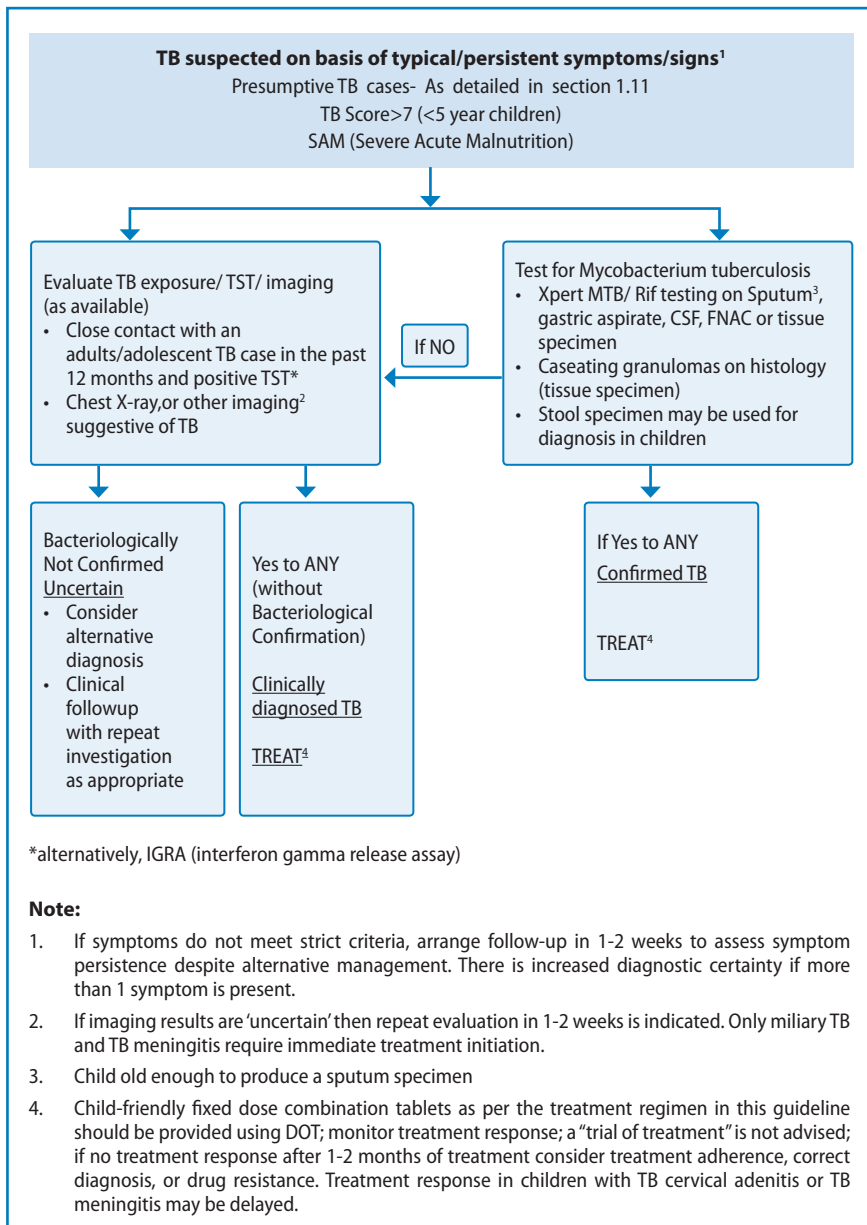
Feature	0	1	2	3	4	Score
Lymph nodes: large, painless, firm, soft sinus in neck/axilla				Yes		
Night sweats, unexplained fever			Yes			
Angle deformity of the spine					Yes	
Malnutrition not improving after 4 weeks of treatment				Yes		
Joint swelling, firm, on-fluid, on- traumatic				Yes		
Unexplained abdominal mass, ascites				Yes		
Coma for more than 48 hours (with or without convulsions)				Yes		

Note: If the child scores 7 or more and has no other disease more likely to explain the illness, confirm using other diagnostic as mentioned and then commence TB treatment based on the result and clinical judgement

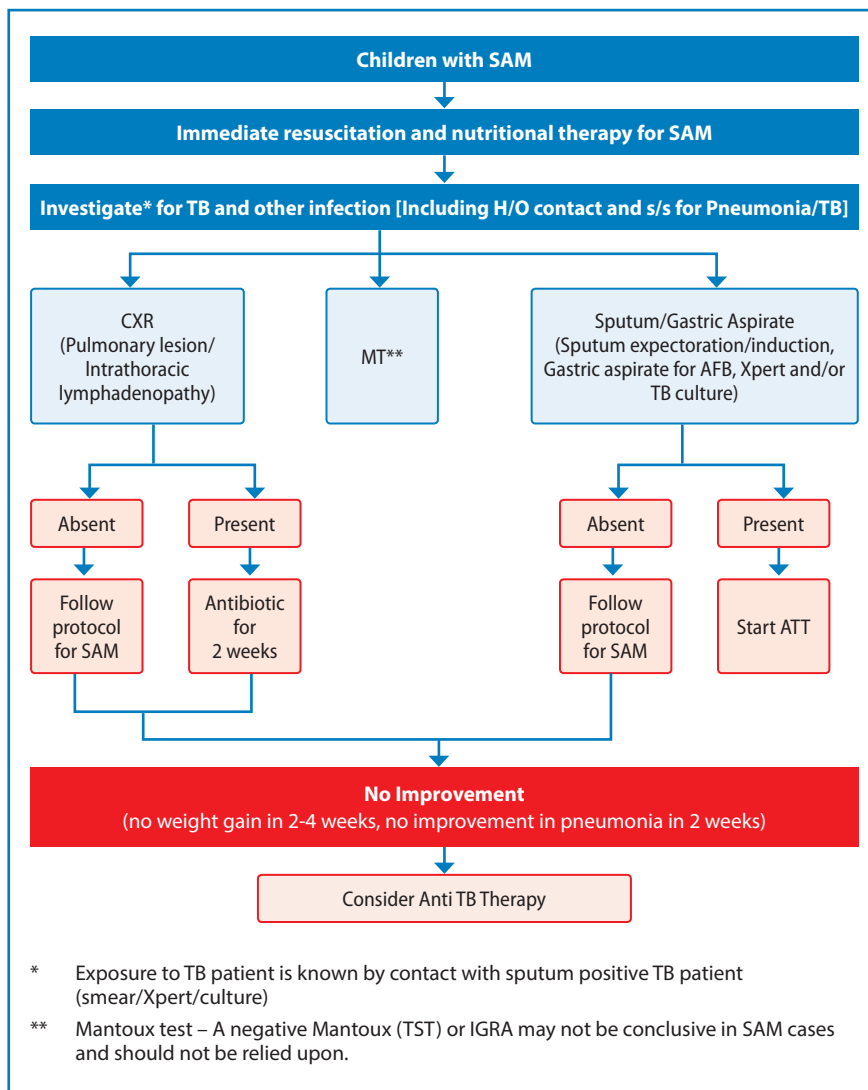
1.12 Critical signs requiring urgent hospital referral

- Severe respiratory distress (TB pneumonia with/without bacterial super infection, Pleural effusion)
- Severe wheezing not responding to bronchodilators (signs of severe airway compression)
- Headache (especially if accompanied by vomiting), irritability, drowsiness, neck stiffness and convulsions (signs of TB meningitis)
- Acutely ill with hepatosplenomegaly and ascites (signs of disseminated TB)
- Breathlessness and peripheral edema (signs of pericardial effusion)
- Acute angulation (bending) of the spine with/without paraplegia (a sign of TB spine-“gibbus”)
- Other co-morbidities e.g. severe anemia, severe malnutrition

1.13 Diagnostic algorithm of TB in Children (<15 years of age)



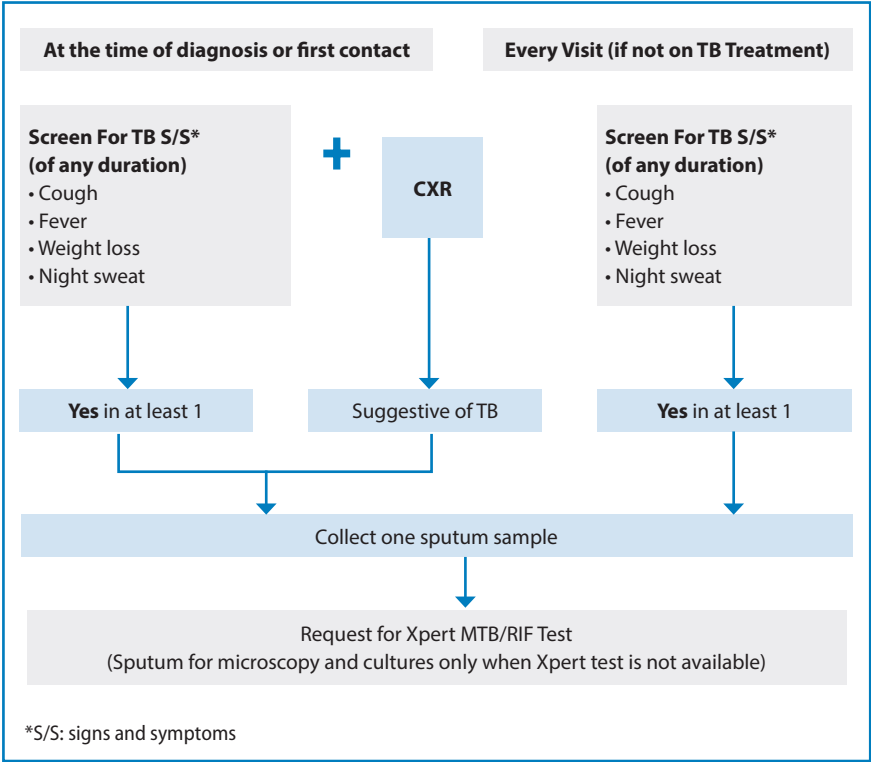
1.14 Screening and management of TB in Severe Acute Malnutrition (SAM) children



Note:

- Xpert MTB/RIF should be prioritized first for the diagnosis of TB among presumptive TB children.
- Stool specimen may be used to perform Xpert MTB/RIF Ultra

1.15 Systematic Screening for the Diagnosis of Active Pulmonary TB Disease among PLHIV, Diabetes and other immune suppressant co-morbid conditions



Drug Susceptible (DS) TB Treatment and Management

Treatment of tuberculosis should be started immediately after confirmation of TB diagnosis. There is NO room for trial treatment. For TB patients to be effectively treated, TB patients must be given the right drugs in the right combinations, appropriate dosage, administered correctly and regularly for the appropriate duration of time under observation.

All TB patients whether bacteriologically confirmed or clinically diagnosed will receive Treatment Regimen (2HRZE/4HR). In patients who require TB re-treatment, drug susceptibility testing should be conducted to inform the choice of treatment regimen. If susceptible to rifampicin and isoniazid, treatment regimen (2HRZE/4HR) should be given and if resistant, should be managed as per resistance pattern. There is no room for the addition of an injectable agent for drug-susceptible mycobacterium.

The following table indicates the drugs and different duration of treatment

2.1 DS TB treatment and anti-TB drug regimens

Type of TB		Intensive phase	Continuation phase
New TB case (Xpert MTB/RIF-Rifampicin sensitive) • Adult • Bacteriologically confirmed or clinically diagnosed • Pulmonary or extra pulmonary		2HRZE	4HR
Complicated or severe EP TB (CNS TB, TB pericarditis, musculoskeletal, miliary TB)		2HRZE	7-10 HRE*
Previously treated cases or Isoniazid resistant (Hr) TB			
Xpert MTB/RIF/Ultra (Rifampicin susceptible)	Xpert MTB/XDR/LPA-INH susceptible	2HRZE	4HR
1st sputum for Xpert MTB/RIF/Ultra testing; if MTB detected/Rifampicin susceptible, follow with Xpert MTB/XDR/LPA for INH and FQ resistance status, and check phenotypic DST for SLD***	Xpert MTB/XDR/LPA - INH resistance, FQ susceptible	6 (H)RZE+Levofloxacin** (full duration)	
	If Xpert MTB/XDR/LPA not available (INH susceptibility not known)	6 HRZE (full duration)	
	INH resistance and FQ resistance	6 (H)RZE****	
Xpert MTB/RIF/Ultra (Rifampicin resistance)	Refer to National DR TB guideline		

* For complicated EP cases, if treatment is required beyond 12 months, then refer to a higher level centre (e.g. NTCC or other specialized hospitals) for treatment decisions

** Addition of FQ to (H)REZ is recommended in Hr-TB except: i. in cases where resistance to rifampicin is not known; ii. known or suspected resistance to FQ; iii. known intolerance to FQ; iv. risk for QT prolongation; and v. if possible, in pregnancy or during breastfeeding (not an absolute contraindication).

*** Depending on the patients' response and laboratory evidence, clinicians at higher-level centers can use laboratory evidence/results to inform further management where necessary.

**** Although WHO recommends 6(H)RZE in these cases, addition of second-line drugs such as Linezolid and Ethionamide may be considered especially if additional resistance is suspected (e.g. to PZA). Refer to higher centers.

Note: For previously treated cases, consider culture and DST to avoid the possibility of rifampicin resistance

2.2 Summary of Extrapulmonary TB (EPTB) treatment

SN	Site of EPTB	Treatment	Remarks
1	TB adenitis	Intensive phase: HRZE 2 months Continuation phase: HR 4 months	If axillary node enlarged on the same side as BCG, consider BCG disease
2	Miliary TB	Intensive phase: HRZE 2 months Continuation phase: HRE 7-10 months	Send CSF for Xpert MTB/RIF and AFB culture and DST Inpatient management initially
3	TB meningitis	Intensive phase: HRZE 2 months Continuation phase: HRE 7-10 months Steroids: Dexamethasone or Prednisolone tapered over 6-8 weeks	Send CSF for Xpert MTB/RIF and AFB culture and DST Inpatient management initially*
4	TB Pericarditis	Intensive phase: HRZE 2 months Continuation phase: HRE 7-10 months Steroid: Prednisolone in tapering dose over 8 weeks	Refer to higher center for pericardial tap and fluid analysis
5	Pleural TB	Intensive phase: HRZE 2 months Continuation phase: HR 4 months	same as pulmonary TB
6	TB Bone and Joints	Intensive phase: HRZE 2 months Continuation phase: HRE 7-10 months	Joint tap for Xpert MTB/RIF
7	Abdominal TB Genitourinary TB Skin TB	Intensive phase: HRZE 2 months Continuation phase: HR 4 months	Send peritoneal fluid for fluid analysis

*For TB meningitis, ethionamide can be added in the treatment regimen full duration

Treatment of DS TB using 6-month regimen

1. New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR
2. Daily dosing frequency throughout the treatment course is recommended
3. The use of fixed-dose combination (FDC) tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB
4. In new pulmonary TB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended

Drug-susceptible TB treatment and antiretroviral therapy (ART) in people living with HIV

5. 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
6. TB patients who are living with HIV should receive at least the same duration of TB treatment as HIV-negative TB patients

The use of adjuvant steroids in the treatment of TB meningitis and pericarditis

7. In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used
8. In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used

Source: WHO Guidelines for DS TB, 2022

2.3 Dosing for DS TB Treatment (Adults and Children)

Standard Regimens for DS-TB: Dosing for Adults

Number of Tablets			
Weight	Intensive phase	Continuation phase	
bands	HRZE 75/150/400/275	HR 75/150	HRZE 75/150/400/275
30-39 kg	2	2	2
40-54 kg	3	3	3
55-70kg	4	4	4
>70 kg	5	5	5

Standard Regimens for DS-TB: Dosing for Children

Number of Tablets			
Weight	Intensive phase		Continuation phase
bands	HRZ 50/75/150	E 100mg	HR 50/75
4-7.9 kg	1	1	1
8-11.9 kg	2	2	2
12-15.9kg	3	3	3
16-24.9kg	4	4	4
25kg+ Use adult dosages and preparations			

First-line Anti-TB Drug Dosing in Children (by body weight)

Anti-TB Drug	Pediatric Daily Doses
Rifampicin (R)	15 mg/kg (10-20mg/day) with a max of 600 mg per day
Isoniazid (H)	10 mg/kg(7-15 mg/kg) with a max of 300 mg
Pyrazinamide (Z)	35 mg/kg(30-40 mg/kg)
Ethambutol (E)	20 mg/kg(15-25mg/kg)

2.4 Monitoring and follow up management of DS TB

Schedule of Sputum follow-up examinations for Bacteriologically confirmed Pulmonary TB on DS-TB Regimen

Follow up	Month of Follow up	Action to take be taken
End of Intensive Phase	2	1. Start the continuation phase. 2. Collect sputum for microscopy 3. If positive, send sputum for Xpert MTB/RIF/Ultra and/or Xpert MTB XDR/LPA, No extension of the intensive phase
In case smear positive at the end of the intensive phase (2nd month) and Rif-and INH sensitive	3	1. Repeat sputum again at 3rd month, continue treatment and if positive; collect sputum and send for Xpert MTB/RIF/Ultra test and/or Xpert MTB XDR/LPA 2. Treat based on Xpert results
During continuation phase	5	1. Repeat sputum. 2. If repeat sputum is negative and no symptoms of TB continue treatment. 3. If repeat sputum is positive: a. Declare failure and record treatment outcome as failed b. Collect sputum and send for Xpert MTB/RIF/Ultra and Xpert MTB XDR/LPA c. Treat based on Xpert results d. If Xpert MTB/RIF/Ultra shows Rifampicin Resistant, Refer to National Guidelines on DR TB management. e. If RR not detected and Xpert MTB XDR/LPA shows INH resistant, start INH resistant regimen*
End of treatment	6	1. Repeat sputum. 2. If repeat sputum smear is negative, determine treatment outcome as "Cured" or "Treatment Completed". 3. If sputum is not being produced and there are no other signs of clinical deterioration, the outcome is treatment completed. 4. If repeat sputum smear is positive: a. Declare failure and record treatment outcome as failed b. Collect sputum and send for Xpert MTB/RIF/Ultra and Xpert MTB XDR/LPA c. Treat based on Xpert results d. If Xpert MTB/RIF/Ultra shows Rifampicin Resistant, Refer to National Guidelines on DR TB management. e. If RR not detected and Xpert MTB XDR/LPA shows INH resistant, start INH resistant regimen*

* Failure cases with H resistance will need additional second-line agents (apart from Lfx) such as Lzd, Cs and Eto to avoid adding a single drug "Lfx" to a failed regimen

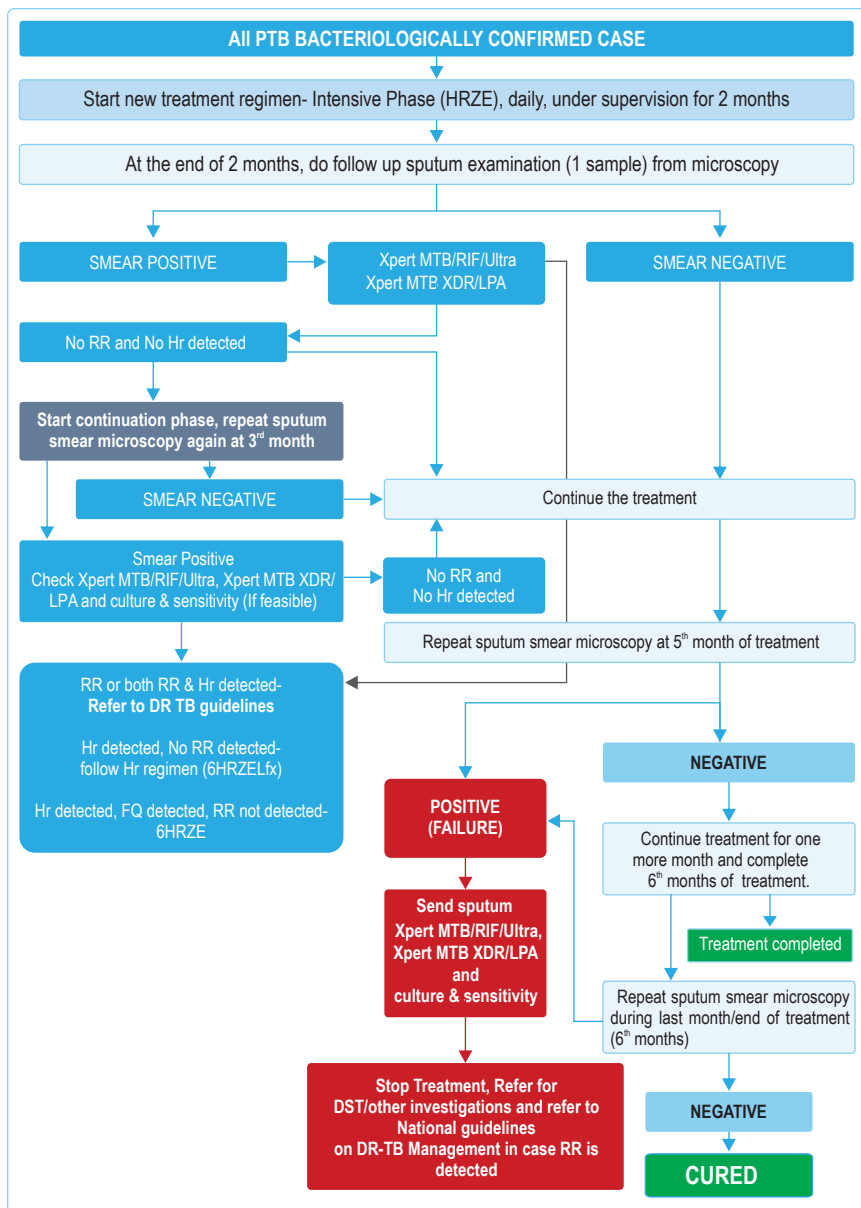
Note:

1. Only one sputum sample is required during each follow up.
2. Xpert test is not used for follow-up examination to monitor treatment because current- generation PCR-based tests are unable to determine *Mycobacterium tuberculosis* viability and may test positive even with nonviable or dead bacilli.
3. Do Xpert testing if smear microscopy is positive at the end of intensive phase (month 2/3), at 5th and end of treatment

Follow up and monitoring of bacteriologically negative PTB and EPTB cases

Monitor treatment of bacteriologically not confirmed PTB and EPTB by clinical assessment, weight and eventually X-Ray. New PTB bacteriologically not confirmed cases and EPTB should have sputum examination at the end of the intensive phase. Both bacteriologically not confirmed PTB and EPTB patients, sputum should be checked in case of suspicion of failure. If a bacteriologically not confirmed PTB and EPTB patient becomes smear/Xpert MTB/RIF/Ultra test positive at the end of the intensive phase, then the patient should be declared treatment failure and should be re-registered as a treatment after failure case. The patient should be restarted on treatment under strict DOT and if rifampicin resistance is detected, refer to latest National Guidelines on Drug Resistant TB management.

2.5 Flow Chart for Management and Follow up of Pulmonary Bacteriologically Confirmed (PBC) TB Cases



Note: Treatment Success = (Cured+Treatment Completed)

2.6 Management of patients who interrupted treatment

Retrieval action should be taken within 24-48 hours if a TB patient misses a dose for more than 24 hours or a treatment supporter or self-administered patient fails to collect drugs. The treatment centre should identify early defaulters and act immediately. Priority is given to bacteriologically confirmed PTB. Treatment is continued and prolonged to make up for missed doses. It is very important to find the cause of the interruption and take appropriate action to prevent further interruptions. A patient is regarded as lost to follow up after he or she misses treatment for more than 2 consecutive months.

The following is the summary of actions to take after interruption of treatment

Interruption for less than 1 month:

Patients who interrupt treatment must be traced urgently within 24-48 hrs, for patients who have interrupted treatment less than 1 month. The interrupted doses must be managed by adding missing doses and continue treatment to prevent the development of drug resistance.

Interruption for 1 up to 2 months:

First	Then, act based on the results of sputum examination	
- Trace the patient - Solve the cause of the interruption - Collect 2 sputum samples and send for microscopy/ Xpert MTB/ RIF/ Ultra	If all the smears are negative, or no RR or if the patient has extra-pulmonary TB	Continue treatment and prolong it to compensate for missed doses. Ensure that the total number of doses planned for the initial phase and continuation phase is given.
	If one or more smears are positive and RR not detected	Restart treatment and complete full course under DOT
	If RR detected	Refer to National Guidelines on Drug Resistant TB

Interruption for 2 months or more:

- | | |
|---|---|
| <ul style="list-style-type: none"> Trace the patient | <ul style="list-style-type: none"> Determine and address the cause of interruption |
|---|---|

Do the following:

First	Then, act based on the results of sputum examination	
- Trace the patient - Solve the cause of the interruption - Collect 2 sputum samples and send for microscopy/ Xpert MTB/ RIF/ Ultra and/or Xpert MTB/XDR	If all the smears are negative, or no RR or if the patient has extra-pulmonary TB	Restart treatment
	If one or more smears are positive and RR not detected	Restart treatment
	If RR detected	Treat as National Guidelines on DR TB

Drug-resistant (DR) TB Treatment and management

3.1 Types of Drug Resistant (DR) TB

Based on drug susceptibility testing (DST) of clinical isolates confirmed to be *M. tuberculosis*, DR TB is classified into below category:

- **Monoresistance:** resistance to one first-line anti-TB drug only.
- **Polydrug resistance:** resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).
- **Isoniazid Resistant TB (Hr-TB):** TB disease caused by a strain of *M. tuberculosis* complex that is resistant to isoniazid but susceptible to Rifampicin
- **Rifampicin resistant (RR TB):** TB caused by *M. tuberculosis* strains that is resistant to Rifampicin.
- **Multidrug resistant (MDR TB):** resistance to at least both isoniazid and rifampicin.
- **Pre-Extensively Drug-Resistant TB (Pre-XDR TB):** TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin)
- **Extensively Drug-Resistant TB (XDR TB):** TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one “Group A” drug (Bedaquiline or Linezolid).

3.2 Treatment of Isoniazid Resistant TB (Hr-TB)

The basic regimen for Rifampicin susceptible but Isoniazid Resistant TB (Hr TB) is treatment with Rifampicin, Ethambutol, Pyrazinamide and levofloxacin for a duration of 6 months.

Hr-TB Regimen - 6(H)RZE-Lfx

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

6(H)RZE may be prescribed daily for 6 months. Failure of first-line anti TB treatment with H resistance will need additional second-line agents (apart from Lfx) such as Lzd, Cs and Eto to avoid adding a single drug “Lfx” to a failed regimen.

Dosages for drugs used in Hr-TB regimen by weight bands for adults and children

S.N.	Drugs	30-39kg	40-54kg	55-70kg	>70kg
Adults					
1	Rifampicin (R-150mg)	2 tab	3 tab	4 tab	5 tab
2	Ethambutol (E-275mg)	2 tab	3 tab	4 tab	5 tab
3	Pyrazinamide (Z-400mg)	2 tab	3 tab	4 tab	5 tab
4	Levofloxacin (Lfx-250mg)	2 tab	3 tab	4 tab	5 tab
Children		4-7.9kg	8-11.9kg	12-15.9kg	16-24.9kg
1	Rifampicin (R-75mg)	1 tab	2 tab	3 tab	4 tab
2	Ethambutol (E-100mg)	1 tab	2 tab	3 tab	4 tab
3	Pyrazinamide (Z-150mg)	1 tab	2 tab	3 tab	4 tab
4	Levofloxacin (Lfx-100mg)	1 tab	2 tab	3 tab	4 tab

Children weighing more than 25kg - Use adult dosages and preparations (up to 1.5g/day)

Levofloxacin dosing for children

If levofloxacin 100mg dispersible tablet is not available, the 250mg tablet can be used with 6(H) RZ+E in children aged 0-14 years, based on a slightly different weight band from the one above:

Weight bands in children	Levofloxacin (250mg)
5-6 kg	½ tablet/ day
7-9 kg	¾ tablet /day
10-11.5 kg	1.5 tablet/day
16-23 kg	1.5-2 tablets/day
24-30 kg	2-2.5 tablets/day
31 kg +	Follow adult schedule (up to 1.5g/day)

Total duration of Hr-TB regimen is 6 months. It can be extended directly to 9 months in certain conditions. In patients with cavitory disease; extensive disease; uncontrolled comorbidity; extra- pulmonary TB; if smear at the end of month 4 is found positive and when regimen is modified, the treatment may be directly extended to 9 months.

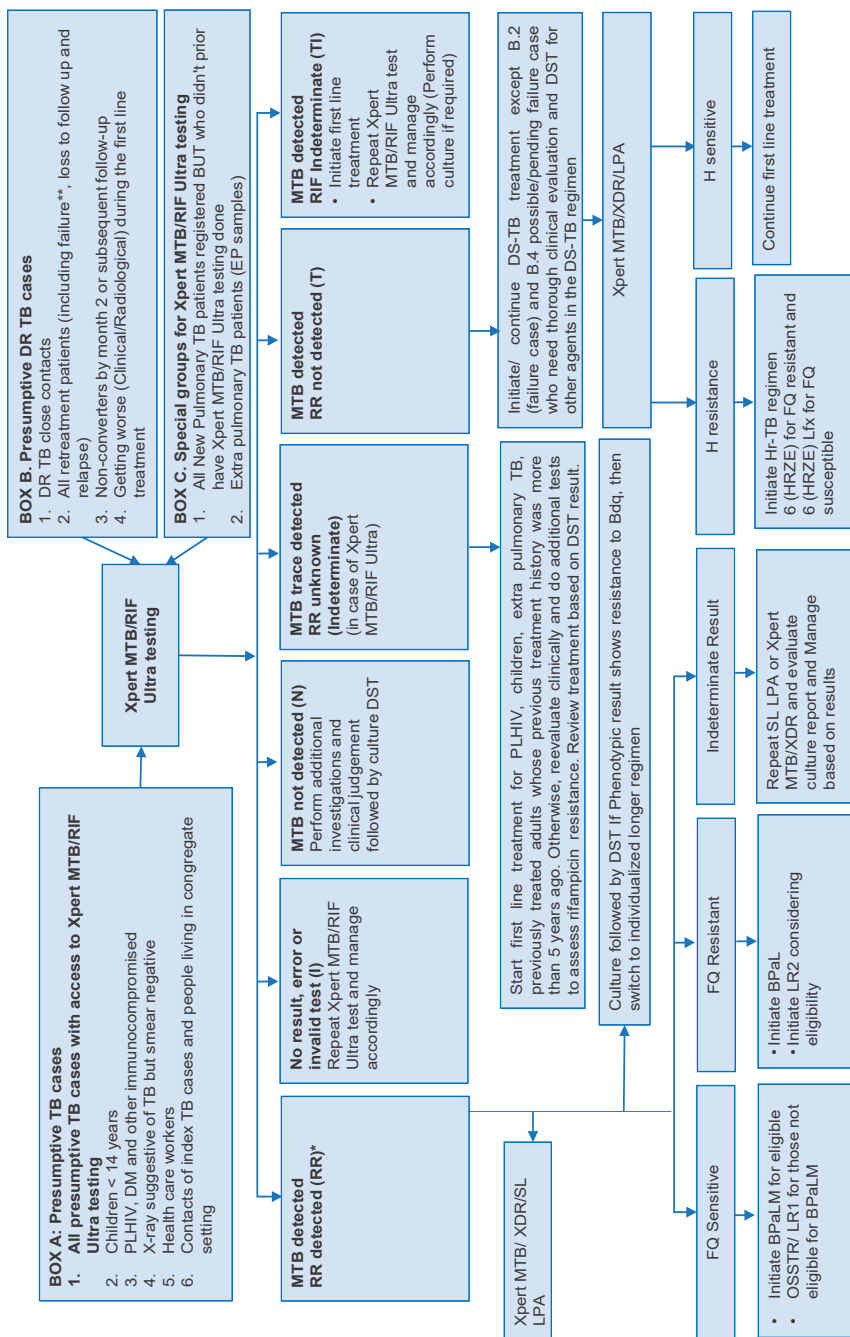
In patients who remain sputum smear positive at the end of month 5 or later, the treatment outcome will be declared as 'treatment failed' and the patient will be re-evaluated as per the diagnostic algorithm as a non-responder.

Situation	Sequence of using replacement drugs
If FQ Resistance	Continue (H)RZE without FQ drugs if H resistance only on InhA, then consider high dose of Isoniazid
If R resistance	Switch to appropriate shorter or longer second line treatment

Follow-up evaluation schedule of Hr-TB patients

Regimen class	Hr-TB regimen
Duration	6 or 9 months (no separate IP/CP)
Clinical + Wt.	Monthly till the end of treatment
Smear microscopy	Monthly from month 3 onwards till the end of treatment Perform sputum smear microscopy within 7 days, if the smear at month 4 or later is positive to rapidly ascertain bacteriological conversion/reversion
Culture	At end of month 3, end of treatment (month 6 and/or 9 if applicable) If the culture results of month 3 are positive, collect one repeat specimen for culture to rapidly ascertain bacteriological conversion/ reversion. If the repeat specimen is culture negative, then ensure specimen collection at the end of treatment
DST	If Smear/culture reversion found

3.3 Decision tree for the diagnosis and treatment of MDR/RR TB



*For new cases with low risk of MDR/RR TB, clinician may consider to repeat the Xpert MTB/RIF/ Ultra testing
 ** In failure cases, if H resistant diagnosed, consider to refer to the TB specialists (NTCC)

3.4 Treatment of Multi-drug/Rifampicin Resistant (MDR/RR) TB

The key factors that define treatment regimen include drug-resistance profile, prior exposure to TB medicines and patient history, drug-resistance profile of close contacts, the patient's age, extent of pulmonary TB disease and localization of extrapulmonary TB lesions. The MDR/RR-TB treatment regimen are:

A. Shorter Regimen

- BPaLM/BPaL regimen – 6 months
- All oral standardized treatment regimen (OSSTR) – 9 months

B. Longer regimen (Standardized or Individualized): 18 months

Regimen	MDR/RR TB fluoroquinolone susceptible	Pre-XDR-TB	XDR-TB	Extensive pulmonary TB	Extrapulmonary TB	Age <14 years
6-month BPaLM/BPaL	Yes (BPaLM)	Yes (BPaL)	No	Yes	Yes - except TB involving CNS/meningitis, miliary TB, osteoarticular TB and pericardial TB	No
9-month all-oral regimen (OSSTR)	Yes	No	No	No	Yes - except TB involving CNS/meningitis, miliary TB, osteoarticular TB and pericardial TB	Yes
18 months Longer Regimen	Yes*/No	Yes*/No	Yes	Yes	Yes	Yes
Additional factors to be considered if several regimens are possible	Drug intolerance or adverse events					
	Treatment history, previous exposure to regimen component drugs or likelihood of drug effectiveness					
	Patient or family preference					
	Access to and cost of regimen component drugs					

BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin, CNS: central nervous system; MDR/RR-TB: multidrug- or rifampicin-resistant TB; TB: tuberculosis; XDR-TB: extensively drug- resistant TB.

* When 6-month BPaLM/BPaL and 9-month regimens could not be used

- The initial preferred regimen for MDR/RR patients should be 6 month BPaLM regimen. Decision will be taken based upon the eligibility criteria for each regimen.
- The initial preferred regimen for Pre XDR TB patients should be BPaL regimen and the decision is taken based upon the eligibility criteria.
- For XDR TB patients treatment, consult with TB specialists at higher centers (NTCC) and longer regimen based on DST profile.

3.4 A. Shorter Regimen

BPaLM (BPaLM) (6 Bdq-Pa-Lzd-Mfx)

The 6-month BPaLM regimen, comprising bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin should be the initial choice for all eligible patients diagnosed with MDR/RR-TB.

- This regimen is used without moxifloxacin (BPaL) in the case of documented resistance to fluoroquinolones (in patients with pre-XDR-TB).
- Drug susceptibility testing (DST) to fluoroquinolones is strongly encouraged, but DST should not delay treatment initiation.
- The duration of BPaLM regimen is largely standardized for 6 months (26 weeks), whereas BPaL can be extended to a total of 9 months (39 weeks) in selected patients.

Indication

- People with MDR/RR TB (BPaLM) or with MDR/RR TB and resistance to fluoroquinolone i-e pre XDR TB (BPaL)
- People with confirmed pulmonary TB and all forms of EP TB except for TB involving CNS, osteoarticular, pericardial TB and disseminated (miliary) TB.
- Adults and adolescents aged 14 years and older.
- All people regardless of HIV status
- 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.

Contraindication

- Severe EPTB such as TB involving CNS, osteoarticular, pericardial and disseminated (miliary) TB.
- 1-month or more previous exposure to bedaquiline, linezolid, pretomanid or delamanid unless resistance to those drugs has been ruled out.
- Pregnant and breastfeeding women

- XDR TB according to 2021 WHO definition
- Children below 14 years
- Patients having allergy to any of the BPaLM component drugs

BPaL Regimen

- The BPaL regimen is provided for those who have proven fluoroquinolone resistance from DST.
- The BPaL regimen uses the same doses of pretomanid, bedaquiline and linezolid as the BPaLM regimen
- If fluoroquinolone resistance is detected while an individual is on the BPaLM regimen, moxifloxacin is omitted from the regimen and BPaL is continued.
- Individuals who switch from BPaLM to BPaL should consider their treatment start date the same as the date BPaLM was initiated.
- The treatment duration of BPaL regimen is 6 months.
- The duration of the treatment can be extended to 9 months (39 weeks) continuing from the start of the therapy with BPaLM or BPaL. The extension of the BPaL regimen to 9 months can occur where there is lack of culture conversion or clinical response (based on the clinical judgement of the treating physician) between 4 and 6 months.

Drug dosing for BPaLM/BPaL regimen

Drug	Formulation	Daily dose
Bedaquiline	100 mg tab	200 mg daily for 8 weeks; then 100 mg daily (18 weeks)
Pretomanid	200 mg tab	200 mg once daily
Linezolid	600 mg tab	600 mg once daily
Moxifloxacin	400 mg tab	400 mg once daily

- Dose modifications for bedaquiline, moxifloxacin and pretomanid are not allowed.
- Given the lack of evidence for the use of other fluoroquinolones, substitution of moxifloxacin with levofloxacin is not recommended.
- Dose modification of linezolid should be avoided in the first 9 weeks of therapy.
- The recommended dose of linezolid is 600 mg once daily, both for the BPaLM and the BPaL regimen.
- Linezolid should be continued at the full dose for the entire duration; however, the dose of linezolid can be reduced to 300 mg or discontinued (and restarted when possible), if there is significant toxicity (depending on the severity of the specific adverse events or serious adverse events) associated with linezolid, including optic neuritis, peripheral neuropathy, or myelosuppression.

Nine months all-oral standardized shorter treatment regimen (OSSTR)

The regimen consists of an initial phase of 4 months (including 6 months of bedaquiline) that may be extended up to 6 months and a continuation phase of 5 months, giving a total duration of 9-11 months.

Composition and duration of the regimen

i. The Linezolid variation

This is the preferred regimen and it is summarized as:

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

ii. The Ethionamide variation

The regimen is summarized as:

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

***Note:** In view of higher risk of QT prolongation with moxifloxacin, when used along with other drugs (Bdq and Cfz), levofloxacin is preferred for OSSTR.

Indications

- Patients with no documented resistance or suspected ineffectiveness or less than 1- month previous exposure to its component drugs i.e., bedaquiline, fluoroquinolones, INH, clofazimine, or ethionamide or linezolid.
- Children (less than 14 years)
- Women who are pregnant or breastfeeding are eligible for the linezolid containing OSSTR.
- Linezolid containing regimen is also preferred* in patients with:
 - serum haemoglobin above 8 g/dL
 - neutrophils above $0.75 \times 10^9/L$
 - platelets above $150 \times 10^9/L$ (at the start of treatment)
 - no evidence of severe peripheral neuropathy, or any sign or suspicion of optic neuritis, at the start of treatment.
- Ethionamide containing regimen is preferred in patients with pre-existing hematological abnormalities (as above) and severe peripheral neuropathy.
- If pretomanid (in BPaLM regimen) is not available for some reason, OSSTR may be used, if eligible.
- In case of mutation to both *InhA* and *KatG*, ethionamide based regimen cannot be used. Thus, linezolid variation should be used in these patients.

* In doubtful cases, expert opinion can be sought

Contraindications

- MDR/RR-TB Patients with FQ resistance.
- Severe EPTB such as TB meningitis, miliary TB, osteoarticular TB and pericardial TB.
- Extensive pulmonary TB disease.

Points to remember:

The nine month all-oral shorter (OSSTR) regimen should be implemented as a standardized package. It is not advisable to change the composition of the regimen or the duration of either the initial or continuation phase, with a few exceptions, as follows:

- Bedaquiline is usually given for 6 months but may be extended to 9 months if the initial phase of the regimen is extended from 4 to 6 months because of positive sputum smears at month 4 of treatment.
- Linezolid is only given for initial 2 months (instead of 4–6 months of ethionamide). If occasional doses of linezolid are missed during that time, the missed doses can be added on to the end of the 2-month period if the patient is tolerating the drug well, however, once fluoroquinolone resistance has been definitively ruled out, it may not be strictly necessary to make up the missed doses.
- The linezolid dose should not be reduced to less than the recommended dose to reduce the severity of adverse effects. If the full dose of linezolid (600 mg in adults) is not tolerated for the first full 2 months of treatment (apart from occasionally missed doses, which can be added to the end of the 2-month period), then the patient must either switch to an ethionamide-containing OSSTR regimen (provided fluoroquinolone susceptibility is confirmed and the patient is not pregnant) or to an individualized longer regimen without linezolid.
- If, for any reason, a patient is unable to tolerate pyrazinamide or ethambutol within the OSSTR, then one (but only one) of these drugs may be dropped during the continuation phase without necessitating a switch to a longer regimen.
- If two or more of these drugs are not tolerated within the OSSTR, the treatment will have to switch to a longer regimen. If any of the other drugs within the 9-month regimen (bedaquiline, levofloxacin/moxifloxacin, linezolid/ethionamide or clofazimine) are stopped early because of toxicity or intolerance then the patient will also have to switch to a new regimen. Patients switching to a new regimen due to toxicity or intolerance need to be reported as “treatment failed”.
- At the fourth month of treatment on the OSSTR, the decision to extend the initial phase from 4 to 6 months is based on the sputum smear status and clinical response. If the specimen is smear negative at month 4 (regardless of smear status at the start of treatment), the patient may move to the continuation phase of treatment. If the specimen is smear positive at month 4, the initial phase is prolonged to 6 months. The duration of the continuation phase remains fixed at 5 months.
- At the sixth month of treatment, the culture result from the specimen taken at month 4 and possibly month 5 should be available.

POSITIVE CULTURE AT 4 MONTHS: The clinician should undertake a full work-up to assess for treatment failure

- Comprehensive clinical assessment
- Review of treatment adherence to address specific challenges
- Radiological assessment
- Collection of another respiratory sample for bacteriological assessment, as well as repeat DST of the most recent positive culture to test for emerging resistance to second-line TB drugs

POSITIVE CULTURE AT 5 & 6 MONTHS (if extended)

- Treatment failure should be suspected, particularly if the patient has had suboptimal adherence to treatment or shows other signs of poor clinical or radiological response to treatment.
- These patients must switch to a different regimen.

Drugs, dosages, frequency, and duration of administration

The OSSTR consists of an initial phase of 4 months with 7 drugs, followed by a continuation phase of 5 months with 4 drugs. If Eto is used, it should be introduced gradually. On day 1, treatment will start with all drugs except Eto. If there is no major adverse event on day 1, Eto 250 mg will be added on day 2. The dosage of Eto will be escalated to 500mg on day 5 if patient can tolerate Eto 250 mg, and further escalated to 750mg (250mg in the morning, 500mg in the evening) on day 8 if necessary, depending on patients' body weight. An antiemetic drug may be used if there is gastrointestinal disturbance.

TABLE 4.5: Medicines used in OSSTR

Month	1	2	3	4	5	6	7	8	9	10	11
Bedaquiline											
High-dose isoniazid											
Ethionamide							Ethionamide Variation				
Moxifloxacin/Levofloxacin											
Clofazimine											
Pyrazinamide											
Ethambutol											
Linezolid			Linezolid Variation								

Orange	OSSTR Regimen
Blue	Added months if still smear/culture positive after 4 months of treatment
Green	added, if necessary
Pink	Only if Linezolid variation is used

3.4 B. Longer regimen

- The use of longer regimens is reserved for patients with MDR/RR-TB who are not eligible for shorter regimens, patients in whom these regimens failed or those with XDR-TB.
- In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of 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.

Grouping of medicines recommended for use in longer MDR-TB regimens

Groups and steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin or Moxifloxacin	Lfx Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cydoserine or Terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin Or meropenem	lpm-Cln Mpm
	Amikacin (or streptomycin)	Am (S)
	Ethionamide or Prothionamide	Eto Pto
	P-aminosalicylic acid	PAS

Important notes:

1. The recommended duration of use of Bdq is 6 months. Bdq can be extended beyond 6 months (up to 12 months) for pre-XDR (FQ resistant) cases. Beyond 6 months, Bdq is considered "Off Label"
2. Bdq and Dlm can be used together to complete the regimen
3. Lzd preferably to be used for whole duration of treatment or less if not tolerated
4. If susceptibility to Z can be confirmed, it can be added as a part of the regimen
5. Imipenem should be used with Amoxiclav
6. Use Am and S; if only susceptible and under close monitoring, preferably in patients who are 18 years or above

Additional Notes:**Drugs that should be included in treatment of MDR/RR-TB patients on longer regimens**

- Levofloxacin or moxifloxacin
- Bedaquiline
- Linezolid

Drugs that may be included in treatment of MDR/RR-TB patients on longer regimens

- Clofazimine and cycloserine or terizidone
- Ethambutol
- Delamanid
- Pyrazinamide
- Imipenem-cilastatin or meropenem
- Amikacin- more than 18 years

Use these drugs only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible

- Ethionamide or prothionamide
- P-aminosalicylic acid

Drugs that should not be included

- Kanamycin and capreomycin

- 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.
- An individualized longer regimen is expected to be used in the following situations:
 - severe extrapulmonary TB;
 - extensive/advanced pulmonary TB, in case BPaLM/BPaL regimen cannot be used - additional resistance to key medicines of the BPaLM/BPaL regimen (except moxifloxacin) or those with XDR TB
 - 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)

MDR/RR-TB -Longer Regimen (Standardized)

Resistance pattern and background history	Regimen	Comments
LR1 Standard longer MDR/RR-TB Regimen for adults and children Non-eligible for BPaLM /BPaL and OSSTR and for those whose FQ results are susceptible Patient on household contact with FQ resistant patients are not eligible	Bdq(6), 18Lfx, Lzd, Cfz	1. In of toxicity or need to decrease or substitute Lzd with Cs, Refer to aDSM relevant section 2. If Lzd is well-tolerated, should be continued throughout the treatment duration 3. If Lzd is not tolerated for the whole treatment duration and if Cs cannot be used, consider another drug from Group C in the place of Lzd
LR2 RR TB with FQ resistance at baseline Non-eligible for BPaL	Bdq(12), 18Lzd, Cfz, Cs	1. High dose Lfx or Mfx can be added once resistance level to FQs is known 2. In patients with intolerance/toxicity to Lzd, stopping Lzd, replacing with Dlm can may be a suitable option. If Dlm cannot be added, then Eto. can be used instead 3. Close and careful monitoring with combination of three cardiotoxic drugs (Bdq, Cfz, Dlm)
LR3 Failed by MDR/RR-TB standard treatment (LR1) /Relapse or recurrence of MDR/RR-TB	Am (6), Dlm (12), 18Eto, PAS (Cs), Cfz (Mfx or Lfx)	1. DST to FLD and SLDs should guide further modification where necessary 2. Use Am if documented susceptibility to it, design regimen based on previous exposure to SLDs and likely effective drugs. 3. If susceptible to FQ, high dose Lfx or Mfx can be used, if resistance to FQ then FQ can be used in line with level of resistance reported 4. Extending use of Dlm for whole duration could be an option 5. If Cs was used as a part of LR1 then use PAS instead 6. Imp Clv can be used when injection (Am) cannot be used, or after Am stopped by 6-8 months

Longer individualized regimen for Pre XDR and XDR patients; Consult with TB specialists at higher treatment centers and treatment based on DST profile

Longer regimen for children <14 years

Treatment Duration:

- 9-12 months for non-severe disease depending on physician's assessment on patient's clinical progress
- 15-18 months for severe or extensive disease

Determine the severity of the disease.

Severity of TB in children is usually defined by the presence of any of the following:

- positive TB bacteriology (smear, Xpert MTB/RIF, culture)
- cavities or bilateral disease on chest radiography or smear-positivity, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression)
- presence of co-morbid condition or disease such as severe malnutrition or advanced immunosuppression.

3.5 Weight based dosing of medicines used in multidrug resistant TB regimens, adults, and children

Medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	Weight-based daily dose	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
GROUP A MEDICINES														
Levofloxacin (Lfx)	100 mg dt (10 mg/mL)	15–20 mg/kg	5 mL (0.5 dt)	1	1.5	2	3	–	–	–	–	–	–	
	250 mg tab (25 mg/mL)		2 mLb	5 mL (0.5 tab) ^b		1	1.5	2	3			4		
	500 mg tab			–	–			1	1.5			2		
	750 mg tab			–	–				1			1.5		
Moxifloxacin (Mfx)	100 mg dt (10 mg/mL)	(10–15 mg/standard dose)	4 mL	8 mL	1.5	2	3	4	4			–		
	400 mg tab (40 mg/mL)		1 mL ^b	2 mL ^b	3 mL ^b	5 mL (0.5 tab) ^b	7.5 mL (0.75 tab) ^b	1		1				
	Standard dose													
	400 mg tab high dose ^c		–	–	–	–	–	–	1 or 1.5	1.5	1.5 or 2	2		
Bedaquiline (Bdq)	20 mg dt		0 to <3 months: 1.5 od (2 weeks); then 0.5 od M/W/F (22 weeks) ≥ 3 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks	0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F 3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F for 2 weeks; then 1 od M/W/F for 22 weeks	3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F for 2 weeks; then 1 od M/W/F for 22 weeks	3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F for 2 weeks; then 1 od M/W/F for 22 weeks	10 od for 2 weeks; then 5 od M/W/F	10 od for 2 weeks; then 5 od M/W/F	20 od for 2 weeks; then 10 od M/W/F			–		

Medicines	Formulation (tablets, water, as applicable)	Weight- based daily dose	3-<5 kg	5-<7 kg	7-<10 kg	10-<16 kg	16-<24 kg	24-<30 kg	30-<36 kg	36-<46 kg	46-<56 kg	56-<70 kg	≥70 kg	Comments
Bedaquiline (Bdq)	100 mg tab (10 mg/mL)		0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/Fb ≥ 3 months: 6 mL od for 2 weeks; then 2 mL od M/W/Fb		0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/Fb 3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/Fb ≥ 6 months: 12 mL od for 2 weeks; then 2 mL od M/W/Fb	3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/Fb 6 months: 12 mL od for 2 weeks; then 2 mL od M/W/Fb	2 od for 2 weeks; then 1 od M/W/F	4 od for 2 weeks; then 2 od M/W/F	4 od for 2 weeks; then 2 od M/W/F	4 od for 2 weeks; then 2 od M/W/F	4 od for 2 weeks; then 2 od M/W/F	4 od for 2 weeks; then 2 od M/W/F	4 od for 2 weeks; then 2 od M/W/F	
	100 mg tab (10 mg/mL)													Dosing scheme is for BPaLM/BPaL regimen (> 14 years).
Linezolid (Lzd)	20 mg /mL susp	15 mg/kg od in 1-15 kg;	2 mL	4 mL	6 mL	8 mL	11 mL	14 mL	15 mL	20 mL	-	-	-	
	150 mg dt (15 mg/mL)		2.5 mL	5 mL (0.5 dt)		1		2 ^e	2	3	-	-	-	
	600 mg tab (60 mg/mL)	10-12 mg/kg od in ≥ 15 kg	-	1.25 mL ^b	2.5 mL ^b	5 mL (0.5 tab) ^e	5 mL (0.5 tab) ^b	7.5 mL (0.75 tab) ^b	1	1	1	1	1	
GROUP B MEDICINES														
Clofazimine (Cfz)	50 mg cap or tab ⁱ	2-5 mg/kg (when dose daily)	1 M/F		1 M/W/F	1	1	2	2	2	2			For children <24 kg, the use of the 50 mg tab is preferred.
	100 mg cap or tab ⁱ		-		1 M/F	1 M/W/F	1 M/W/F	1	1	1	1			
Cycloserine or terizidone (Cs/Tz)	125 mg mini cap (Cs) (12.5 mg/mL)	15-20 mg/kg in 7 to <30 kg	2 mLb, g	4 mL ^b	1	2	3	4	4	4	-	-	-	
	250 mg cap (25 mg/mL)	10-15 mg/kg in a 30 kg and above	1 mLb, g	2 mL ^b	5 mLb	1	2	2	2	2	3	3	3	

Medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	Weight- based daily dose	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
GROUP B MEDICINES														
Ethambutol (E or EMB)	100 mg dt (10 mg/mL)	15–20 mg/kg	5 mL (0.5 dt)	1	2	3	4	–	–	–	–	–	–	
	400 mg tab (40 mg/mL)		1.5 mL b	3 mL ^b	4 mL ^b	6 mL	1	1.5	2	3	4	4	4	
Delamanid (Dlm)	25 mg dt		1 od	<3 months: 1 od ≥3 months: 1 bd	1 bd	1 bd	2 mornings 1 evening	2 bd	2 bd	–	–	–	–	
	50 mg tabh (5 mg/mL)		5 mL (0.5 tab)	<3 months: 5 mL (0.5 tab) odb ≥3 months: 5 mL (0.5 tab) bd ^b	5 mL (0.5 tab) bd ^b	5 mL (0.5 tab) bd ^b	10 mL (1 tab) morning 5 mL (0.5 tab) evening	1 bd	1 bd	2 bd	2 bd	2 bd	2 bd	
			5 mL (0.5 dt)	1	2	3	5	–	–	–	–	–	–	
Pyrazinamide (Z or PZA)	150 mg dt (15 mg/mL)	30–40 mg/kg	5 mL (0.5 dt)	1	2	3	5	–	–	–	–	–	–	Only to be used with clavulanic acid.
	400 mg tab (40 mg/mL)		2.5 mL ^b	5 mL (0.5 tab) ^b	7.5 mL (0.75 tab) ^b	1	2	2.5	3	4	5	5	5	
	500 mg tab (50 mg/mL)		2 mL ^b	5 mL (5 mL) ^b	5 mL (5 mL) ^b	1	1.5	2	2.5	3	4	4	4	
Impipenem – clastatin (ipm/Cln)	500 mg + 500 mg powder for injection, vial (10 mL)		Not used in patients aged <15 years (use meropenem)											Only to be used with clavulanic acid.
Meropenem (Mpm)	1 g powder for injection, vial (20 mL)	20–40 mg/kg in every 8 hours	1 mL tid	2 mL tid	4 mL tid	6 mL tid	9 mL tid	11 mL tid	1 vial tid or 2 vials bd	1 vial tid or 2 vials bd	1 vial tid or 2 vials bd	1 vial tid or 2 vials bd	1 vial tid or 2 vials bd	
Amikacin (Am)	500 mg/2 mL solution for injection, ampoule		– i	– i	– i	– i	– i	– i	– i	– i	– i	– i	– i	Recommended only in adults aged > 18 years.
Streptomycin (Sm)	1 g powder for injection, vial		– i	– i	– i	– i	– i	– i	– i	– i	– i	– i	– i	Recommended only in adults aged > 18 years.

Medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	Weight- based daily dose	3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	30–<36 kg	36–<46 kg	46–<56 kg	56–<70 kg	≥70 kg	Comments
Ethionamide or Prothionamide (Eto/Pto)	125 mg dt (Eto) (12.5 mg/mL)	15–20 mg/kg	3 mL ^b	7 mL ^b	1	2	3	4	4			–		Although once daily dose advised, two divided doses can be also given to improve tolerance.
	250 mg tab (25 mg/mL)		–	3 mL ^b	5 mL (0.5 tab) ^b	1	2		3			4		
P-aminosalicylic acid (PAS)	PAS sodium salt (equivalent to 4 g PAS acid) sachet	200–300mg/kg/in 2 divided doses	0.3 g bd	0.75 g bd	1 g bd	2 g bd	3 g bd	3.5 g bd		4 g bd			4–6 g bd	Usually given in divided doses.
GROUP B MEDICINES														
Isoniazid j (INH or H) (high dose)	50 mg/5 mL soln	15–20 mg/kg (high dose)	5 mL	9 mL	15 mL	20 mL	–	–	–	–				Pyridoxine is always given with high-dose isoniazid in children (1–2 mg/kg) and in people at risk of side-effects (e.g. those with HIV or malnutrition). In infants, pyridoxine may be given as part of a multi-vitamin syrup.
	100 mg dt or tab (10 mg/mL)	5 mL (0.5 dt)	1	1.5	2	3	4	4	4.5	–				
	300 mg tab		–	–	–	–	1	1.5	1.5	2				
Clavulanic acid/j (as amoxicillin/ clavulanate) (Amx/Clav)	62.5 mg clavulanic acid as amoxicillin/ clavulanate (250/62.5 mg), powder for oral solution, 5 mL		1.5 mL tid	2 mL tid	3 mL tid	5 mL tid	8 mL tid	10 mL tid	10 mL bd or tid	–				Only available in combination with amoxicillin. To be given with each dose of imipenem/cilastatin (bd) or meropenem (tid).
	125 mg clavulanic acid as amoxicillin/ clavulanate (500/125 mg) tab		–	–	–	–	1 tid	1 tid	1 bd or tid					
Pretomanid (Pa)	200 mg tab		–	–	–	–	–	–	–	1				Currently only used as part of the BPaLM/ BPaL regimens.

- bd: two times a day; BPA-L: bedaquiline, pretomanid and linezolid; BPA-LM: bedaquiline, pretomanid and moxifloxacin; cap: capsule; DR-TB: drug-resistant TB; dt: dispersible tablet; g: gram; GDG: Guideline Development Group; HIV: human immunodeficiency virus; kg: kilogram; MDR/RR-TB: multidrug-resistant TB; MDR/RR-TB: multidrug or rifampin-resistant TB; mg: milligram; mL: millilitre; M/F: Monday and Friday; M/W/F: Monday, Wednesday and Friday; od: once daily; soln: solution; susp: suspension; tab: tablet; TB: tuberculosis; tid: three times a day; WHO: World Health Organization.
- Dosing guidance is based 2022 WHO operational handbook on tuberculosis.
 - Dissolving of crushed adult tablets or capsule content in 10 mL of water is required for administering this dose. The number of mL in the table reflects the dose to provide. This avoids fractionating solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (use of dispersible tablets is preferred).
 - 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
 - Bedaquiline adult tablets (100 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole. Vigorous stirring/shaking is needed prior to administering the 100 mg tablet crushed and suspended in water
 - When using the 600 mg tab and the 150 mg dt to dose children weighing 16 to <24 kg, the dose in mg/kg will exceed 10–12 mg/kg and clinicians may opt to administer 1.5 dt or 4 mL of the 600 mg tab dispersed in 10 mL water.
 - Glofazamine tablets are technically not dispersible, but they do slowly (this takes approximately 5 minutes) dissolve in water (5 mL and 10 mL for the 50 mg and 100 mg tablets, respectively). The suspension should be stirred prior to administration. The 100 mg soft gel capsule is difficult to swallow for young children and therefore countries are strongly encouraged to make the 50 mg tablet formulation available.
 - In children weighing 3 to <7 kg doses are lower than previously recommended. This is because of relatively high exposures associated with risk of neuropsychiatric adverse events, which is especially concerning when co-administering cycloserine with delamanid.
 - Delamanid adult tablets (50 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole.
 - Amikacin and streptomycin may be used in adults aged 18 years or more, in situations where an effective regimen cannot otherwise be designed using oral agents, when susceptibility is demonstrated and when adequate measures are in place to monitor for adverse events. Given the profound impact that hearing loss can have on the acquisition of language and the ability to learn at school, the use of injectable agents in children should be exceptional and limited to salvage therapy, and the treatment needs to be provided under strict monitoring to ensure early detection of ototoxicity. If used, the weight-based daily dose for amikacin is 15–20 mg/kg and for streptomycin it is 20–40 mg/kg for children aged 2 years and older. To determine the dosing for infants and children aged below 2 years, a paediatric DR-TB expert should be consulted and a lower mg/kg dose used to compensate for immature clearance. Co-administration with lidocaine is advised to reduce pain at the injection site (156).
 - These medicines are only recommended as a companion agent (amoxicillin/clavulanic acid) or are not included in Groups A, B and C, because of a lack of data from the latest analysis on longer MDR/RR-TB regimens in adults (isoniazid).

Specific comments on dosing children with medicines used in second line MDR/RR-TB regimens:

- For dosing of premature and low birth weight infants weighing <3 kg, advice should be sought from a paediatric DR-TB expert.
- For dosing of infants weighing 3 to <5 kg, a paediatric DR-TB expert should be consulted whenever possible.
- The use of child-friendly dispersible tablets in infants and young children is preferred over manipulating adult tablets or administering or manipulating capsules. Where applicable, the dosing provided is based on dissolving the dispersible formulation in 10 mL of water and administering the number of mL (aliquots). The number of mL in the table reflects the dose to provide. The dissolved solution should be used immediately and the remainder of the 10 mL should be discarded.
- For some weight bands, dosing is indicated with both child-friendly, dispersible formulations and adult formulations. If adult formulations are used, the table provides the dose using aliquots in mL and tablet fractions where applicable (if the fraction is 0.5 or more). Aliquots refer to the volume to administer after crushing and dissolving the tablet in 10 mL of water.

3.6 Follow up and Monitoring of DR TB patients

Preparation prior to starting second-line treatment

Before second-line treatment can be prescribed, the patient must be thoroughly evaluated clinically, radiologically and biomedically. These examinations are performed at the DR TB treatment center. The initial evaluation serves to establish a baseline (for comparison when investigations are done during treatment) and may identify patients who are at risk for adverse side effects or poor outcomes. Prior to initiating treatment, all patients must receive albendazole.

Baseline and follow up monitoring of patients taking BPaLM/BPaL regimen for DR-TB

Response to treatment should be monitored on the basis of Monthly sputum smear microscopy and culture (ideally at the same frequency) It is also important to follow up patients after the completion of treatment to ensure that there is no treatment relapse or unexpected adverse events

Considerations when initiating the BPaLM/BPaL regimen are

- Patients with a history of cardiac disease should be considered with caution. Population of concern include those with a baseline corrected QT interval by Fridericia (QTcF) of more than 450 ms, history of cardiac disease with syncopal episodes, significant arrhythmias, personal or family history of congenital QTc prolongation, torsade de pointes (tdP), bradyarrhythmia or cardiomyopathy.
- Linezolid is associated with anaemia and thrombocytopenia. Care should also be taken for patients who have haemoglobin level of less than 8g/dL or progressive decline in platelet count
- Patients with liver enzymes at levels three times greater than the upper limit of normal should be excluded from the regimen.
- Those with pre-existing peripheral neuropathy of Grade 3-4 should be treated with caution. Alternatively, to decrease the risk of peripheral neuropathy exacerbation, individualized longer regimen without linezolid can be used.
- Patients who are moribund or with advanced disease should have considerations made for symptoms control and palliative care over the initiation of the treatment. Decision should be guided by the clinical judgement and the patient's preferences.

Treatment modifications and discontinuation of the regimen

- The treatment duration of BPaLM regimen is 6 months (26weeks).
- The treatment duration of BPaL regimen is 6 months but can be extended to 9 months (39 weeks) when there is a lack of culture conversion or clinical response (based on the clinical judgement of the treating physician) between months 4 and 6. However, the extension of BPaL to 9 months should be done with caution in patients with a high number of missed linezolid dosages.

- Switching to an individualized longer regimen is considered when more than 2 weeks of consecutive treatment interruption of all medicines in the regimen occurs; or more than 4 weeks cumulative of nonconsecutive treatment interruption of all medicines in the regimen..
- In case of severe toxicity of the component drugs of BPaLM/BPaL regimen, the following factors should be considered:
 - If either Bedaquiline or Pretomanid needs to be permanently discontinued, the entire BPaLM/BPaL regimen should be discontinued.
 - If linezolid is permanently discontinued during the initial 9 consecutive weeks of treatment, the entire regimen should be discontinued.
 - If linezolid is withheld in the later weeks of the regimen, with the total remaining duration of the regimen not exceeding 8 weeks, the regimen is considered completed with the remaining component drugs; and
 - If moxifloxacin alone is discontinued, the regimen can be continued as the BPaL regimen.
- The regimen is discontinued in case of treatment failure, early linezolid intolerance or pregnancy that may occur during treatment.

Patient is considered failure and treatment regimen has to be terminated or permanently changed to new treatment regimen due to any of the following:

- Adverse drug reactions
- Persistent positive sputum culture (no conversion or reversion) from months 4 to the end of the treatment.
- Acquired drug resistance to drugs in the regimen during the treatment (i-e baseline is susceptible and monitoring culture demonstrates resistance)

Patients on BPaLM/BPaL regimen should be monitored for the following adverse events: Hepatotoxicity, Nephrotoxicity, Cardiac toxicity, Optic neuritis, Neuropathy, Myelosuppression, Lactic Acidosis, Acute Pancreatitis

The monitoring schedule should consider the following:

- laboratory and ECG monitoring should be continued at monthly intervals for the duration of treatment (i.e. 9 months in the case of treatment prolongation);
- in the case of electrolyte disturbances, haematologic or ECG abnormalities, more frequent monitoring may be performed; and
- more frequent monitoring may be advisable in specific situations; for example, in older people, PLHIV, those affected by hepatitis (caused by hepatitis B virus [HBV] or hepatitis C virus [HCV]), those with diabetes mellitus, those with moderate to severe hepatic or renal impairment, or those with baseline anaemia or visual disturbances (e.g. glaucoma, cataract or colour blindness).

Baseline, routine and post-treatment monitoring examinations schedule for the BPaLM/BPaL regimen

Examination	Baseline	Two weeks	Monthly	End of treatment	Post treatment (After 6- and 12-months)
Clinical evaluation					
Clinical assessment ^a	√	√	√	√	√
Psychosocial assessment ^b	√	√	√	√	√
Weight/BMI	√	√	√	√	√
Performance status	√				
Peripheral neuropathy screening	√	√	√	√	
Visual acuity and colour discrimination screening	√	√	√	√	
Assessment and follow-up of adverse events	√	√	√	√	√
Outcome consultation				√	√
Bacteriological evaluations					
Sputum smear	√		√	√	√
Sputum culture	√		√	√	√
Sputum DST ^c	√		√ If smear or culture positive		
Other samples (smear/ culture/DST)	√		√ If no documented response to treatment		
Radiology, ECG, and laboratory evaluations					
Chest X-ray	√			√	√
ECG	√	√	√	√	
Full blood count	√	√	√	√	
Liver function tests (AST, ALT and bilirubin)	√	√	√	√	
Serum electrolytes	√				
Urea, creatinine	√				
Pregnancy test	√				
HIV/HBV/HCV tests	√				
RBS/HbA1c	√				

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; RBS: Random blood sugar level; DST: drug susceptibility testing; ECG: electrocardiography; HbA1c: glycosylated haemoglobin; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; TB: tuberculosis; WHO: World Health Organization.

- a Vital sign, TB symptom screen, pain, nausea, appetite and nutrition, diarrhoea and candidiasis. Clinical assessment should focus on monitoring the response to treatment and addressing common symptoms associated with TB treatment and long-term antibiotic use, with the goal of supporting adherence.
- b Food security, housing, mental state and 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, as per country-specific questionnaires.
- c Ideally, the patient should at baseline have a WHO-recommended rapid molecular test (for rifampicin and fluoroquinolone resistance). Other investigations, if available, include culture-based second-line DST, next-generation sequencing, and DST for the BPaLM component drugs.

Monitoring of patients taking nine month all oral shorter regimen (OSSTR)

- Response to treatment is monitored by monthly sputum smear microscopy and culture.
- Older children who had microbiological confirmation of TB disease should also be encouraged to produce respiratory samples for monitoring whenever possible.
- Treatment response can also be monitored through regular clinical assessment of signs and symptoms of TB disease, and children should be monitored for changes in weight, height and BMI using age-appropriate growth charts.
- Repeat radiological assessment during treatment is not always necessary because some radiological abnormalities may persist throughout and beyond treatment completion but do not necessarily indicate poor response or failure of treatment.

Example of a monitoring schedule for patients receiving OSSTR

Time on treatment	Baseline	Months 0-2	Month 3-6	Months 7-9 (or11)
Clinical history and examination a	√	√ (monthly)	√ (monthly)	√ (monthly)
Treatment literacy and adherence counselling	√	√ (At every HCW interaction)	As required throughout treatment	
Substance use and mental health screen (with appropriate intervention and support)	√	√ (monthly)	√ (monthly)	√ (monthly)
Weight / height / BMI (and nutritional support)	√	√ (monthly)	√ (monthly)	√ (monthly)
Family planning, and pregnancy testing	√	√ (monthly)	√ (monthly)	√ (monthly)

Time on treatment	Baseline	Months 0-2	Month 3-6	Months 7-9 (or 11)
Respiratory sample for smear microscopy and TB culture (DST if indicated)	✓	✓ (monthly)	✓ (monthly)	✓ (monthly)
Chest X-ray (or other radiological assessment)	✓	✓		
HIV testing	✓		✓ (if previously negative, repeat every 3 months in high prevalence settings, or indicated)	✓ (if previously negative, repeat every 3 months in high prevalence settings, or indicated)
Finger-prick blood glucose	✓	Check regularly if clinically indicated		
Full blood count and differential (if receiving Lzd)		✓ (at weeks 2, 4 and 8 if receiving Lzd)	Repeat if clinically indicated	
Liver function tests (at least ALT, AST and bilirubin)	✓	Repeat regularly if clinically indicated: vomiting, right upper quadrant pain, jaundice or if person is unwell or has any evidence of liver injury		
Creatinine	✓	Repeat regularly if clinically indicated (i.e., if person becomes unwell, or if baseline creatinine was abnormal or renal drug dosing required)		
Serum electrolytes	✓	Repeat regularly if clinically indicated (i.e., if person becomes unwell, is vomiting, has diarrhoea or has QTcF prolongation)		
TSH (if receiving Eto)	✓	Repeat at 3 months if on Eto, or when QTcF is prolonged		
ECG (calculate QTcF)	✓	✓ (monthly)	✓ (monthly)	✓ (monthly)
Peripheral neuropathy and visual acuity screen (if receiving Lzd) ^b	✓	✓ (monthly)	Repeat regularly if clinically indicated	

ALT: alanine transaminase; AST: aspartate aminotransferase; BMI: body mass index; DST: drug susceptibility testing; ECG: electrocardiography; Eto: ethionamide; HCW: health care worker; HIV: human immunodeficiency virus; Lzd: linezolid; MDR/RR-TB: multidrug- or rifampicin-resistant TB; QTcF: corrected QT interval by Fridericia; TB: tuberculosis; TSH: thyroid stimulating hormone.

a Clinical assessment of TB signs or symptoms and adverse events.

b It may be difficult to perform detailed assessments for peripheral neuropathy or visual acuity in young children, but the risk of these events appears to be lower in this group; therefore, this should not be a reason to withhold linezolid from young children who would otherwise benefit from this drug.

Source: WHO Operational Handbook on Tuberculosis; Module 4: Treatment (Drug-resistant tuberculosis treatment), 2022 update

Baseline and follow up investigations of Longer Regimen for DR-TB

The performance of sputum culture in addition to sputum smear microscopy is recommended to monitor the treatment response. Treatment failure includes the situations where a patient's treatment regimen has been terminated or permanently changed to a new treatment regimen, owing to

- no clinical or bacteriological response to treatment (Bacteriological failure is considered when patients treated with a longer regimen remain positive without conversion or revert to positive following initial conversion to negative)
- adverse drug reaction
- evidence of additional drug resistance to medicines in the regimen

Frequency of follow-up examinations during longer regimen

Examinations	Baseline	Treatment duration/ Month															Remarks
		1	2	3	4	5	6	7	8	10	12	14	16	18			
Clinical history and examination	√	√	√	√	√	√	√	√	√	√	√	√	√	√			
Treatment literacy and adherence counselling	√	√	√	√	√	√	√	√	√	√	√	√	√	√			
Substance use and mental health screen	√	√	√	√	√	√	√	√	√	√	√	√	√	√			
Weight/BMI nutritional support	√	√	√	√	√	√	√	√	√	√	√	√	√	√			
Family planning and pregnancy testing	√	√	√	√	√	√	√	√	√	√	√	√	√	√			
Respiratory sample for Sputum smear)	√	√	√	√	√	√	√	√	√	√	√	√	√	√			
Sputum culture (DST if indicated	√	√	√	√	√	√	√	√	√	√	√	√	√	√			
Chest X-ray or other radiological assessment	√						√				√			√			
ECG (Calculate QTcF) ¹	√	√	√	√	√	√	√	√	√	√	√	√	√	√	Monthly or as required		
Complete Blood Count ²	√	√	√	√	√	√	√	√	√	√	√	√	√	√	2 weeks initially, then monthly if Lzd. If no Lzd: as required		
HIV testing	√	if previously negative, repeat every 3 months in high HIV prevalence settings, or if indicated															

Examinations	Baseline	Treatment duration/ Month															Remarks
		1	2	3	4	5	6	7	8	10	12	14	16	18			
Liver function tests (LFT) ³	√	Repeat regularly if clinically indicated: vomiting, right upper quadrant pain, jaundice or if person is unwell or has any evidence of liver injury															
Thyroid function tests (TFT)	√			√			√				√				√	TSH, T3, T4 Only if Eto, Pto, or PAS is used	
Uric acid	√		√		√		√		√							Only if Z is used	
Renal function tests (RFT) ⁴		√	√	√	√	√	√									Only if Am is used	
Serum glucose	√	Repeat regularly if clinically indicated															
Peripheral Neuropathy Assessment	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	See Annex 5	
Audiometry only if Am is used	√	√	√	√	√	√	√										
Visual acuity (for optic neuritis); Monthly if LZD used or as required	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		
Xpert MTB/XDR/LPA and DST	√	On any cultures that are positive four months or beyond after treatment initiation															

- 1 Calculate the Q-T interval with Fridericia's correction (QTcF): see Annex 3
- 2 RBC count, haemoglobin, haematocrit, WBC count, WBC differential count, platelet count
- 3 Bilirubin, AST, ALT, albumin
- 4 Serum creatinine (calculate the estimated creatinine clearance based on the Cockcroft-Gault equation: see Annex 4), serum potassium (also magnesium and calcium if potassium is low)

Monitoring and Management of Adverse Events

4.1 Side effects of first line TB medicines and management

(Note: For detailed discussion on side effects of TB drugs and it's management, refer to National TB Management Guidelines 2019)

Side Effects	Drugs Responsible	Management
Minor Adverse Effects		
Anorexia, nausea, vomiting, Abdominal pain (and no jaundice)	Pyrazinamide, Rifampicin	Take drugs with food or juice or before sleeping and reassurance.
Joint pain	Pyrazinamide	Aspirin/ Indomethacin
Burning sensation in the feet, tingling	Isoniazid	Pyridoxine 100mg daily (when better reduce to 25 mg/day)
Confusion, sleep disturbance	Isoniazid	Pyridoxine 25 mg/day
Orange/ red urine	Rifampicin	Reassurance
Itching, rash without blisters	Any drug (or skin disease)	Anti allergic medicines
Adverse Effects		
Jaundice (other causes excluded), hepatitis	All drugs but commonly isoniazid. Also, rifampicin and Pyrazinamide	Stop anti-TB drugs, start the same regimen after two weeks or refer.
Confusion	Most anti-TB drugs	Stop anti-TB drugs, refer
Difficulty with vision	Ethambutol	Stop ethambutol, refer
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin, refer

4.2 Side effects of second line TB medicines

Main or rare but serious adverse effects	Drug	Pregnancy
QT prolongation, hepatitis, GI toxicity, others.	Bedaquiline	May be used
Red discoloration of skin, eyes, body fluids; GI toxicity; photosensitivity; others.	Clofazimine	May be used
CNS toxicity (psychiatric symptoms, seizures usually occur at peak concentrations >35 mcg/mL but may occur in the normal therapeutic range), peripheral neuropathy, dermatologic effects include serious cutaneous hypersensitivity reactions. Administration of pyridoxine (50 mg orally once daily for every 250 mg of cycloserine) may be useful in preventing or reducing neurotoxicity.	Cycloserine	Potential choice when there are no suitable alternatives
GI toxicity, QT prolongation.	Delamanid	May be used
Visual disturbance (optic neuropathy, manifested as decreased visual acuity or red-green colorblindness) at higher doses.	Ethambutol	May be used
GI toxicity (antiemetic premedication is often helpful), hepatic toxicity, metallic taste, neurotoxicity including optic neuritis (administer with pyridoxine 100 mg orally once daily), endocrine effects including hypothyroidism (treat with thyroid replacement).	Ethionamide	Avoid
GI toxicity, seizures.	Imipenem-cilastatin	Potential choice when there are no suitable alternatives
Hepatitis, peripheral neuropathy hypersensitivity, others.	Isoniazid, high dose	May be used
GI toxicity, CNS effects, rash, dysglycemia, tendonitis, tendon rupture, QT prolongation.	Levofloxacin	Potential choice when there are no suitable alternatives
Myelosuppression, GI toxicity, neuropathy (optic and peripheral), Lactic acidosis, pancreatitis;	Linezolid	May be used
GI toxicity, seizures.	Meropenem	Potential choice when there are no suitable alternatives

Main or rare but serious adverse effects	Drug	Pregnancy
GI toxicity, CNS effects, rash, dysglycemia, tendonitis, tendon rupture, QT prolongation, hepatotoxicity.	Moxifloxacin	Potential choice when there are no suitable alternatives
GI toxicity, hepatotoxicity, hypothyroidism (treat with thyroid replacement).	Para-aminosalicylic acid	Potential choice when there are no suitable alternatives
Peripheral and optic neuropathy, myelosuppression, hepatotoxicity, lactic acidosis were all reported; these were largely attributed to adverse effects of high-dose linezolid.	Pretomanid	No adequate human data in pregnancy are available
Hepatotoxicity, rash, arthropathy.	Pyrazinamide	May be used
Ototoxicity, vestibular toxicity, nephrotoxicity, electrolyte disturbances, local pain with IM injections.	Amikacin	Avoid

4.3 Approach to hepatotoxicity caused by first-line antituberculous drugs in adults

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
ALT (SGPT)	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
AST (SGOT)	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 xULN
Total Bilirubin		<3mg/dl	≥3mg/dl	
Action	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Continue treatment regimen if asymptomatic. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Stop all drugs, including anti-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.	Stop all drugs, including anti-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.

4.4 Dose adjustment in renal impairment

Drug	Recommended dose and frequency for patients with creatinine clearance <30 ml/min or for patients receiving haemodialysis (unless otherwise indicated dose after dialysis)
Isoniazid	No adjustment necessary
Rifampicin	No adjustment necessary
Pyrazinamide	25–35 mg/kg per dose three times per week (not daily)
Ethambutol	15–25 mg/kg per dose three times per week (not daily)
Streptomycin	12–15 mg/kg per dose two or three times per week (not daily)
Amikacin	12–15 mg/kg per dose two or three times per week (not daily)
Ofloxacin	600–800 mg per dose three times per week (not daily)
Levofloxacin	750–1000 mg per dose three times per week (not daily)
Moxifloxacin	No adjustment necessary
Cycloserine	250 mg once daily, or 500 mg/dose three times per week
Terizidone	Recommendations not available
Prothionamide	No adjustment necessary
Ethionamide	No adjustment necessary
Para-aminosalicylic acid	4 g/dose, twice daily maximum dose
Bedaquiline	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution).
Linezolid	No adjustment necessary
Clofazimine	No adjustment necessary
Amoxicillin/clavulanate	For creatinine clearance 10–30 ml/min dose 1000 mg as amoxicillin component twice daily; for creatinine clearance <10 ml/min dose 1000 mg as amoxicillin component once daily
Imipenem/cilastatin	For creatinine clearance 20–40 ml/min dose 500 mg every 8 hours; for creatinine clearance <20 ml/min dose 500 mg every 12 hours
Meropenem	For creatinine clearance 20–40 ml/min dose 750 mg every 12 hours; for creatinine clearance <20 ml/min dose 500 mg every 12 hours
High dose isoniazid	Recommendations not available

TB treatment in special circumstances

5.1 TB in People with HIV Infection

Screening and Diagnosis

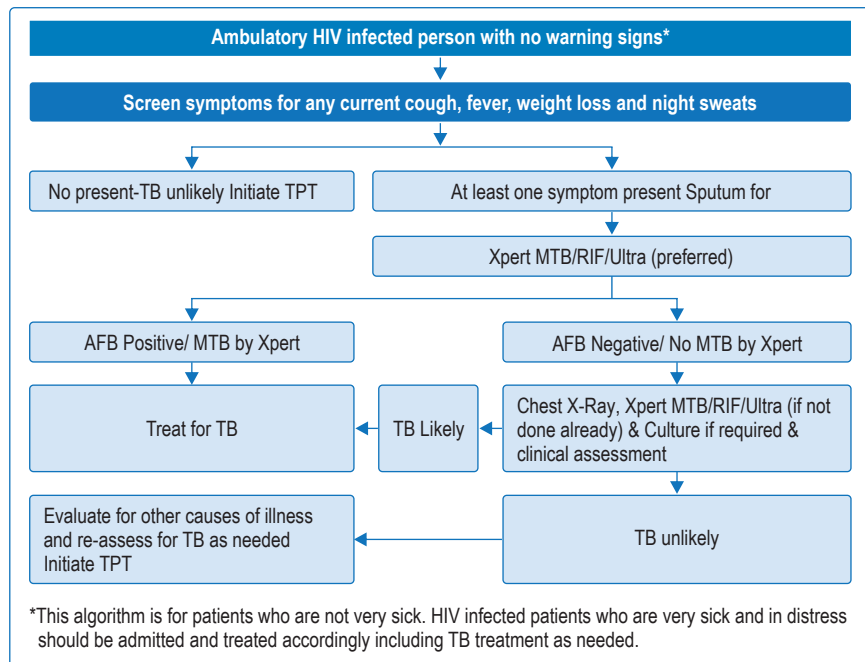
All HIV infected should be screened for TB and all TB patients should be tested for HIV infection.

Following tools for TB screening are recommended

1. WHO-recommended four symptom screen: cough, fever, weight loss or night sweats
2. chest X-ray
3. mWRD, e.g. Xpert MTB/RIF/Ultra

Among children younger than 10 years who are living with HIV, systematic screening for TB disease should be conducted using a symptom screen including any one of current cough, fever, poor weight gain or close contact with a TB patient.

Algorithm for TB screening for ambulatory patients with HIV



TB treatment in person living with HIV

1. Drug Susceptible TB

- TB patients who are living with HIV should receive 6 months of TB treatment with 2 HRZE + 4HR
- Daily dosing should be given
- ART should be started as soon as possible within 2 weeks of starting TB treatment except with TB meningitis when ART should be started after 4-8 weeks of starting TB treatment.
- Use adjuvant corticosteroids for TB meningitis and pericarditis
- Careful attention should be given for ATT-ART interactions: adjust dosages as needed and monitor adverse events

2. Drug Resistant TB

- Treatment regimen for MDR/RR TB in PLHIV is similar to that with patient without HIV.
- For MDR/RR TB, ART should be started within the first 8 weeks of treatment to reduce the risk of Immune Reconstitution Inflammatory Syndrome (IRIS).
- Careful attention should be given to drug-drug interactions like bedaquiline and efavirenz.

Drug interactions and management of ATT and ART

ATT	ART	Interactions	Recommendations
Bedaquiline	All PIs	With LPV/r: Bedaquiline AUC ↑ 1.9-fold With other PI/r, ATV/c, or DRV/c: ↑ bedaquiline possible	1. Do not coadminister, unless benefit outweighs risk. 2. Monitor liver function and ECG for QTc pro
Rifampicin	All PIs	↓ PI concentration by >75%	1. Contraindicated. - Increasing the dose of RTV does not overcome this interaction and may increase hepatotoxicity. - Increasing the Cobicistat dose is not recommended. 2. Consider rifabutin if a rifamycin is indicated.
Rifapentine	ALL PIs	↓ PI expected	Do not coadminister

5.2 TB in Pregnancy and Breast Feeding

- **Clinical Features**
 - Clinical manifestations: are similar to the nonpregnant patients, including fever, cough, weight loss, night sweats, and malaise.
- **Approach to diagnosis**
 - same as in nonpregnant individuals: clinical history and physical examination, followed by chest radiography (with appropriate shielding to protect the fetus), and microbiological investigation (Xpert MTB/RIF/Ultra)
 - although a positive test is indicative of infection, TST (Mantoux test) and IGRA do not differentiate between TB infection from active disease. They may be negative even in patients with active TB disease.

■ Approach to Treatment

Pregnancy

- Pregnancy is not a contraindication for the treatment of DR-TB but it poses great risk to both mother and fetus.
- For drug susceptible TB- use HRZE for intensive phase and HR for continuation phase for total duration as for non-pregnant patients. The first line anti-TB drugs are safe for use in pregnancy. Pregnant women should be advised that successful treatment of TB with the standard regimen is important for successful outcome of pregnancy.
- Owing to the limited evidence on the safety of pretomanid, BPaLM/BPaL regimen is not recommended for pregnant and breastfeeding women.
- For pregnant and lactating women, it is recommended to use linezolid variation of nine month all oral shorter regimen for DR-TB treatment (OSSTR)
- Bedaquiline containing longer regimen can be introduced to pregnant and breastfeeding women with linezolid if nine month all oral shorter regimen/OSSTR is not applicable for some reasons (Dose of linezolid to be tapered to half after 6-8 months based on bacteriological response). Modify regimen if one or more drugs cannot be used due to the reasons of resistance, tolerability, contraindications, availability etc.
- If patients on BPaLM/BPaL regimen become pregnant during treatment, it is necessary to discontinue the regimen and switch to OSSTR, if eligible or longer regimen

Breast Feeding

- Breast feeding mother should be given normal full course of TB treatment.
- Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to the baby.
- Pyridoxine 10 mg daily supplementation is recommended for all pregnant or breastfeeding women taking isoniazid (INH).
- The baby should be continued to be breastfed. Mother should use mask while breast feeding and practice other infection control measures.
- The termination of pregnancy may be considered if would carry a significant risk to mother's life
- After active TB in the baby is ruled out, the baby should be given 3 months RH preventive therapy, followed by BCG vaccination.

Treatment regimen for MDR/RR TB in pregnancy

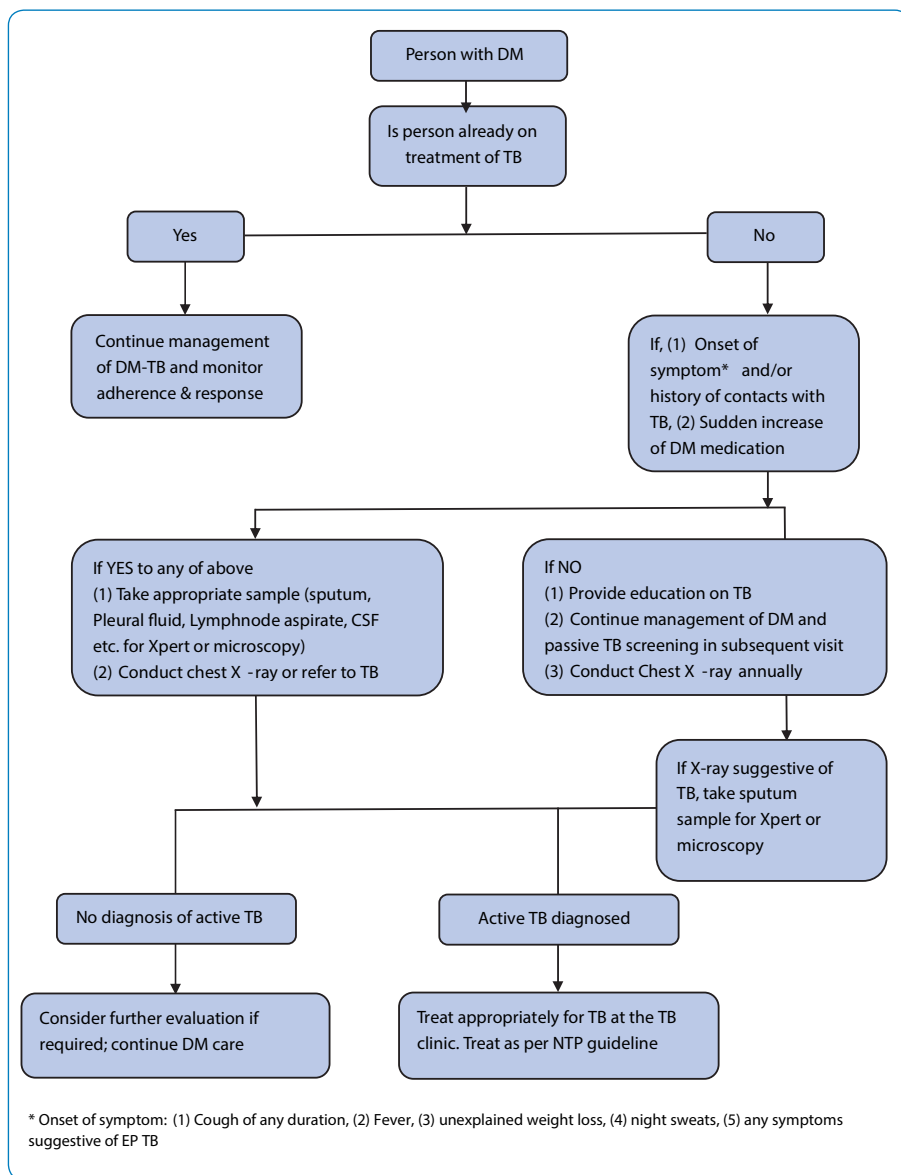
MDR/RR-TB treatment in Pregnancy	<u>OSSTR</u> 4–6 Bdq(6 m)- Lzd(2 m)- Lfx/Mfx-Cfz-Z-E-Hh / 5 Lfx/Mfx- Cfz-Z-E	1. May be considered eligible for the linezolid containing 9-month regimen but should not receive the 9-month regimen containing ethionamide 2. After delivery switch the back to the original applicable regimen
	<u>LR1</u> Bdq (6), 18Lfx, Lzd, Cfz	1. In of toxicity or need to decrease or substitute Lzd with Cs, Refer to aDSM relevant section 2. If Lzd is well tolerated, should be continued throughout the treatment duration 3. If Lzd is not tolerated for the whole treatment duration and if CS cannot be used, consider another drug from Group C in the place of Lzd

5.3 TB and Diabetes Mellitus

Persons with latent TB infection and diabetes have an increased risk of progression to active TB. Also, outcome for patients who have both TB and diabetes are poorer compared to TB patients without diabetes. Thus, collaborative efforts are required to manage TB and Diabetes is pertinent.

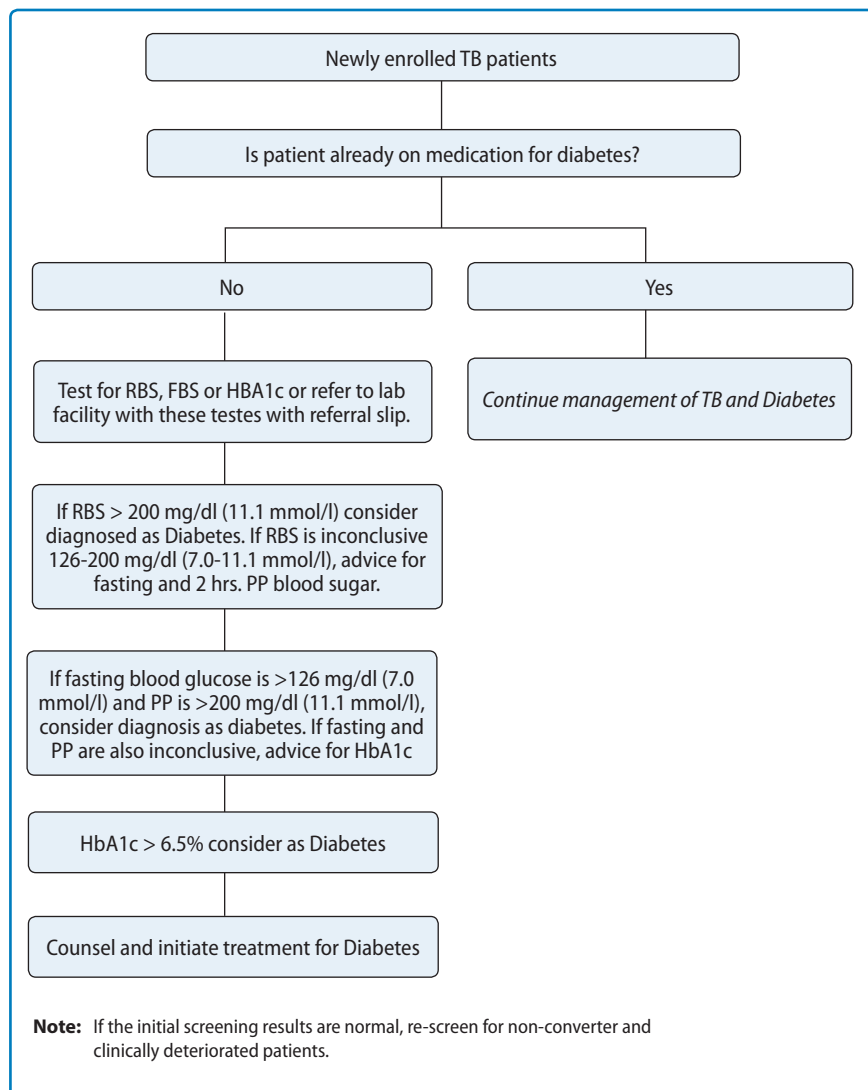
Detect and Manage TB in Patients with Diabetes Mellitus

Algorithm for the screening people with diabetes for Tuberculosis



Detect and Manage Diabetes Inpatients with Tuberculosis

Algorithm for the diagnosis diabetes among the newly enrolled TB patients.



5.4 TB and Tobacco Use

ABC approach for smoking cessation

ABC for TB is a simple three-step method to be used each time a patient attends the tuberculosis services.

The three steps of ABC are: A is for Ask At each visit, ask all patients if they currently smoke and if anyone smokes inside their home.

B is for Brief advice each visit, give all patients brief advice to quit smoking or to continue not to smoke. Advise patients to make their home smoke free. Personalise the advice by linking smoking and exposure to smoking with tuberculosis and any other associated diseases or conditions.

C is for Cessation support at each visit, provide all patients with cessation support to help them to quit smoking or to continue not to smoke. Support patients to make their home smokefree.

TB Infection Control and Prevention

Preventing the spread of TB infection and stopping its progression to disease is critical to reducing TB incidence, as outlined by the End TB Strategy. To achieve this, the World Health Organization (WHO) recommends several health interventions:

- TB preventive treatment (TPT) for
 - People living with HIV (PLHIV)
 - Household contacts of people with TB
 - Other high-risk groups such as health care workers, prisoners, migrants, homeless people, people who use drugs, people in congregate settings, immigrants, and refugees.
- TB infection prevention and control
- Vaccination of children with the Bacillus Calmette-Guérin (BCG) vaccine.

6.1 TB Infection Control

Three levels of infection prevention and control: A three-level hierarchy of controls has been shown to reduce and prevent the risk of transmission and exposure to MTB.

1. Administrative controls: These are management measures that are intended to reduce the risk of exposure to persons with infectious TB.

- Triage of people with TB signs and symptoms, or with TB disease
- Respiratory separation / isolation of people with presumed or demonstrated infectious TB
- Prompt initiation of effective TB treatment of people with TB disease
- Respiratory hygiene (including cough etiquette) in people with presumed or confirmed TB

2. Environmental controls: use of environmental controls to prevent the spread of infectious droplet nuclei and reduce their concentration.

- Upper-room germicidal ultraviolet (GUV) systems are recommended to reduce M. tuberculosis transmission in healthcare settings and other setting with high risk of transmission
- Ventilation systems, such as natural, mixed-mode, mechanical ventilation and recirculated air through high-efficiency particulate air [HEPA] filters, are recommended to prevent transmission at high-risk places.

3. Respiratory protection controls: the use of respiratory protection controls which consists of the use of personal protective equipment in situations that pose a high risk of exposure to MTB.

- A respiratory protection programme and use of appropriate respirators are recommended to protect health workers and other persons attending health care facilities at risk of exposure.

6.2 TB Preventive Treatment (TPT)

The main objective of TPT is to prevent the progression of the early stages of TB infection into TB disease. In Nepal, TPT is being implemented as part of the NTP with a focus on two approaches - contact tracing and provision of TPT to eligible <5 year household contacts of PBC patients and PLHIV. Currently, TPT regimen being provided are Isoniazid (H) for six months to PLHIV and a three-month regimen of Isoniazid and Rifampicin (3HR) to children <5 years of household contacts of PBC patients. No TPT is being provided to contacts of DR TB and other high risk groups.

The National TPT Protocol has recently been developed and endorsed in 2024 that aimed to expand the TPT to other household contacts of PBC patients aged 5 years or more. While TPT is provided to under 5 years household contacts of PBC patients and PLHIV based on the presence or absence of symptoms, other groups (contacts aged > 5 years) should undergo additional tests (X-ray, bacteriological, and/or serological test) to rule out active TB, and only then TPT can be provided. The preferred TPT regimen is a combination containing isoniazid and rifampentine (HP). However, children <2 years will still receive HR and HP is provided to those aged 2 years and above. (For more details on the regimen, dosing and others, please refer to the national TPT protocol 2024).

References and Further Reading Materials

- National TB Management Guidelines, 2019
- National Guideline on Drug Resistant TB Management, 2023
- WHO guidelines on tuberculosis. Module 4 - DR TB Treatment 2022 update
- WHO guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease, 2021
- WHO guidelines on tuberculosis. Module 3: diagnosis - rapid diagnostics for tuberculosis detection, 2021 update
- Use of Xpert MTB/RIF and Xpert MTB/RIF Ultra on GeneXpert 10-colour instruments WHO policy statement, 2021
- Definitions and reporting framework for tuberculosis– 2013 revision, WHO (updated December 2014 and January 2020)
- WHO TB Preventive Therapy Guidelines, 2020
- WHO guidelines on tuberculosis infection prevention and control 2019 update
- Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Geneva: World Health Organization; 2014
- National Tuberculosis Preventive Treatment Protocol, 2024
- National Tuberculosis and Diabetes Management Guideline, 2023



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