



FIJI NATIONAL **TUBERCULOSIS MANAGEMENT GUIDELINES**



DISCLAIMER

This guideline provides the operational standards and procedures for tuberculosis (TB) prevention, diagnosis, case management, treatment monitoring, and reporting within the Ministry of Health and Medical Services (MHMS). It is intended for use by all healthcare workers across national, divisional, subdivisinal, community, and outreach settings.

While the guideline reflects the best available evidence and current WHO-aligned recommendations, its implementation must consider available resources, facility capacities, medicine and diagnostic supplies, workforce constraints, and contextual variations across Fiji's health system. MHMS expects that staff will apply the guideline in good faith, adhering to administrative directives, infection prevention and control policies, and national reporting requirements.

The guideline does **not** replace clinical judgement, divisional specialist advice, or programme-level directives issued in response to emerging epidemiological or operational challenges. MHMS accepts no liability for adverse events, treatment outcomes, or operational decisions made outside the scope of these guidelines or contrary to established procedures.

Periodic updates may be issued through MHMS circulars, the National Tuberculosis Programme, or other authorised mechanisms. Users are responsible for ensuring they apply the most current version and follow official communication regarding changes to diagnostic algorithms, treatment regimens, surveillance requirements, or supply-chain procedures.



ACKNOWLEDGEMENTS

The Ministry of Health and Medical Services extends its gratitude to all partners and individuals who contributed to the development of the Fiji National Tuberculosis Guidelines. This updated resource supports healthcare workers, programme managers, and stakeholders in delivering timely diagnosis, effective management, and strengthened prevention of TB across Fiji.

We acknowledge the leadership of the National Tuberculosis Programme (NTP) in coordinating the revision process and ensuring alignment with the 2025 WHO TB recommendations. We also thank the WHO Country Office for ongoing technical support, including contributions from Dr Ignacio Monedero Recuero, Dr Patricia Macías, and Dr Matthew Shortus, whose expertise and guidance were instrumental in shaping this edition.

Our appreciation is extended to the Clinical Services Network—including Internal Medicine, Paediatrics, Obstetrics & Gynaecology, HIV Programme, and Laboratory Services—for their valuable review and endorsement of clinical algorithms and infection-control protocols.

We also acknowledge the contributions of Dr Sam Fullman and the wider clinical teams who provided technical insights to ensure the guidelines are responsive to Fiji’s epidemiological realities, including the challenges posed by MDR-TB, co-infections, and non-communicable diseases.

We commend the dedication of Fiji’s healthcare workforce—clinicians, nurses, public health teams, and community health workers—whose frontline experience shaped the practical applicability of this document. We further thank community leaders, patient advocates, and TB survivors for sharing their lived experiences and reinforcing the importance of a patient-centred approach.

Finally, we thank all partner agencies and supporting institutions for their continued collaboration toward strengthening Fiji’s TB control efforts.



CONTRIBUTORS

This work was made possible through close collaboration with a diverse group of local and overseas experts whose contributions were essential to ensuring that the guideline reflects current evidence, strengthens clinical practice, and supports quality TB care across Fiji.

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FOREWORD

Tuberculosis (TB) remains a major public health concern in Fiji, with significant implications for individuals, families, and communities across the country. Despite ongoing efforts, the persistence of TB, including drug-resistant forms and TB-HIV co-infection, highlights the continued need for strong, coordinated, and evidence-based responses at all levels of the health system.

The Fiji National Tuberculosis Management Guidelines (5th Edition, 2025) represent an important milestone in strengthening our national response to TB. This updated guideline reflects the latest World Health Organization recommendations and international best practices, while being carefully contextualised to Fiji's epidemiological profile, health system capacity, and geographic realities. It provides clear, practical guidance for the prevention, diagnosis, treatment, and management of TB across hospital, primary health care, and community settings.

I commend the National Tuberculosis Programme, clinical experts, technical partners, and frontline health workers who contributed their expertise and commitment to the development of this guideline. Their collective efforts ensure that this document is not only technically robust but also practical and relevant for daily use by health professionals throughout Fiji.

The Ministry of Health and Medical Services remains fully committed to supporting the implementation of these guidelines as part of our broader efforts to strengthen health systems, improve treatment outcomes, and reduce TB transmission. I urge all health workers and partners to use this guideline as the standard reference in TB care and control, as we work together towards the shared goal of ending tuberculosis as a public health threat in Fiji.

Dr Luisa Cikamatana
Acting Permanent Secretary

Ministry of Health and Medical Services, Fiji.



BACKGROUND

Tuberculosis (TB) remains a major public health challenge in Fiji and the wider Pacific, with the intersecting burdens of TB–HIV co-infection and increasing drug-resistant TB (DR-TB and RR-TB) threatening to undermine hard-won progress in disease control. As a regional health hub, Fiji plays a critical leadership role in surveillance, coordinated programme management, and capacity building across Pacific Island countries.

From 2014 to 2022, Fiji recorded 4,067 TB cases, with a case notification rate averaging 51 per 100,000 population (range 38–73). During this period, treatment success rates declined markedly—from 72.5% in 2014 to 50.3% in 2022—while case fatality remained high at 7–14%. The burden is particularly severe among vulnerable groups, including children under five (8.1% mortality) and people living with HIV (28.6% mortality). These epidemiological trends underline the urgency of a strengthened, context-appropriate, and resilient national TB response. These guidelines align with the World Health Organization (WHO) End TB Strategy and Sustainable Development Goal 3.3 and are grounded in the principles of Universal Health Coverage (UHC) to ensure equitable access to high-quality TB services without financial hardship. They also reflect the Asia Pacific Health Security Action Framework II (APHSAF II), which prioritizes multisectoral coordination, readiness, and system-wide resilience against infectious disease threats.

Incorporating the Weaving Framework, the guidelines embed Pacific cultural perspectives into TB care and health systems strengthening. Anchored in Primary Health Care (PHC) approaches, they promote decentralized, community-centered service delivery across nursing stations, health centers, and provincial hubs. They also integrate key innovations—including GeneXpert MTB/RIF Ultra, urine LF-LAM assays, and optimized TB preventive therapy (TPT) regimens—to enhance early detection and continuity of care. By reinforcing infection prevention and control (IPC), strengthening interoperable surveillance systems, and elevating community engagement, Fiji reaffirms its commitment to reducing TB transmission, safeguarding vulnerable populations, and accelerating progress toward TB elimination by 2030.



SCOPE AND PURPOSE

The purpose of this Tuberculosis (TB) Guideline is to provide clear, evidence-based recommendations for the prevention, diagnosis, treatment, and management of TB in Fiji. It aims to support clinicians, public health practitioners, programme staff, and other healthcare workers in delivering consistent and high-quality TB services across all levels of the health system.

This guideline defines the national standards of care for TB, outlines clinical and operational pathways, and ensures alignment with current global recommendations adapted to Fiji's epidemiological context. It also serves to strengthen early detection, effective case management, infection prevention and control, and appropriate follow-up. The scope of this guideline covers the management of drug-susceptible and drug-resistant TB, TB in special populations (including children, pregnant women, and individuals with comorbidities), and programmatic approaches essential for a coordinated national TB response.

WHO IS THIS GUIDELINE FOR

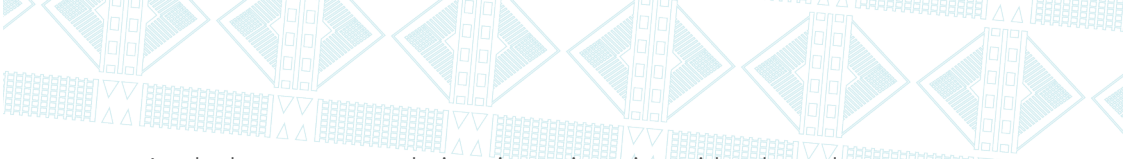
This Guideline is intended for all health workers involved in TB care and control in Fiji, including:

- Medical Officers, Nurse Practitioners, Nurses, and Clinical staff.
- Laboratory personnel and radiology teams
- Outreach teams
- Public health and Clinical staff at national, divisional, and subdivisional levels
- Partners supporting TB services, including WHO, UNDP/Global Fund, NGOs, and workplace health programs

HOW TO USE THIS GUIDELINE

Use the Guideline as the standard reference for clinical and public health decision-making in TB care.

Follow the diagnostic and treatment algorithms, flowcharts, and SOPs to support consistent, timely, and correct patient management.



Apply the recommendations in conjunction with other relevant guidelines, including the TB/HIV Integrated Guidelines, Paediatric TB guidance, and NTP Standard Operating Procedures.

REVIEW AND UPDATES

This Guideline will undergo a formal review **every 5 years**, or earlier if:

- New WHO TB recommendations are issued
- Significant epidemiological changes occur (e.g., TB/HIV coinfection trends, new diagnostics, new medicines)
- Programmatic updates arise within the National TB Program

Minor updates may be released intermittently through NTP Circulars or Technical Working Group (TWG) endorsements to ensure the Guideline remains current and responsive.

ABBREVIATIONS

AII	Airborne Infection Isolation
APHSAF II	Asia Pacific Health Security Action Framework II
ART	Antiretroviral Therapy
BCG	Bacillus Calmette–Guérin
CHW	Community Health Worker
CNR	Case Notification Rate
CPD	Continuing Professional Development
CQI	Continuous Quality Improvement
CTB	Core Tuberculosis Indicators
DOT	Directly Observed Therapy
DR-TB	Drug-Resistant Tuberculosis
DST	Drug Susceptibility Testing
EQA	External Quality Assessment
GeneXpert	Cartridge-Based Nucleic Acid Amplification Test for
MTB/RIF Ultra	Mycobacterium tuberculosis and Rifampicin Resistance
HIV	Human Immunodeficiency Virus
IC	Infection Control
ICF	Intensified Case Finding
INH	Isoniazid
IPC	Infection Prevention and Control
LAM	Lipoarabinomannan Assay
LPA	Line Probe Assay
MDR-TB	Multidrug-Resistant Tuberculosis
MHMS	Ministry of Health and Medical Services
MoH	Ministry of Health and Medical Services
NCD	Noncommunicable Disease
NGO	Non-Governmental Organisation
NTP	National Tuberculosis Programme
PCR	Polymerase Chain Reaction
PHC	Primary Health Care
PLHIV	People Living with HIV
PMDT	Programmatic Management of Drug-Resistant Tuberculosis
RR-TB	Rifampicin-Resistant Tuberculosis
SDG	Sustainable Development Goal
TB	Tuberculosis
TPT	Tuberculosis Preventive Therapy
UHC	Universal Health Coverage
WHO	World Health Organization
XDR-TB	Extensively Drug-Resistant Tuberculosis

Anti TB drugs	
Am	Amikacin
Amx-Clv	Amoxicillin–clavulanic acid
Bdq	Bedaquiline
Cfz	Clofazimine
Cm	Capreomycin
Cs	Cycloserine
Dlm	Delamanid
E/EMB	Ethambutol
Eto	Ethionamide
Gfx	Gatifloxacin
H or INH	Isoniazid
H ^H or INH ^H	high-dose isoniazid
Imp-Cln	imipenem–cilastatin
Km	Kanamycin
Lfx	Levofloxacin
Lzd	Linezolid
Mfx	Moxifloxacin
Mpm	Meropenem
Pa	Pretomanid
PAS	Para Amino Salicylic Acid
Pto	Prothionamide

R or RIF	Rifampicin
Rpt	Rifapentine
S Trd	Streptomycin Terizidone
Z or PZA	Pyrazinamide
Anti-TB regimens and TB preventive regimens	
2RHZE/4RH	Category I regimen comprising daily rifampicin, isoniazid, ethambutol and pyrazinamide for 2 months and rifampicin and isoniazid for 4 months
BPaL/BPaLM	A short treatment regimen comprising daily bedaquiline, pretomanid, linezolid and moxifloxacin for 6 to 9 months
1HP	1 month of daily rifapentine plus isoniazid
3HP	3 months of weekly rifapentine plus isoniazid
3HR	3 months of daily rifampicin plus isoniazid
4R	4 months of daily rifampicin monotherapy
6H	6 months of daily isoniazid monotherapy
6Lfx	6 months of daily levofloxacin
9H	9 months of daily isoniazid monotherapy

GLOSSARY AND DEFINITIONS

Term	Simplified Definition (British English)
Active case finding (ACF)	Also called <i>systematic screening</i> for TB disease. Usually done outside health facilities to find people with TB, early.
Adolescent	A person aged 10–19 years.
Adult	A person older than 19 years.
Child	A person younger than 10 years.
Close contact	Someone not from the same household but who has spent long periods in the same enclosed space as the person with TB during the three months before treatment started.
Contact	Any person exposed to someone with TB (the index case).
Contact investigation	A process to find people with TB disease or TB infection among those exposed to the index case or in high-risk places. Includes checking symptoms, testing, and giving treatment or TB preventive treatment (TPT) as needed.
Drug susceptibility testing (DST)	A lab test to see if TB bacteria are resistant or sensitive to specific medicines, done by genetic testing or by growing the bacteria.
High TB transmission setting	A place with many undiagnosed TB cases or where infectious TB patients is present, increasing the risk of spread—especially in crowded or poorly ventilated areas or where vulnerable people are present.
Household contact	A person who has lived in the same enclosed space as the person with TB for one or more nights, or for long periods during the day, in the three months before treatment began.

Index person with TB	The first identified person with TB in a household or similar setting. May not be the source of infection. Investigation should include all household and close contacts, especially if the index case has pulmonary TB, MDR-TB, XDR-TB, HIV, or is a child under 5.
Infant	A child younger than 1 year.
mWRD (molecular WHO-approved rapid diagnostic test)	A quick genetic test to confirm TB, currently using GeneXpert.
People who use drugs	People who use psychoactive substances in a way that may harm their health, relationships, finances, or legal situation.
Tuberculosis (TB) or active TB disease	Illness caused by bacteria from the <i>Mycobacterium tuberculosis</i> complex. The main cause in humans is <i>M. tuberculosis</i> . Refers to active TB, not TB infection.
Tuberculosis infection (TBI)	Immune response to TB bacteria without signs or symptoms of disease. People are not sick but can develop TB disease later. Previously called “latent TB infection” (LTBI). No single perfect test exists.
TB preventive treatment (TPT)	Medicines given to people with TBI who are at risk of developing TB disease, to reduce that risk. Previously called “treatment for latent TB infection.”

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Underweight	Adults (≥ 19 years): BMI < 18.5 kg/m ² . Children/adolescents (< 19 years): weight-for-age < -2 z-scores.



TABLE OF CONTENTS

DISCLAIMER	i
ACKNOWLEDGEMENTS.....	ii
CONTRIBUTORS	iii
FOREWORD.....	iv
BACKGROUND.....	v
ABBREVIATIONS.....	viii
GLOSSARY AND DEFINITIONS	xi
TABLE OF CONTENTS.....	1
CHAPTER 1: UNDERSTANDING MYCOBACTERIUM TUBERCULOSIS	2
CHAPTER 2: DIAGNOSIS OF TUBERCULOSIS DISEASE	12
CHAPTER 3. DRUG SUSCEPTIBLE TUBERCULOSIS TREATMENT.....	32
CHAPTER 4. PATIENTS FOLLOW UP.....	37
CHAPTER 5. DRUG-RESISTANT TUBERCULOSIS TREATMENT	57
CHAPTER 6. TB IN CHILDREN AND ADOLESCENTS	68
CHAPTER 7. MANAGEMENT OF TB-HIV IN ADULTS AND CHILDREN	81
CHAPTER 8. SPECIAL SITUATIONS: TB-DM, TB-PREGNANCY	97
CHAPTER 9. TB PREVENTION: BCG, INFECTION CONTROL AND TPT	103
REFERENCES.....	125
ANNEXES.....	130

CHAPTER 1:

**UNDERSTANDING
MYCOBACTERIUM
TUBERCULOSIS**

CHAPTER 1: UNDERSTANDING MYCOBACTERIUM TUBERCULOSIS

THE PATHOGEN

Tuberculosis (TB) is an infectious disease caused by a group of closely related bacteria known as the *Mycobacterium tuberculosis* Complex (MTBC).

This group includes:

- *Mycobacterium tuberculosis* (Mtb) – the most common cause of TB in humans
- Other TB-causing species such as *M. bovis*, *M. caprae*, *M. africanum*, *M. microti* and others.

All species in the complex cause diseases that look the same clinically, are diagnosed using the same tests (including GeneXpert), and are treated in the same way. For simplicity, in these guidelines, **MTBC** and **Mtb** are used interchangeably. Globally, TB is the 10th leading cause of death and remains the leading killer among infectious diseases.

Key microbiological features of Mtb

- **Shape and cell wall** – Gram-positive, rod-shaped (bacillus) bacteria with a thick cell wall rich in mycolic acids. This wall makes the bacteria highly resistant to harsh environmental conditions and many disinfectants.
- **Staining** – Cannot be seen with a normal Gram stain. Requires Ziehl–Nielsen staining or similar techniques as it is an acid-fast bacillus (AFB).
- **Growth needs** – Prefers oxygen-rich environments (aerobic) and a neutral pH.
- **Survival states:**
 - **Active form** – Multiplies when oxygen, neutral pH, and nutrients are available, leading to disease.
 - **Latent form** – Survives in harsh conditions, such as inside immune cells (macrophages) or within granulomas. In this state, it is inactive but can reactivate years or even decades later.

Bacterial Feature	Impact on Disease & Treatment
Thick cell wall	Slows bacterial growth and makes the disease progress gradually.
Ability to remain dormant	Allows infection to stay hidden (latent TB), with the risk of reactivation later.
Two growth states (active & dormant)	Medicines must target both forms for a complete cure, but not all TB drugs work on both.

Public health implications: MTB's unique biology contributes to its high mortality rate and complicates elimination efforts.

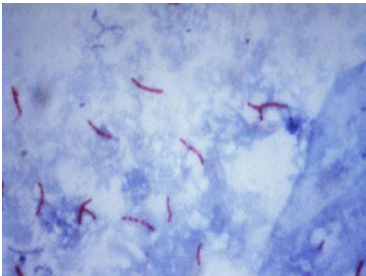


FIGURE 1.1 MTB SEEN UNDER THE MICROSCOPE USING ZIEHL-NIELSEN STAIN ON SPUTUM SMEAR.

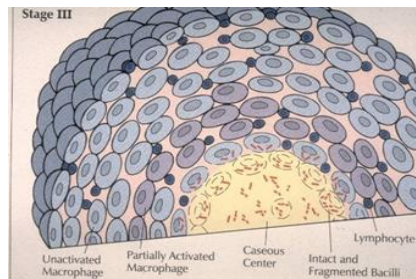


FIGURE 1.2 SCHEMATIC REPRESENTATION OF AN EFFECTIVE GRANULOMA.

THE HUMAN HOST RESPONSE

In TB, the strength of the immune system plays a major role in whether infection stays under control or progresses to active disease. The symptoms and clinical features depend on how well the immune system is functioning.

Mechanism	Role in TB
Alveolar macrophages	Specialized immune cells in the lungs, that engulf and attempt to destroy Mtb when it enters the air sacs (alveoli). Activated macrophages may phagocytose and destroy Mtb, infection is stopped. If not, a second line of defence is triggered.
Granuloma formation	A cluster of immune cells that walls off and contains Mtb to prevent spread. A well-formed granuloma may undergo necrosis (cell death) and calcification, effectively controlling infection for years.

Progression to disease:

If granulomas are **ineffective** due to high numbers of bacteria, more aggressive strains, or a weakened immune system, Mtb can escape and disseminate, leading to active TB disease.

Immune function can be reduced by:

- Malnutrition
- HIV infection
- Immunosuppressive medicines (e.g., steroids, chemotherapy)
- Chronic stress
- Certain cancers

THE TB SPECTRUM: FROM EXPOSURE TO INFECTION AND TO DISEASE

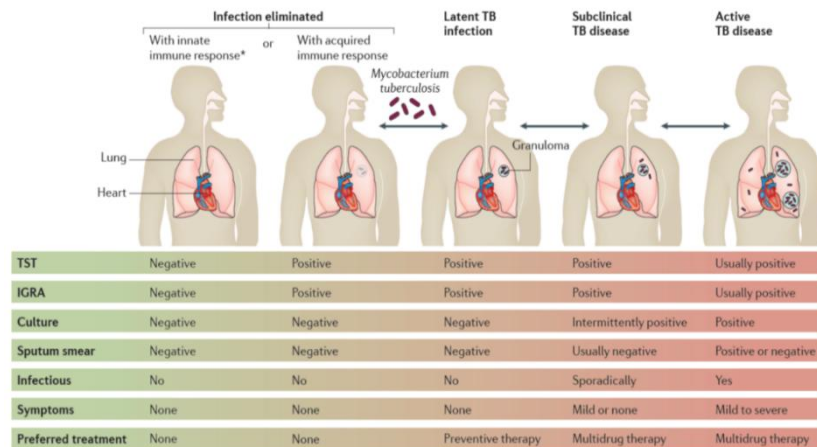
TB's progression is more complex than most bacterial diseases. Instead of moving directly from "healthy" to "sick", TB moves along a **continuum** that can last years or decades. It is not fully clear whether this progression is always one-way or if people can move between stages.

STAGES OF THE TB SPECTRUM:

STAGE	DESCRIPTION	KEY POINTS
<i>1. TB EXPOSURE</i>	Encountering Mtb from someone with active TB. Common in high-prevalence areas or crowded conditions (e.g., prisons, informal settlements, some hospitals).	Exposure does not always lead to infection.
<i>2. TB INFECTION</i>	Mtb reaches the lung alveoli and escapes destruction by macrophages. Granulomas form to contain it. People have no symptoms and are not infectious. It can only be detected by immune-based tests (PPD skin test or IGRA blood test).	Lifetime risk of progressing to TB disease: 5–10%, highest within 2 years of infection.
<i>3. TB DISEASE</i>	Granulomas fail to contain Mtb, which multiplies and causes symptoms. Most often affects the lungs but can involve other organs.	
<i>– ASYMPTOMATIC OR MINIMALLY SYMPTOMATIC TB</i>	Found early, often through contact tracing or chest X-ray, before major damage occurs. The best way to treat the bacterial load is low and disability can be prevented. However, patients can still transmit TB.	

<p>– ADVANCED TB DISEASE (CLASSIC PRESENTATION)</p>	<p>Most common stage at diagnosis. Patients have been infectious for a long time, with lung tissue damage already present.</p>	
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FIGURE 1.3 TB DISEASE SPECTRUM PRESENTATION AND ASSOCIATED SYMPTOMS, COMPLEMENTARY TESTS AND OTHERS. MODIFIED FROM PAI M ET AL (NATURE REVIEWS, 2016).



Clinical Implications: Recognising TB as a **spectrum of disease**—rather than a single stage—underscores the need for early detection, preventive action, and tailored treatment to stop progression.

Early TB Symptoms: Often systemic (whole body) and non-specific. Common symptoms include:

- Fever
- Unexplained weight loss (or *failure to thrive* in children)
- Night sweats
- Loss of appetite
- Malaise or general feeling of being unwell
- Persistent cough
- Symptoms **develop slowly**, which often delay diagnosis.

- Some people, especially in the early stages—may have **no symptoms** at all.

Progression of Disease: As the bacterial load increases and tissue damage develops (from direct bacterial injury or the body's immune response), TB moves into more severe stages.

- Advanced TB is marked by **significant symptoms**, worsening lung damage, and—in the absence of treatment—can lead to death.
- Late diagnosis** is common at this stage, which makes treatment more difficult and outcomes poorer.

Mortality Estimates:

Patient group	Risk without treatment
Immunocompetent adults with smear-positive pulmonary TB	~70% die within 2–5 years
Immunosuppressed patients (including children, people with HIV, or those who are malnourished)	Progression to death is faster and more frequent

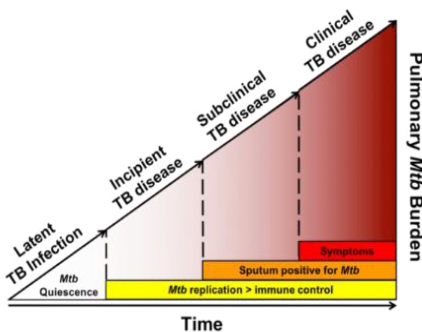


FIGURE 1.4 MODEL OF PROGRESSION FROM INFECTION TO ACTIVE DISEASE. MODIFIED FROM DRAIN ET.AL. (2018)

Clinical implication: Early diagnosis and treatment are critical to prevent mortality and manage TB effectively across both pulmonary and extrapulmonary forms.

DISEASE SPREAD AND PRESENTATION:

TB can spread within the body through three main routes:

1. Bronchogenic (airways)
2. Lymphatic (lymph nodes)
3. Haematogenous (bloodstream)

Pulmonary TB (Bronchogenic Dissemination)

- **Most common form** – about 80% of TB cases, as *M. tuberculosis* prefers oxygen-rich lung tissue.
- **Early stage:** May cause small nodules or minimal lung infiltrates, often with mild or no symptoms.
- **Advanced stage:** Granulomas break down, forming cavities in the lungs. This causes cough, breathlessness, chest pain, and further lung damage. Cavities also increase infectiousness.

Lymph Node TB (Lymphatic Dissemination)

- Bacilli are carried by immune cells (macrophages) to lymph nodes.
- Common in **children**, often affecting intrathoracic or cervical lymph nodes.
- Ruptures of infected lymph nodes can spread bacteria to surrounding tissues.

Extrapulmonary TB (Haematogenous Dissemination)

- Bacilli enter the bloodstream, potentially affecting **any organ**: brain, liver, spleen, bones, and others.
- More common in **immunocompromised individuals** (e.g., people living with HIV, children, elderly).
- Often severe, harder to diagnose, and prone to complications such as organ damage or long-term disability.

Disseminated TB

- TB spreads widely through the bloodstream, infecting **multiple organs at once**.
- If untreated, it can cause **multi-organ failure**.
- Most often affects children, the elderly, people living with HIV, and other immunosuppressed groups.
- This is the **most lethal form** of TB.

TB DYNAMICS AND TRANSMISSION

Mode of transmission: Mtb spreads mainly via airborne transmission from infectious patients. Droplets (<5 *microns*) are expelled by individuals with pulmonary TB through coughing, sneezing, speaking, or singing. These droplets can **stay in the air for over six hours** and infect others when inhaled, usually settling in the lower lungs.

Factor	Details
Main sources of infection	People with high bacterial loads, especially those with large lung cavities or smear-positive pulmonary TB. Risk is higher when treatment is incorrect or incomplete (e.g., MDR-TB managed with ineffective regimens).
Extra-pulmonary TB	Much lower risk of transmission compared to pulmonary TB.
Bronchial spread	Bacteria can seed other lung areas and be expelled into the air, especially from high-oxygen cavities.
Reduction in infectiousness	Risk falls quickly once effective treatment starts.
Infectivity estimates	One infectious patient may infect 10–20 people, with about 2 developing active TB.

The bacilli dissemination through the bronchial tree will seed Mtb bacteria in other sites of the lungs but also will send bacilli to the air and environment through a cough. The high oxygen concentration in the cavity will support bacilli replication.

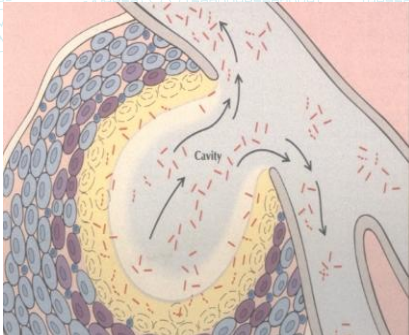


Figure 1.5 Schematic representation of a granuloma in the lung. When it enlarges into the bronchi, the pus and bacilli content of the granuloma leak into the bronchi. Bronchi irritation creates a cough, and the granuloma is emptied creating a cavity.

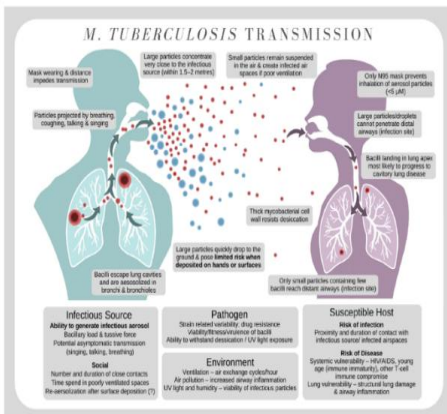


Figure 1.6 TB Transmission. Modified from Coleman et.al (Pathogens 2022)

Factors increasing transmission risk

- High HIV prevalence in the community
- Malnutrition
- “Super-spreaders” – patients with very high bacterial loads and multiple contacts
- Overcrowded, poorly ventilated settings (e.g., prisons, informal housing, some hospitals)

Vertical (mother-to-child) transmission: Pregnancy causes relative immune suppression, which can allow hematogenous spread of Mtb to the placenta. Vertical transmission (across the placenta) is more common than previously recognized.



Fetal impact:

- Congenital TB (infection before birth)
- Disseminated TB soon after birth
- Both carry a high risk of newborn death.

Public Health implications: Early diagnosis and correct treatment are critical to stopping TB spread. Targeted measures are required for high-risk populations and high-risk environments to interrupt transmission.

Prevention: Early diagnosis and prompt, effective treatment in pregnant women is essential to protect the baby and prevent complications.

CHAPTER 2:

**DIAGNOSIS OF
TUBERCULOSIS
DISEASE**

CHAPTER 2: DIAGNOSIS OF TUBERCULOSIS DISEASE

CLINICAL SYMPTOMS

Tuberculosis is a multi-system disease that can mimic many other conditions. Because *M. tuberculosis* grows slowly, symptoms often develop gradually but progressively, leading to delayed health-seeking behaviour and late diagnosis. A high index of suspicion is essential for any person presenting to a health facility with symptoms suggestive of TB—especially in high-burden settings.

BOX 2.1 TB SIGNS AND SYMPTOMS:

Common constitutional and systemic symptoms (early and advanced TB stages)	Fever, unexplained weight loss, failure to thrive in children, night sweats, lymph node swelling at any location, body weakness, decrease appetite
Respiratory	Cough of any duration, shortness of breath, chest pain (associated with pleural effusion or pericarditis), hemoptysis
Neurological	Headache that has either been intermittent or persistent for 2 -3 weeks Meningitis signs and mental status change (subtle initially) Others: new onset of seizures, lateralizing signs, cranial nerve palsy
Skeletal	Back pain or stiffness evolving into Pott's Disease, lower extremity paralysis, arthritis (usually involving only 1 joint, most often the hip or knee, followed by the ankle, elbow, and wrist)
Genitourinary	Dysuria with negative regular urine culture. In men, a painful scrotal mass, prostatitis, orchitis, or epididymitis. In women, symptoms mimicking pelvic inflammatory disease
Gastrointestinal	Non-healing ulcers of the mouth or anus. Difficulty swallowing (with esophageal disease) Abdominal pain mimicking peptic ulcer disease (with gastric or duodenal

	infection). Malabsorption (with infection of the small intestine. Pain, diarrhea, or hematochezia (with infection of the colon)
Any other organ	TB may affect any organ , especially when TB is disseminated by blood (frequent in TB-HIV and children): liver, spleen, bone marrow, heart, skin...

In addition to constitutional systemic symptoms (Fever, weight loss, night sweats), ss physical examination findings are associated with the organs involved.

- *PTB*:
 - Abnormal breath sounds, on most occasions, over the upper lobes. However, usually noted around the affected areas
 - Crepitations or bronchial breath sounds which indicate consolidation
 - Decreased breath sounds over affected areas
- *EPTB*: Known as **“the great pretender”** in internal medicine—can mimic diseases of virtually any organ.
- *Chronic or severe TB disease (with or without HIV)*: marked cachexia and pallor.

Not every cougher has TB, not every TB has a cough.

Asymptomatic or pauci-symptomatic TB: TB diagnosed in early stages (e.g. TB contacts) or in the case of HIV infection or children/elder may present very little or no symptoms perceived by the patient. CXR, GeneXpert history of contact or HIV infection can be fundamental to TB disease presumption. These cases may transmit disease to others and given time may evolve into severe TB forms, therefore needing treatment.

The absence of any significant physical findings does not exclude active TB.

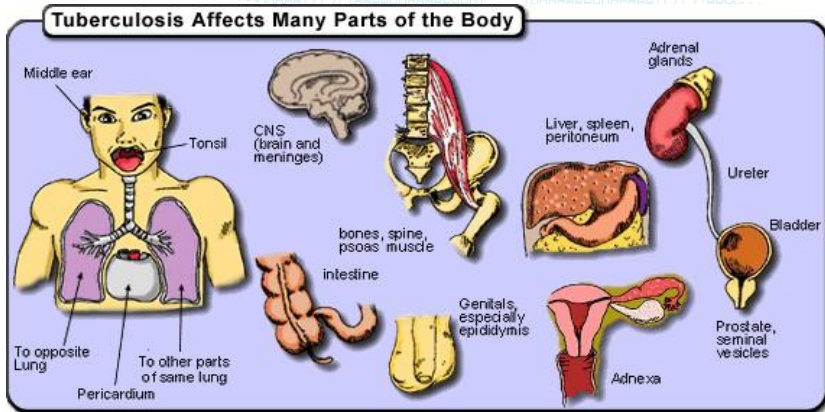


Figure 2.1 Different parts of the body are affected by TB.



Figure 2.2 From left to right: Spinal TB (Potts Disease), abdominal/peritoneal TB, cervical-lateral lymph lymphadenopathies and cervical-lateral lymphadenopathies with fistula, pus discharge and scars (scrofula)

IMAGING TESTS AND CHEST X-RAY

Imaging (CXR, CT scan, ultrasound) is highly sensitive and can detect TB alterations, even in the early stages when the patient is asymptomatic which is a great advantage over for example, a sputum smear. Imaging is widely available, relatively inexpensive (e.g., CXR), provides quick results, and is useful for presumptive diagnosis, especially in immunosuppressed patients (e.g., HIV, children) where bacteriological tests may be negative.



Chest X-Ray (CXR):

- Cavities are a hallmark of TB and can be predicted of the disease.
- The radiographic patterns of TB can vary, with the presence of cavities and the extent of lung damage (e.g., fibrotic tracts) being linked to bacterial load and prognosis. See Box 2.2.
- Clinical correlation: Interpretation of CXR results must be done in conjunction with the patient's clinical history and symptoms.
- Immunosuppressed populations: CXR may show atypical patterns or even normal results, especially in HIV-positive or severely immunocompromised individuals.
- Artificial intelligence (AI) assistance: AI programs help interpret imaging findings, offering probability levels for TB and other potential diagnoses.

Chest computed tomography scan (CT scan):

- Offers higher sensitivity than CXR but at a higher cost, with restricted availability of reference hospitals.
- Radiation exposure is higher than CXR, making it less suitable for frequent use.
- Useful for uncertain or initial TB cases, with the “tree in bud” pattern being a key TB marker.
- Provides detailed visualization of the mediastinum and lymph nodes, helping to detect lymph node fistulas.

Magnetic Resonance Imaging (MRI):

- Offers better sensitivity than CT for detecting TB, especially in the mediastinum, brain (tuberculomas, hydrocephalus, meningitis), liver, spleen, and lymph nodes.
- Highly useful for extrapulmonary TB, offering clear images of organs outside the lungs.

Ultrasound:

- Increasingly available and cost-effective, with portable devices linked to mobile phones and tablets.

- Essential for diagnosing extrapulmonary TB (EPTB), especially in intrathoracic, abdominal, and lymph node TB, as well as atypical liver and spleen patterns.
- Particularly valuable for disseminated TB cases, offering real-time, portable diagnostics.

Box 2.2 Most frequent CXR patterns in TB:

1. Upper lobes cavities with a mediastinal lymph node (Gohn's complex).
2. Nodules: can be solitary or multiple nodules. These are granulomas in initial phases before transformation into cavities, reflecting early stages of TB disease with lymph nodes (big or small) in the mediastinum. This is the typical presentation of TB in the child.
3. Opacities and alveolar infiltrates: a reflection of nodules when they grow and create peripheral inflammation. Sometimes there can be consolidations with or without lymph nodes and be very similar to the typical findings in community pneumonia. Typical form in children and immunosuppressed patients presenting primary TB (quick transition from infection to TB disease).
4. Lymph nodes: this is a very frequent finding in TB patients' CXRs, but usually unnoticed. When there are enlarged lymph nodes, the size of the mediastinum may enlarge, or even a clear rounded mass of variable size (from marble to lemon size) can be clearly seen.
5. Calcifications: high-density images as end phase of lymph node inflammation.
6. Pleural effusion: may present as a single CXR finding or presented with a peripheral nodule or cavities, which increase the likelihood of TB in the differential diagnosis.
7. Enlargement of cardiac silhouette: this tends to appear in TB pericarditis and should be an add-on sign to the symptoms of pericarditis.
8. Miliary TB: multiple micro-nodular patterns scattered in both lungs' reflection blood dissemination of Mtb affecting the lungs.

When present Miliary TB may alert of the possibility of disseminated TB affecting the brain and other organs

9. Destructive patterns: in very advanced TB, cavities may collapse creating, lobe collapse consolidations, fibrotic tracts with trachea traction, atelectasis or hyperinflation of the remaining lobes or segments. Under complete destruction, the lung may appear as a “white lung”.

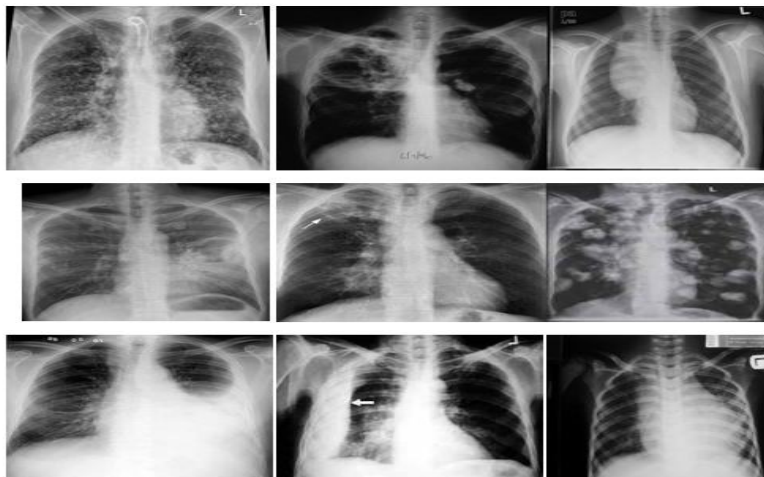


Figure 2.3 Chest X-ray panel for Pulmonary TB. Note that TB may present not only with cavities but with a wide variety of CXR abnormalities. Lateral CXR can be very helpful to diagnose lymphadenopathies in the Thorax that can key to diagnose TB in children (see chapter 6)

CXR SCREENING WITH CAD IN HIGH-RISK GROUPS.

For congregate and high-risk settings (e.g., prisons/detention, PLHIV clinics, silica-exposed workers, other vulnerable groups), implement periodic chest X-ray (CXR) screening. Where radiologist capacity is limited, use WHO-endorsed computer-aided detection (CAD) to support CXR reading in individuals ≥ 15 years, followed by Xpert Ultra for CAD-positive screens. Portable digital CXR units may be used to reach remote settings.

BACTERIOLOGICAL TEST

Bacteriological tests are the most specific tests in TB diagnosis. The diagnosis should be as much as possible confirmed with a bacteriologic test, which is also useful for confirming drug susceptibility or resistance. However, confirmation should not delay treatment enrolment, especially in critically ill cases like children and PLHIV.

Sputum smear microscopy for acid-fast bacilli (AFB) is mainly useful in patients with advanced disease; therefore, it does not support early diagnosis. Genetic tests, or more precisely nucleic acid amplification tests (NAATs), aid in early specific diagnosis of TB and prompt initiation of therapy. NAATs are more sensitive for detecting *M. tuberculosis* complex (MTBC) than AFB microscopy and are more specific.

GeneXpert is the current first line tool to confirm TB diagnosis in Fiji.

Bacteriologic Tests used in Fiji:

Test	What it is	Recommendations	Availability
Xpert MTB/RIF Ultra	Automated molecular test runs on the GeneXpert platform. Detects <i>Mycobacterium tuberculosis</i> complex (MTBC) and rifampicin resistance in ~2 hours. Higher sensitivity than earlier Xpert (limit of	First-line diagnostic test (adults & children) for TB and rifampicin resistance in sputum, preferred over smear microscopy/culture/DST. Use for TB meningitis on CSF and for TB detection in lymph node aspirates, pleural/peritoneal/pericardial/synovial fluid, or urine. In HIV-positive patients with signs of disseminated TB, may be used on blood. Not for treatment monitoring or relapse diagnosis (remains positive long after cure).	Hospitals, TB reference units, some peripheral sites.

	<p>detection: 16 CFU/mL vs 114 CFU/mL). It can be used at point of care but requires stable power, temperature control, and annual calibration.</p>		
Xpert MTB/XDR	<p>Uses 10-colour GeneXpert modules. Detects MTBC DNA and mutations for resistance to isoniazid, fluoroquinolones, second-line injectables (amikacin), and ethionamide, in ~90 minutes. Same workflow as Xpert Ultra.</p>	<p>Initial test for patients with rifampicin-resistant TB or contacts of such patients with suspected TB. May replace phenotypic DST for rifampicin/isoniazid resistance detection. Not for treatment monitoring or relapse diagnosis.</p>	<p>Hospitals, TB reference units.</p>
Urine TB LF-LAM	<p>Detects lipoarabinomannan (LAM) antigen in urine. Point-of-care test with results in <30 minutes. Does not provide drug resistance information.</p>	<p>Use in HIV-positive adults, adolescents, and children with advanced HIV disease (CD4 <100–200 cells/mm³) who are seriously ill or have TB symptoms, for both pulmonary and extrapulmonary TB.</p>	<p>Planned decentralisation to all TB units, primary care, and hospitals (2025–26).</p>
Sputum smear	<p>Detects acid-fast bacilli</p>	<p>Use when GeneXpert is not available. Also useful for</p>	<p>Hospitals, TB</p>

microscopy	(AFB) in sputum. Simple, low-resource test with high specificity but reduced sensitivity (needs ~10,000 bacilli/mL). Best yield with early-morning samples; at least two samples recommended.	estimating infectiousness, monitoring treatment progress, and diagnosing relapses (unlike molecular tests, which may stay positive post-cure).	reference units, peripheral areas.
Phenotypic & genotypic DST	Culture-based methods (solid/liquid) with high sensitivity (95%), detecting 5–10 bacilli/mL. Allows species ID and drug susceptibility testing. Turnaround: 10–45 days depending on method.	Gold standard for decades; now largely replaced by molecular tests for speed/accuracy. Still used for DR-TB monitoring, in the absence of molecular testing, or when resistance patterns are complex.	National Reference Laboratory (Tamavua Hospital).
Targeted next-generation sequencing (tNGS) & whole genome sequencing	tNGS sequences specific TB genes to detect strain type and resistance; WGS sequences the entire TB genome	Detects resistance mutations to first- and second-line drugs; useful for surveillance and tracking TB transmission clusters.	National Reference Laboratory and Fiji CDC.

ing (WGS)	(mainly for research). Highly sensitive.		
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Below is a summary of the laboratory diagnostic algorithm for Fiji based on the available diagnostic tools in country.

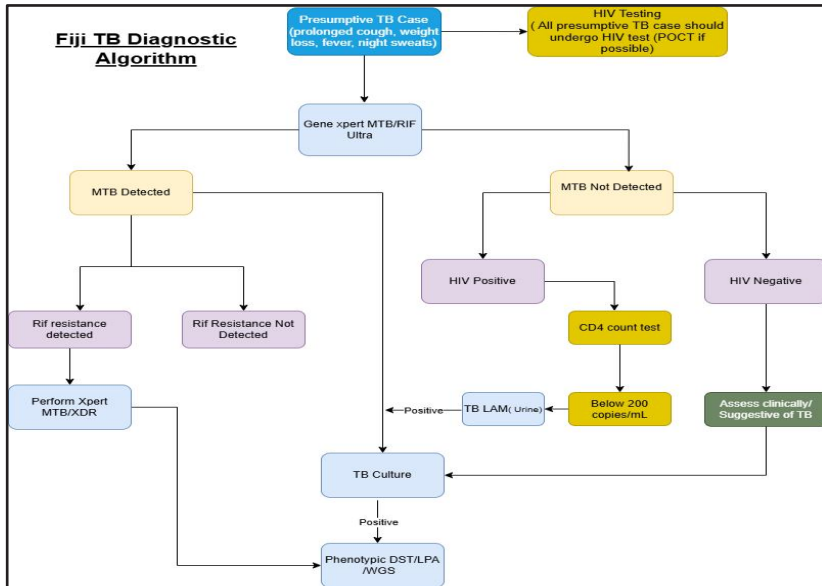


Figure 2.4 TB Laboratory Diagnostic Algorithm

Specimen transport protocols

Specimens from subdivisional or rural hospitals should be sent to the CWM Hospital / National Public Health Laboratory (and for some tests, Fiji CDC) using the Ministry of Health’s designated transport chain.

Turnaround times:

- Xpert Ultra/XDR: ~1–2 working days from receipt.

- Smear microscopy: same day if on-site; 1–2 days if transported.
- Culture & phenotypic DST: 10–45 days depending on growth.
- Urine LF-LAM: <30 minutes if on-site.
- tNGS/WGS: variable (days to weeks, depending on sequencing workflow).

For suspected MDR-TB: prioritise same-day dispatch; use cold-chain transport where needed; complete requisition forms clearly indicating *drug resistance suspicion*.

LABORATORY QUALITY ASSURANCE AND CONNECTIVITY

Turnaround time standards.

Xpert Ultra/XDR results should be communicated within 24 hours of sample receipt (assay time <2 hours)- no later than 48 hours in cases beyond laboratory opening hours. Culture/DST results are reported promptly on availability with interim notices for contamination/delays. Rifampicin-resistant results are critical and are relayed immediately to clinicians/NTP.

Digital connectivity.

Implement connectivity (e.g., GxAlert/Cepheid Remote Connectivity) so results and alerts (e.g., RR-TB detected) transmit in near real-time to clinicians and the TB program, and instrument performance is monitored centrally. Integrate outputs with the electronic TB register to reduce missing data and shorten time-to-treatment.

MAKING A TB DIAGNOSIS

TB diagnosis is a process that comprises the combination of multiple pieces of information, including:

1. **Presence of a potential TB contact or risk factors**, including HIV infection, socio-economic vulnerability (prison, migrants, minorities, IDUs, etc.), and clinical vulnerability (PLHIV, child, other alteration of immune system or immunosuppressant medication, etc.), health care workers [HCWs]. In case of children, consider the TB risk of parents, close relatives, or household members.
2. **Signs and symptoms**

Adults and children aged >10 y/o: comprising the systemic 4 symptoms (fever, weight loss, night sweats, and cough) plus other localized symptoms compatible with TB disease.

Children aged <10 y/o: fever, failure to thrive, lethargy, etc. Full description and score system in chapter 6 (2022 WHO paediatric algorithms – Fig 6.1 & Fig 6.2)

Asymptomatic TB: keep in mind that in contacts, cases of early TB stage, or children or PLHIV, TB may appear with little or no symptoms.

3. **Imaging tests**: mainly CXR. Ultrasound and CT/MRI scan orientate in case of internal lymphadenopathies or lesion compatible with granulomas in spleen, liver, brain (tuberculomas) or others.

4. **Bacteriological confirmation**: GeneXpert or urine TB LF-LAMs if available in case of clinical and/or CXR abnormalities. Others: TB culture, NGS.

5. **Other tests suggesting potential TB disease**: positive HIV test, C-reactive protein (indicator of systemic inflammation), alteration in blood test consistent with different types of TB (e.g., low haemoglobin, alteration in transaminase, etc.), ascites or cerebrospinal fluid, PPD or IGRAs (indicating not in disease but exposure or infection in the past), and others

If there are no active TB symptoms but the patient is at risk of progressing from infection to TB disease, people screened should undergo TB infection testing (e.g., Tuberculin Skin Test or IGRAs) if available and consider TB preventive (TPT) treatment if positive. People with high risk of progression to TB disease (children, PLHIV, immunosuppressed patients) should be directly considered for TPT after active TB has been ruled out.

In the advent of the current generalized TB-HIV epidemic in Fiji, the value of TB presumptive diagnosis in the smear and Xpert negative patient will gain an increasing value.

Due to high sensitivity and high specificity, low complexity Molecular WHO-approved rapid diagnostic test like GeneXpert to be used on respiratory samples as an initial diagnostic test for TB rather than smear microscopy/culture. See in figure 2.5 the WHO preferred algorithm for adult TB diagnosis.

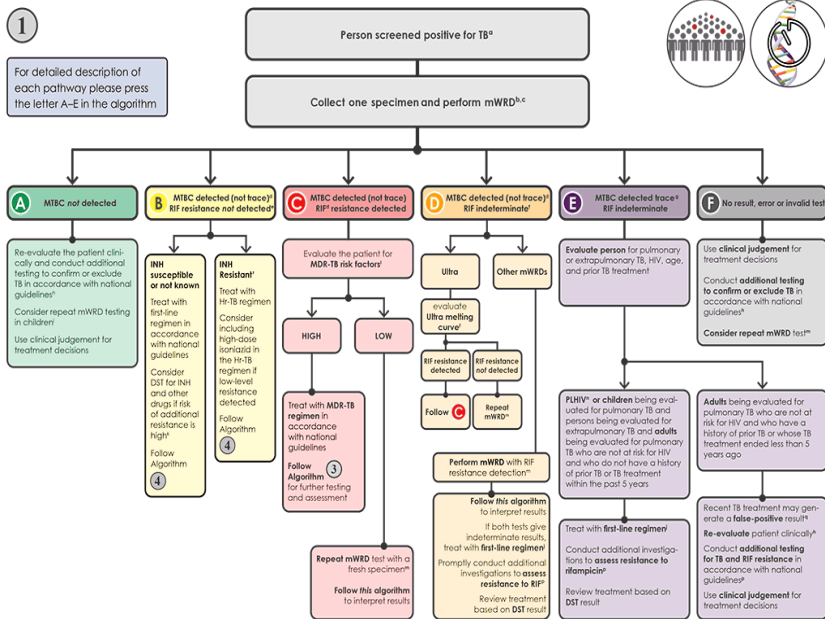


Figure 2.5 Molecular WRD as the initial diagnostic test for TB. Source: WHO TB knowledge sharing platform. Model algorithms <https://tbksp.who.int/en/node/>

OTHER TESTS THAT HELP ORIENT TOWARDS TB DIAGNOSIS

These tests do not bacteriologically confirm TB, but they can support the diagnosis of TB infection or TB disease, especially when primary microbiological tests are negative or inconclusive.

Test	What it is / How it works	Recommendations	Advantages	Limitations	Availability in Fiji
<p>Tuberculin Skin Test (TST)</p>	<p>Detects immune response to <i>M. tuberculosis</i> using intradermal injection of purified protein derivative (PPD). Induration measured 48-72 hrs later. Positive cut-offs vary by risk group: ≥5 mm (high risk), ≥10 mm (moderate risk). Cannot distinguish active from past infection.</p>	<p>May be used in people at risk of TB exposure and considered for TB preventive therapy; also useful in symptomatic patients with negative bacteriology (children/adults).</p>	<p>Low-cost; simple to perform; widely available.</p>	<p>False positives from BCG vaccination/other mycobacteria; false negatives in immunosuppression, very young children, recent exposure (<2 months), or incorrect administration.</p>	<p>Available at hospitals, TB reference units, and some subdivisional health facilities.</p>
<p>New PPDs ("TBST")</p>	<p>Skin tests using Mtb-specific antigens (ESAT-6, CFP-10). Endorsed types:</p>	<p>Like TST; can provide more reliable results in certain groups.</p>	<p>More specific than TST; safe; cost-effective; feasible.</p>	<p>Requires same procedure as TST; not yet widely available.</p>	<p>Limited to central hospitals and National TB Reference Unit</p>

	<p>C-Tb (India), C-TST (China), Diaskintest (Russia). Similar specificity to IGRA, better than TST in BCG-vaccinated, children, and PLHIV.</p>				<p>for pilot/early implementation.</p>
<p>Interferon-Gamma Release Assays (IGRAs)</p>	<p>Blood tests measuring IFN-γ release after TB-specific antigen exposure (ESAT-6, CFP-10). Two main types: QuantiFERON-TB Gold Plus (ELISA), T-SPOT.TB (ELISPOT).</p>	<p>May be used for TB preventive therapy eligibility and to support diagnosis in symptomatic patients with negative bacteriology.</p>	<p>Higher specificity than TST; unaffected by BCG; single patient visit; no booster effect.</p>	<p>Higher cost; lab facilities; false negatives in immunosuppressed; cannot distinguish latent from active TB.</p>	<p>Available at Fiji CDC and selected hospital laboratories with ELISA/ELISPOT capacity.</p>
<p>Biopsy & Histopathology</p>	<ul style="list-style-type: none"> Tissue sampling from affected organs (e.g., lymph node, pleura, bone marrow) for 	<p>Valuable in presumptive extrapulmonary TB when bacteriology is negative. Always combine with</p>	<p>Gold standard for some extrapulmonary sites; allows exclusion of other diseases.</p>	<p>Invasive; granulomas are not TB-specific; AFB may be negative in low-bacillary-load cases.</p>	<p>Available through surgical/biopsy services at divisional hospitals, with analysis at CWMH</p>

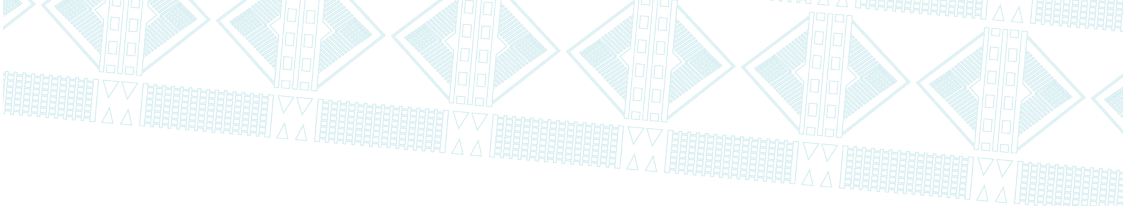
	<p>histology and microbiology. Caseating granulomas, with central necrosis and surrounding epithelioid histiocytes, Langhans giant cells, and lymphocytes, are classic for TB; AFB stains confirm if positive. TB culture and NAAT on biopsy tissue increase diagnostic yield.</p>	<p>clinical and other test findings.</p>		<p>Pathology Laboratory and National TB Reference Laboratory.</p>
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ASSESSMENT AND CLASSIFICATION OF TUBERCULOSIS CASES

For selecting the appropriate regimen and registration (relevant to analysis of treatment outcomes and program evaluation), patients are classified according to different categories.

Classification of patients based on clinical and bacteriological findings	
Presumptive TB	Refers to a patient who presents with symptoms or signs suggestive of TB (previously known as a TB suspect).
Bacteriologically confirmed TB	refers to TB diagnosed in a biological specimen by smear microscopy, culture, or a WHO-approved rapid diagnostic test such as Xpert® MTB/RIF or a urinary lipoarabinomannan assay.
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.
Pulmonary TB (PTB)	Refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as PTB because there are lesions in the lungs. Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of PTB.
Extrapulmonary tuberculosis (EPTB)	Refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. Pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, and meninges.
Extensive (or advanced) pulmonary TB disease	Presence of bilateral cavitory disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.
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) is considered severe.
Classification of patients based on history of previous TB treatment (patient registration group)	
New case	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.
Previously treated	Refers to patients who had received 1 month or more of anti-TB drugs in the past
Treatment after failure	Refers to patients who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment.
Treatment after relapse	Refers to patients who had previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by re-infection).
Treatment after LTFU	Refers to patients who had previously been treated for TB and were declared lost to follow-up during their most recent course of treatment (previously known as treatment after default).
Classification of patients based on the pattern of resistance	
DS-TB	TB disease caused by a strain of <i>M. tuberculosis complex</i> with no resistant result or no risk factors for resistance presumption.
MDR-TB	TB disease caused by a strain of <i>M. tuberculosis complex</i> that is resistant to rifampicin and isoniazid.
RR-TB/MDR-TB	Refers to either multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB).
Extensively drug-resistant TB (XDR-TB)	TB disease caused by a strain of <i>M. tuberculosis complex</i> 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 other "Group A" drug (bedaquiline or linezolid).
Pre-extensively drug-resistant TB (pre-XDR-TB):	TB disease caused by a strain of <i>M. tuberculosis complex</i> 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).



If Xpert is negative but suspicion remains high, do not rule out TB. In children, PLHIV, or any seriously ill patient with strong clinical/radiological evidence, proceed with additional investigations and start treatment empirically when indicated—do not delay because the first Xpert was negative. Repeat Xpert on a new or alternative specimen, add urine LF-LAM (if PLHIV with advanced disease/serious illness), send culture/LPA, and obtain imaging as appropriate. Document such cases as “clinically diagnosed TB.” Continue attempts at bacteriological confirmation in parallel.

TB is a fatal disease, that progresses with disability and transmits to the community if left untreated. It is crucial that if there is a sound TB presumption based on the aforementioned information, the search for bacteriological confirmation does not delay treatment enrolment. This is crucial in patients at risk of death from TB like children and PLHIV, where bacteriological confirmation only occurs in the advanced and late stages of the disease.

ACTIVE CASE FINDING AND RISK GROUPS

Active case-finding activities may increase the notification rate and early case management in households of TB-affected families, institutions prone to TB outbreaks (e.g. prisons) or in high-risk groups due to high exposure to TB bacilli or risk of disease development after infection.

Contact tracing activities are the starting point for: early TB detection and identification of exposed persons likely to be infected and benefit from TB preventive treatment (TPT)

Box 2.3 Outline of Active Case-finding Strategies:

1. **Passive case finding: regular contact tracing.** Identify close contacts of the diagnosed TB patient, including household members and those spending ≥ 3 hours/day together in the same enclosed space. These contacts should come to the TB facility and be screened for active TB disease. If no active TB symptoms exist but are at risk of progressing from infection to disease, they should undergo TB infection testing (e.g., Tuberculin Skin Test or IGRAs) and consider TB infection treatment if positive.
2. **Active case finding: direct household screening** or outbreak investigation (TB infection and TB disease) activities for DS and especially for DR-TB contacts
3. **Massive screening in high-risk groups: early detection and periodic active TB screening strategies.** People living in congregate settings like prisoners or detention centres, migrants from high-incidence countries living in challenging circumstances or camps, HCWs, Miners or people exposed to silica dust,
4. **Specific intensive case-finding strategies for vulnerable individuals:** TB disease and infection should be ruled out in all PLHIV and other immunosuppressed patients like the use of immunosuppressant medication (e.g. anti-TNF alpha), haemodialysis, candidates for haematological or solid organ transplant, patient with cancer or on chemotherapy. Other high-risk groups in countries like Fiji include indigenous people, prisoners, migrants, miners, substance misusers, and individuals with chronic diseases (e.g., diabetes, renal failure).
5. **Reverse contact tracing:** from TB or TB-HIV children, the parents and relatives can be diagnosed

CHAPTER 3:

**DRUG SUSCEPTIBLE
TUBERCULOSIS
TREATMENT**

CHAPTER 3. DRUG SUSCEPTIBLE TUBERCULOSIS TREATMENT

BACTERIOLOGICAL PRINCIPLES FOR TB TREATMENT

Mycobacterium tuberculosis (*Mtb*) is a pathogen very different from most human pathogens. It needs special treatment to kill bacilli in the different metabolic states (the active and dormant bacteria).

Tuberculosis therapy has three main objectives:

1. Exert **a bactericidal effect**, thus reducing the actively growing bacterial load, the severity of the disease (its morbidity and mortality), and stopping transmission
2. Eliminate populations of persisting dormant bacteria through its **sterilising effect**, preventing relapse once the treatment is stopped
3. **Prevent the selection of drug-resistant bacilli** during therapy

Decades of research and multiple clinical trials have shown the need for treatment regimens that include multiple drugs acting through different mechanisms and sites of action, minimising drug toxicity and increasing treatment adherence (see Box 3.1 for the bacteriological basis for TB regimens).

Cure of an individual patient saves the life of the patient but also stops the transmission in the community; it is both humanitarian and a community success.

Once a TB diagnosis is made, treatment must be commenced immediately, and the divisional TB Control Officer must document the details of the diagnosis in the divisional register within 3 calendar days. Following the TB diagnosis, a set of actions and baseline tests, like HIV testing, are necessary as set in **Chapter 4**.

All newly diagnosed Bacteriologically Confirmed patients **MUST** be registered regardless of initiation of treatment.

Box 3.1 Bacteriological Basis for Adequate TB Treatment Regimens:

1. BACTERICIDAL DRUGS: These drugs kill bacilli in metabolically active or replicative mode. These drugs reduce the patient's infectiousness but also prevent the patient's death, as multiplying bacilli are the ones responsible for the clinical situation. As well these drugs, because they reduce the bacilli burden, not only improve symptoms but also protect against resistance selection: the lower the number of bacilli, the lower the chances of mutants and therefore, resistance. Most antibiotics are developed for bacteria in this situation. The best bactericidal drug is INH.

2. STERILIZING DRUGS: These drugs kill the bacilli in a dormant or latent state, which are responsible for relapses. The greater the sterilising capacity of a drug or a regimen, the better the capacity to cure without relapses in a short period. If the drugs used in the regimens are not very sterilising, the treatment period becomes very lengthy. The best sterilising drug is RIF, which at the same time is also a good bactericidal one; this drug is indeed the core drug of the regimen and the cornerstone of TB treatment. When resistances to RIF emerge, those strains are called rifampicin-resistant TB (RR-TB) or multidrug-resistant TB (MDR-TB) and need special management with longer and more complicated regimens (more in section 13).

3. DRUG COMBINATION TO AVOID SELECTION OF RESISTANCES. Provided that for nearly every million bacilli, there is 1 naturally resistant bacillus, the way to avoid selection of natural mutants is to combine 3-4 drugs. An effective regimen from a bacteriological point of view, especially when the bacilli burden is high (cavities and AFB+), needs at least 3 or 4 drugs.

4. DAILY AND SINGLE DOSE ADMINISTRATION. Giving all drugs in one intake daily (instead of splitting the drug into multiple intakes throughout the day) creates high peak levels of drug concentration in the blood.

This peak concentration is linked to both greater sterilising and greater bactericidal capacity, in other words, killing the bacilli better.

3.2 DRUG SUSCEPTIBLE TB TREATMENT OPTIONS FOR ADULTS

OPTION 1. TREATMENT OF DRUG-SUSCEPTIBLE TB USING A DAILY 6-MONTH REGIMEN. 2RHZE/4RH

Candidates: New patients with pulmonary TB and extrapulmonary TB (except TB meningitis, bone and joint and disseminated TB)

Composition and duration: 6 months daily (7 days per week)

- Intensive phase: 2 months daily with RHZE
- Continuation phase: 4 months daily with RH

Cases with **TB meningitis, bone and joint and disseminated TB:** 12 months daily (7 days per week)

- Intensive phase: 2 months daily with RHZE
- Continuation phase: 10 months daily with RH (larger continuation phase to avoid relapses)

Recommendations:

- Supervision and support for all TB patients to ensure completion of the full course of therapy.
- Use of fixed-dose combination (FDC) tablets

Potential problems:

- Missed doses are directly correlated to higher levels of relapse
- If a positive sputum smear is found after the intensive phase, a sputum sample should be analysed for drug resistance with rapid molecular tests.

TABLE 3.1 NUMBER OF TABLETS DAILY NEEDED TO TREAT TB IN ADULTS BY WEIGHT BANDS IN FDCs UNDER CATEGORY I REGIMEN.

Weight Range	No. of tablets for the daily treatment		
	INTENSIVE Phase: 2 months HRZE* daily	CONTINUATION Phase: 4 months HR** daily	Pyridoxine (50mg)
25-<30 kg	2	2	1
30-<35 kg	3	3	1
35 -<65 kg	4	4	1
> 65 kg	5	5	1

* Also, for Children weighing above the weight of 25kg.

*Every 4FDC tablet contains R150/H75/Z400/E275. ** Every 2FDCs tablet contains R150/H75

Source: WHO operational handbook on tuberculosis Module 4: Treatment – drug-susceptible tuberculosis treatment. Geneva: World Health Organization; 2022. License: CC BY-NC-SA 3.0 IGO.

OPTION 2. TREATMENT OF DRUG-SUSCEPTIBLE TB USING 4-MONTH REGIMENS. 2HPMZ/2HPM

Candidates: >12 years old with drug-susceptible pulmonary TB.

Before starting this treatment, **resistance** to isoniazid, rifapentine, and fluoroquinolones should be excluded. **In the absence of quick access to DST, this regimen cannot be recommended.** Subgroups excluded from the recommendation for a 4-month regimen:

- people weighing less than 40 kg
- people with certain forms of extra-pulmonary TB (such as TB meningitis, disseminated TB, osteoarticular TB, and abdominal TB)
- persons living with HIV infection with a CD4 count of less than 100 cells/mm³
- children less than 12 years of age
- pregnant, breastfeeding, and postpartum women

Composition and duration: 4-month regimen of isoniazid (300mg/day), rifapentine (1,200 mg/day), moxifloxacin (400mg/day) with pyrazinamide (25 mg/kg/day) during an intensive phase of 2 months followed by 2 months of continuation with isoniazid, rifapentine, and moxifloxacin.

OTHER IMPORTANT GOALS IN TB TREATMENT

The management of other common co-morbidities like malnutrition, HIV, DM, mental illness, and addictions are a fundamental part of the patient-centred care, highly linked to positive outcomes.

The use of adjuvant steroids should be considered in patients with:

1. Tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone (2 mg/kg/day) tapered over 6–8 weeks should be used.

2. Tuberculous pericarditis: an initial adjuvant corticosteroid therapy may be used.

Tips on the management of other clinical complex circumstances are included in Annex 1.

TB TREATMENT OUTCOME DEFINITIONS

Current treatment outcome definitions are similar for both drug-susceptible and drug-resistant tuberculosis and are listed in the box below.

Box 3.2 TB Treatment Outcome Definitions:

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

CHAPTER 4:

**PATIENTS
FOLLOW-UP**

CHAPTER 4. PATIENTS FOLLOW UP

PATIENT-CENTRED CARE

TB disease highly affects the poor and socially excluded. TB patients face many other socioeconomic barriers that may interact with treatment and adherence. The patient's needs (clinical, social, economic, spiritual), choices, and preferences should guide us in the selection of the best possible care and accompaniment that are required during the long continuum of treatment and care. A patient-centred approach with a social and flexible orientation is particularly necessary for the most vulnerable groups and outlying populations. Considering adherence, patient education, psycho-emotional support, and managing side effects promptly helps the patient to endure the multiple emotional and socio-economic problems that may appear along the whole length of the treatment. There is a need for a care package focused on the patient's circumstances, needs, and choices. These are determinants for the treatment success rate.

Box 4.1 The Four Essential Components of TB Patient-centred Care:

1. **Use of a holistic approach:** patients are defined by more than just their physical illness. Also, the social, cultural and economic reality of people, their families and communities should be considered.
2. **Use of an individualised package** considering and responding to the needs of individual persons.
3. People living with TB should be **empowered** to take an active role in their own follow-up.
4. **Decision-making** should involve people when it comes to making decisions about their own health and care.

As a minimum, patients on TB treatment should receive

Basic health education on TB disease

Counselling treatment adherence. Several treatment adherence interventions comprising enablers and incentives are

complementary and not mutually exclusive (see table below), and psychological/spiritual support.

Regarding treatment administration, several options may be offered to patients on TB treatment:

When possible, community or home-based directly observed treatment is recommended over health facility-based adherence support or unsupervised/unsupported treatment.

The use of video communication technology, when available, can be appropriately organised and operated to increase communication between healthcare providers and patients.

Patients with TB (susceptible or resistant) should be treated using mainly ambulatory care rather than models of care based principally on hospitalisation. Decentralised models of care are recommended over a centralised model.

PATIENT FOLLOW-UP

The minimal set of actions to monitor TB:

- Initial evaluation and fundamentals from multiple aspects are summarised in Box 4.2.
- Minimum of 4 follow-up sputum examinations and clinical visits at the end of the 1st, 2nd, 5th and 6th months (see tables below). In case of critically ill, not improving or persistence of important symptoms or toxicity, etc the number of visits may need to be increased (or even hospitalisation).
- If possible, visits should be monthly, needing blood tests in the intensive phase to diagnose early liver toxicity
- Sputum smear monitors the bacteriological course of the treatment and the progression into cure or failure. Only one sputum sample is required during each follow-up.
- CXR is used on the initial diagnosis (to obtain suitable information regarding lung damage and bacilli burden) and at the end of the treatment to check the potential disability after cure. CXR can be used during the treatment in case of complications (new fever, suspicion of community pneumonia, others) or as a surrogate monitoring marker.

1ST VISIT (BASELINE AT DIAGNOSIS)

Box 4.2 First Visit of the TB Patient. Basic Healthcare Worker (hcw) Actions

Once the patient is diagnosed with TB, the HCW needs to:

1. **Fill out the TB patient treatment card** accurately and on time. Record and notify the TB diagnosis (bacteriologically confirmed or clinically diagnosed) in the book of cases or Divisional TB register, including the basic contact and clinical data: type of disease (PTB or EPTB), category of entry (New cases or failure, relapse, LTFU recovered), AFB smear, GeneXpert, etc. Include data to contact the patient in the future.
2. **Quality clinical history.** Apart from the minimal program notification consider additional data on potential malnutrition, co-infections (HIV, HBV, HCV...), co-morbidities (DM, alcoholism, mental disease), circumstances altering the immune system (children, HIV infection, Diabetes Mellitus, pregnancy, use anti-TNF or other immunosuppressive medication) and socio-economic or other constraints (e.g. distance) that could jeopardise adherence.
3. **Weight and height of the patient:** calculate the body mass index (BMI), which is a risk factor for bad outcomes and malnutrition. BMI <16-18 kg/m² is a major severity criterion. Use the weight band dose to determine the number of FDC tablets needed for the intensive and continuation phase, and to determine the body mass index (BMI).
6. **Follow-up model.** Assign for a DOT modality according to the patients' possibilities and needs: by HCW, by HCW online (video DOT or VOT), by community/religious leader, or, if there is no other option, by a family member. This can also include the local public health teams of the subdivisions where patients reside, as part of their Monthly domiciliary visits /reviews.
7. **Involve the patient,** when possible, in the decisions affecting his health, including:
 - a. Train the patient and/or the family to understand the very basics of TB disease that is fundamental to achieving good treatment adherence
 - b. Explain potential side effects and the importance of quick notification and management. Alert on basic drug effects (E.g. red urine) and drug-drug interaction (E.g. interaction with contraceptive pills and some oral antidiabetics).
 - c. Program contact tracing activities among the close contacts of the patient (direct or indirect activities).
 - d. Basic health counsel: avoid alcohol use, consider giving up smoking, and careful glycaemic control while on TB treatment

- e. Explain basic infection control measures at home: need to use the mask until the first smear negative or at least the first 15 days of treatment, sleep in a different room, good natural ventilation, etc.
8. **Consider the next appointment and request the needed follow-up tests:** blood and bacteriological tests (sputum smear).
9. **Childbearing age woman**
 - a. Consider a pregnancy test on the spot
 - b. Advise the patient on contraception. Pregnancy is not a contraindication but might be relevant to avoid further problems for the mother and foetus. RIF interacts with oral contraceptives, decreasing their action. Consider non-hormonal methods of contraception.
10. **Select the type of treatment and number of pills** as per the indications in Chapter 3
11. **Offer HIV tests on the spot** to all TB patients regardless of age.
12. **Initiate contact tracing activities**

With all this information, it is highly desirable to establish a plan for management and follow-up to identify risk factors early that may lead to inconsistent adherence, leading to resistance or ending in loss to follow-up (LTFU). Patient follow-up and a good relationship between the HCW and the patient is fundamental to achieving good TB outcomes and mitigating the risk of LTFU.

2ND MONTH VISIT

The end of the second month is a critical moment, as it is the point to change into the continuation phase.

A. Negative sputum smear at the end of the 2nd month: change to the continuation phase after checking the weight and considering the need to modify the dose of FDCs.

B. Positive sputum smear at the end of the 2nd month: this should be a clear call to attention. Require a **GeneXpert test** to differentiate if the delay in sputum conversion is because of RIF resistance or other issues, such as:

- inadequate adherence
- suboptimal drug absorption related to malnourishment or other factors
- massive TB burden needing longer periods of treatment

- o potential INH resistance, needing to readjust the regimen into 6-9 HRZE or other (see chapter on resistance)

Action on non-conversion (end of 2 months)

Collect a sputum sample and perform an Xpert MTB/RIF Ultra test- or Xpert MTB/XDR to investigate Isoniazid and fluoroquinolone resistance. This rapid molecular test at the end of Month 2 is required to determine if the lack of sputum conversion is due to rifampicin-resistant TB or other issues. Continue the patient therapy while awaiting results, and evaluate adherence and other factors

- If the Xpert result at the end of Month 2 shows rifampicin-sensitive TB, then proceed with the continuation phase as planned. Ensure the patient received intensive adherence support and address any potential causes of delayed sputum conversion, such as malabsorption of high bacillary burden.
- If the Xpert result shows rifampicin-resistant TB, this constitutes **treatment failure** of first-line therapy. Immediately refer the patient to the TB control officer and obtain further DST (culture and phenotypic DST or Xpert XDR) for fluoroquinolones and other second-line drugs. The regimen will need to be switched to an appropriate MDR-TB treatment regimen without delay.

5TH OR 6TH MONTH VISIT

A. Negative sputum smear at the end of 5th or 6th month: If the patient does not present symptoms or is clearly improved and the sputum smear is negative, declare the patient's outcome as **“cured”**. Frequently, patients at the end of the 5th and 6th month do not produce sputum; consider doing an induced sputum technique, or if there is no sample available, consider it as **treatment completed**. The same may happen with extrapulmonary cases and most children: if they are clinically improving (no cough, gaining weight, improvement

in imaging test, or organ-specific symptoms), consider them as **"treatment completed"**. In case extrapulmonary TB and not clinically improving, consider bacteriological tests (e.g., GeneXpert from lymph node aspiration or faeces) to check for resistance or other tests related to the existence of other additive conditions that may justify the lack of improvement.

B. Positive sputum smear at the end of 5th or 6th month: Declare the patient's outcome as **"treatment failure"**. All treatment failures have an increased risk of resistance amplification. They could have been resistant from the very beginning. All failures need a DST (phenotypic or preferably a rapid genetic test/GeneXpert) to make the most suitable decision. If a patient is found to harbour a RR or MDR-TB strain during therapy, declare as a failure and refer to the nearest DR-TB management facility as soon as possible. Consider the possibility of delayed sputum conversion in those cases with massive lung destruction on CXR and still pan-susceptible DST results.

TELEMEDICINE

Provided the difficulties and the indirect cost imposed on patients living in isolated areas, consider, when possible, doing some of the follow-up visits using telemedicine through mobile phone applications. These can be helpful for Clinically Diagnosed patients, both PTB and EPTB, for direct patient advice or to direct link between specialised physicians and rural HCWs.

This technology can generate a direct link between specialists, primary health, and families affected by TB for the overall benefit of the NTP.

MINIMAL COMPLEMENTARY TEST TO FOLLOW UP TB TREATMENT

The medicines included in the selected regimen determine what monitoring tests are needed. Depending on the clinical circumstances, risk factors, and co-morbidities, patients will need an extra test (like those who are inpatients) , but most DS-TB patients

will require, at a minimum, the following tests and evaluations along the different months under treatment:

WHEN THE PATIENT IS REFERED TO ANOTHER TB UNIT

Continuation of treatment is fundamental. When a TB patient is referred or transferred to another facility or DOT Facility, a referral or transfer form should be filled and sent with the patient. Whether a patient is transferred or referred or travels temporarily, the patient should be supplied with treatment for the duration of travel. The DOT facility that receives the transferred patient should record them as a “transfer in” and is responsible to report the final patient treatment outcome.

TABLE 4.2 SET OF MINIMAL VISITS & ACTIONS FOR SUSCEPTIBLE TB FOLLOW-UP

Month of follow up	Follow up visit	KEY ACTIONS NEEDED
0	Visit 1 Diagnosis and treatment initiation	1. See Box- 4.2 above, with all special actions needed on the first visit
1	Visit 2 First follow-up visit	1. Clinical evaluation after treatment initiation. 2. Weigh the patient and adjust medication if necessary. 3. Consider adherence, side effects, and involvement of family in contact tracing activities 4. Advise on sputum collection at the end of the 2 nd month visit

2	<p>Visit 3 End of intensive phase</p>	<p>1. Clinical evaluation after treatment initiation.</p> <p>2. Weigh the patient and adjust medication if necessary</p> <p>3. Consider adherence, side effects, and involvement of family in contact tracing activities if not done</p> <p>4. Actions according to the sputum smear result If NEGATIVE: Continue treatment and start continuation phase If POSITIVE: Collect sputum and send for Xpert MTB/RIF Ultra test- or Xpert MTB/XDR to investigate Isoniazid and fluoroquinolone resistance. Continue with the continuation phase or consider RHZE if INH resistance or bad adherence is suspected</p> <p>5. Advise on sputum collection at the end of the 5th month visit</p>
5	<p>Visit 4 During treatment</p>	<p>1. Clinical evaluation after treatment initiation.</p> <p>2. Weigh the patient and adjust medication if necessary</p> <p>3. Consider adherence, side effects, and involvement of family in contact tracing activities if not done</p> <p>4. Actions according to the sputum smear result If NEGATIVE and no symptoms: Continue treatment, provide date for the 6th month visit</p>

		<p>If POSITIVE: Collect sputum and send for Xpert MTB/RIF Ultra test or Xpert MTB/XDR test to rule out INH and fluoroquinolone resistance. Consider the clinical situation and if suitable, declare as Treatment Failure.</p> <p>a. If Xpert MTB/RIF test shows Rifampicin Sensitive, assess adherence support, restart treatment under strict DOT and send sample for DST or LPA or Xpert XDR for INH resistance</p> <p>b. If Xpert MTB/RIF test shows Rifampicin Resistant, refer to the nearest DR-TB facility. Send sputum for culture and DST, or send sample for LPA or Xpert XDR for INH and FQ resistance</p>
6	Visit 5 End of treatment	<ol style="list-style-type: none"> 1. If there was no sample in the 5th months and the patient is asymptomatic consider as treatment completed 2. If the patient presented a NEGATIVE smear in the 5th month and the patient is asymptomatic consider as cured 3. Consider family contact tracing activities if not done

MANAGEMENT OF PATIENTS WHO INTERRUPTED TREATMENT

If a TB patient misses a dose for more than 24 hours or a treatment supporter or self-administered patient fails to collect drugs, retrieval actions should be taken within 24-48 hours. The local DOT Centre should identify early loss to follow-up (LTFU) patients and contact

them immediately. Priority is given to bacteriologically confirmed PTB and critically ill patients. 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 LTFU after he or she misses treatment for more than 1 month. After 2 months, there is a complete regrowth of bacterial populations, and the treatment needs to be started from the beginning; prior to re-start, a DST is necessary to check for potential resistance acquisition.

TABLE 4.3 MINIMAL SET OF CLINICAL ACTIONS AND TEST ACCORDING TO THE MONTHS OF TREATMENT

Actions and Test	Months on treatment						
	0	1	2	3	4	5	6
Physical exam	X	X	X	X	X	X	X
Patient education, active search of side effects and adherence counsel	X	X	X	X	X	X	X
Contact tracing and active case finding in families affected by TB	X		X			X	X
Weight and BMI	X	X	X	X	X	X	X
Pregnancy test	X						
HIV test	X						
Xpert MTB/RIF	X						
Sputum smear	X		X		X	X	X
CXR	X						X
Hb	X		X			X	
Liver function test	X		X			X	
BSL/HbA1c	X		X			X	
ECG	X						

FIGURE 2.6 APPROACH TO DS-TB TREATMENT INTERRUPTIONS IN CHILDREN AND ADOLESCENTS ON DS TB TREATMENT.

Continuation phase (6-month 2HRZE/4HR regimen)		
Continuation phase (6-month regimen) and bacteriologically negative at initiation	Completed ≥80% of doses within 16 weeks	Further treatment not necessary
Continuation phase (6-month regimen) and bacteriologically positive at initiation	Completed ≥80% of doses within 16 weeks	Complete remaining doses of treatment If consecutive lapse is >2 months, use clinical judgement
Continuation phase (6-month regimen)	Completed <80% of doses and cumulative interruption <2 months	Complete remaining doses of treatment
Continuation phase (6-month regimen)	Completed <80% of doses and cumulative interruption ≥2 months	Restart treatment from beginning of intensive phase, particularly if interruption was consecutive

In all circumstances, if TB symptoms recur during the interruption, reassess the child or adolescent with a rapid molecular test and culture/DST to assess for drug resistance.

FIGURE 2.6 TREATMENT INTERRUPTION. SOURCE: WHO TB KNOWLEDGE SHARING PLATFORM. [HTTPS://TBKSP.WHO.INT/EN/NODE/2161](https://tbksp.who.int/en/node/2161)

Treatment phase of interruption	Details of interruption	Management
Intensive phase		
Intensive phase: applies to 4- and 6-month regimens	Interruption <14 days	Continue treatment and complete all intensive phase doses
	Interruption ≥ 14 days	Restart intensive phase
Continuation phase (4-month 2HRZ(E)/2HR regimen)		
Continuation phase (4-month regimen)	Completed ≥80% of doses within 8 weeks	Further treatment not necessary
Continuation phase (4-month regimen)	Completed <80% of doses and cumulative interruption <1 month	Complete remaining doses of treatment
Continuation phase (4-month regimen)	Completed <80% of doses and cumulative interruption >1 month	Restart treatment from beginning of intensive phase

RECORDING AND REPORTING SYSTEM

These guidelines do not suppose important changes in the internal structure of the Fiji NTP or the recording and reporting systems. Monitoring and evaluation practices, including process and impact program indicators, remain similar to ones proposed in previous guidelines and internal programmatic standard operational procedures.

However, it is recommended that the NTP conduct a rigorous assessment and analysis of the current TB reporting and surveillance system to identify bottlenecks and weaknesses towards an e-based system in the future to improve patient management and public health responses.

SIDE EFFECTS

Side effects are frequent but usually do not represent life-threatening conditions and should be managed immediately to relieve suffering, minimise the risk of treatment interruptions, and prevent morbidity and mortality.

Patients with advanced TB disease, malnutrition, multiple comorbidities, or the elderly are much more vulnerable to side effects and drug-drug interactions.

SIDE EFFECTS SEVERITY

Side effects (e.g., vomiting) can be presented in different levels of severity (from mild nausea after drug intake to constant vomiting and dehydration). The actions needed to control side effects will depend on the grade of severity:

- GRADE 1, Mild: do not interfere significantly with the patient's normal functioning.
- GRADE 2, Moderate: produces some impairment in the patient's functioning but is not hazardous to the patient's health.
- GRADE 3, Severe: significant impairment or incapacitation of functioning.

- GRADE 4, Life-threatening: extreme impairment of functioning, requiring hospitalisation. If left untreated could result in the death or important patient disability.

REFERRING TO THE PATIENT TO THE HOSPITAL:

TB physicians need to understand the management of the side effects of TB drugs. However, it is necessary to refer patients to the hospital when the side effects cannot be controlled, when great disability may appear or in case of an impending life-threatening situation.

Usually, the main risk of death caused by TB drug toxicity corresponds to the fact that the patient stops the medication and, either deteriorates and dies from TB or increases the pattern of resistance and ends up dying after transmitting DR-TB to others. The management of the most frequent side effects (that tend to be mild, like nausea and vomiting) is fundamental at clinical and programmatic levels. Never reduce the dose to control side effects as this affects the regimen's effectiveness. In case of uncontrolled side effects shift the culprit drug to a different one with similar characteristics (sterilizing/bactericidal).

HEPATOTOXICITY IN TB TREATMENT

Definition and Risk Factors: The most frequent severe or life-threatening side effect on the management of DS-TB. Common risk factors: viral hepatitis, alcoholism, non-alcoholic steatohepatitis (NASH), pregnancy, old age, immunosuppression (e.g., malnutrition, children, PLHIV), and use of hepatotoxic drugs like efavirenz.

TRANSAMINITIS

Clinical presentation: Asymptomatic; resolves spontaneously or with brief treatment interruption.

Complementary test: Elevated ALT/AST is $\geq 5x$ the upper limit of normal in the absence of symptoms. Affects ~20% of patients

HEPATITIS

Clinical presentation: jaundice, fever, abdominal pain, nausea, vomiting. Usual onset: 4-8 weeks into treatment.

Complementary test: ALT/AST is $\geq 3x$ the upper limit of normal in the presence of symptoms.

Incidence ~1% but 6-12% Mortality rate if untreated.

- **Cytolytic Hepatitis:** Destruction of hepatocytes; elevated AST/ALT, bilirubin. Linked to pyrazinamide and isoniazid.
- **Cholestatic Hepatitis:** Obstructive pattern with bile flow reduction; hepatomegaly, elevated bilirubin, GGT, ALP. Associated with rifampin and liver TB.

Management: Stop suspected drugs; manage risk factors and provide supportive care. Consider drug re-challenge after liver normalization: Gradual reintroduction starting with less hepatotoxic drugs (e.g., ethambutol → rifampin → isoniazid → pyrazinamide). Use liver-friendly regimens if hepatotoxicity persists; often stop pyrazinamide and extend continuation therapy by 2-3 months.

MAJOR TOXIC HYPERSENSITIVITY REACTIONS

Rare but severe immune reactions can outweigh the dangers of TB itself, with high mortality. Common risk factors: weakened clinical condition, genetic predisposition, concurrent infections, and polypharmacy.

STEVENS-JOHNSON SYNDROME (SJS):

Triggers: genetic predisposition, infections (e.g., HIV), and drugs (commonly rifampin).

Symptoms: flu-like onset, red/purple rash, blisters (skin loss), and extensive skin and mucosal shedding.

Management: Stop suspected drugs immediately to reduce the risk of relapse and mortality. Supportive care: corticosteroids, antihistamines, infection and dehydration prevention. Intensive care may be needed for severe skin loss. Do not re-challenge the culprit drug.

DRESS SYNDROME (DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS):

Triggers: genetic predisposition, infections (e.g., HIV), and drugs (commonly rifampin).

Onset: delayed hypersensitivity reaction (≥ 1 month after starting treatment).

Symptoms: maculopapular rash (no blisters/mucosal damage), face swollen, fever, eosinophilia (or other blood alterations), lymphadenopathy, and organ involvement (commonly liver: increase in ALT/AST).

Management: Stop suspected drug; do not introduce them to avoid relapse. Supportive care: corticosteroids, antihistamines. Use liver-friendly regimens (e.g., levofloxacin, ethambutol, cycloserine).

TABLE 4.5 FREQUENT SIDE EFFECTS OF ANTI-TB DRUGS

Drug Category	Side Effect	Frequency	Description /Clinical Features	Management / Remarks
Isoniazid (INH)	Peripheral neuropathy	Common (especially in malnourished, HIV, diabetic, pregnant, and alcoholic patients)	Burning feet, discomfort, pain in extremities; reversible	Give pyridoxine (Vit B6 25–50 mg daily) routinely when using INH or cycloserine
Rifampicin (RIF)	Reddish discoloration of body fluids	Very common	Red-orange urine, tears, and contact lenses	Reassure patient; harmless and reversible
Pyrazinamide (Z)	Asymptomatic hyperuricemia	Common	Raised uric acid without joint symptoms	No treatment needed if no inflammation

Drug Category	Side Effect	Frequency	Description /Clinical Features	Management / Remarks
	Arthralgia	Very common	Joint discomfort or stiffness	Provide analgesics; encourage mild exercise
	Gout (acute arthritis)	Uncommon / Serious	Painful, red, swollen joints (feet/knees)	Stop Pyrazinamide; treat gout symptomatically
Ethambutol (E)	Optic neuritis (optic neuropathy)	Uncommon / Serious	Blurred vision, dyschromia (colour blindness), reduced visual acuity; dose-related (> 25 mg/kg)	Stop Ethambutol immediately if suspected; usually reversible if detected early; safe at 15–20 mg/kg/day
All TB Drugs (General)	Nausea & Vomiting	Very common	Can occur with any TB drug; worsened on a full stomach	FLDs: give on an empty stomach for better absorption. If persistent: give with light meals. Second-line drugs (SLDs): take with meals. Management: <ul style="list-style-type: none"> • Metoclopramide 30–45 min before drug

Drug Category	Side Effect	Frequency	Description /Clinical Features	Management / Remarks
				intake. Severe cases: ondansetron or short corticosteroid course. For oral intolerance: temporarily hold or split doses (2–3 intakes/day) until tolerance returns. For gastritis: use omeprazole or ranitidine
All TB Drugs (General)	Skin Rash	Common	Often, mild allergic reactions may appear early in treatment	Use antihistamines ± corticosteroids to maintain tolerance. If rash involves fever, blisters, mucosa, or organ dysfunction → suspect toxicity and stop offending drug(s); manage per severity

DRUG-DRUG INTERACTIONS

A full drug history should be taken to check for drug-drug interactions. RIF and rifapentine (RPT) may induce an increase in the clearance of many different drugs (e.g., oral contraceptives), reducing its efficacy. All childbearing-age women should be advised on the use of barrier methods to avoid pregnancy while on TB treatment. It may also reduce the levels of many oral anti-diabetic medications (except metformin) and some oral anticoagulants. Another frequent interaction is between RIF and antiretroviral drugs used for the treatment of HIV infection, which can result in sub-therapeutic antiretroviral drug concentrations. In addition, TB drugs and antiretroviral drugs have additive (pharmacodynamic) interactions as reflected in overlapping adverse effect profiles.

The groups and drugs highly affected are:

- Integrase Strand Transfer Inhibitors (INSTIs)
 - **Dolutegravir (DTG)**: if concomitantly used with RIF, DTG dose should be increased from once to twice daily dose with RIF. The morning DTG dose can be with rifampicin, but the evening DTG dose must be taken alone to maintain adequate plasma levels
 - **Raltegravir (RAL)**: if concomitantly used with RIF, RAL should be used at double dose. Use 800 mg twice daily instead of 400 mg twice daily.
- Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs):
 - **Efavirenz (EFV)**, RIF slightly reduces its levels, but it is not considered critical and doses of 600mg of EFV od are considered correct.
 - **Nevirapine (NVP)**: should not be together as RIF r dramatically reduces its concentration.
- Protease Inhibitors (PIs): RIF and PIs initially should not be together as RIF reduces its concentration dramatically.

In case of doubt on drug-drug interactions, this can be easily checked in different free websites or smart phone applications for example

- https://www.drugs.com/drug_interactions.html
- <https://www.hiv-druginteractions.org/>

TB MANAGEMENT UNDER UNFAVORABLE PROGRAMMATIC CONDITIONS

Always balance the good of the patient and the community against the cost of inaction. Seek support as soon as possible in case of doubt. Revert to regular management as per these guidelines as soon as the programmatic difficulties are solved.

UNDER THE RISK OF XPERT CARTRIDGE STOCK OUT

- Alert the NTP immediately and communicate with other TB facilities for mutual support
- Consider diagnosis based on:
 1. History of previous TB disease or contact with TB patients
 2. Clinical symptoms: fever, cough, weight loss, night sweats, and other local and systemic symptoms. Follow the protocol for TB diagnosis in children
 3. Chest X-ray or other imaging test
 4. Consider other alternative diagnostic tools (if available):
 - Bacteriological: sputum smear, urine TB LF-LAMs, biopsy (anatomic pathology)
 - Not diagnostic but orientate tools: ADA determination, Mantoux test, or IGRAs
- In case of the presence of DR-TB risk factors like failure to previous TB treatment, being a DR-TB contact, former prisoner, intermittent treatment, chronic disease (more than 6-12 months on treatment), non-response to FLDs treatment despite good adherence, or others:
 1. Send a sample for culture and ask for phenotypic DST at the national reference laboratory
 2. In consultation with other NTP colleagues or the DR-TB committee, consider on a case-by-case basis the need to start a DR-TB regimen likely to be curative according to the previous history of drugs (whenever possible, a standard short treatment regimen)
- Perform similarly in case of other diagnostic test stock out, trying to maximize diagnosis even in unfavorable conditions.



UNDER THE RISK OF MEDICATION STOCK OUT:

- Alert the NTP immediately and communicate with other TB facilities for mutual support
- Perform an in-depth inventory of available medications in the facility
- Consume first those with a nearest expiration date
- Assure that each patient has all pills necessary for his treatment. For that aim create **nominal medication boxes per patient** (each patient should have a box with all the medication needed for his whole treatment)

CHAPTER 5:

**DRUG RESISTANT
TUBERCULOSIS
TREATMENT**

CHAPTER 5. DRUG-RESISTANT TUBERCULOSIS TREATMENT

Antimicrobial resistance (AMR) is an ongoing global health crisis that is enhanced by the disruption of health services and complex emergencies. DR-TB is among the top 4 priorities and the highest in terms of deaths from a single resistant pathogen. In Fiji, the number of cases is still low, but without control and action, the numbers will increase, as in many other countries.

MANAGEMENT OF ISONIAZID MONORESISTANCE TB (HR-TB)

INH-R TB is defined as TB only resistance to INH and therefore can benefit from the bactericidal and sterilising effect of RIF. After decades of use of INH, resistance is quite frequent in most countries, with an estimated prevalence of 13% of new TB cases globally. Resistance to INH mainly arises from a mutation in the Kat G gene (high-level resistance) and the inh A gene (low-level resistance and conferring cross-resistance to Ethionamide/Protionamide). Other less frequent mutations may exist in the genes oxyR and ahpC. When there is resistance to INH the regimen 2RHZE/4RH is considered substandard and may lead to RIF resistance.

If Hr-TB is confirmed before TB treatment starts (may only happen if the resistance diagnosis is done by Xpert XDR:

- 6(H)REZ-Lfx started immediately
- Consider test for FQ resistance

If Hr-TB is discovered after starting 2HREZ/4HR regimen:

- Do an Xpert test to RIF resistance
- Consider test for FQ resistance
- Once rifampicin resistance is excluded: 6(H)REZ-Lfx
- Duration: driven by the need to give levofloxacin for 6 months. Implies that first-line medicines are taken for longer than 6 months.

If the Hr-TB result arrives after five months of treatment with 2HREZ/4HR and the patient is clinically and bacteriology improving:

- The clinician to decide whether to start 6(H)REZ-Lfx at that point or complete the 2HREZ/4HR and monitor for relapse thereafter.
- If there is presumption but no access to RIF and FQ resistance 9RHZE with active follow-up after treatment might be considered.

MANAGEMENT of MDR/RR-TB

Multidrug-resistant TB is defined as presenting resistance to the most sterilising drug (RIF) and the most bactericidal drug (INH). Most mutations (>95%) conferring resistance to RIF are in the *rpoB* gene. Therefore, second-line drugs (SLDs) are necessary to cure the patient and stop community transmission. Drugs to be used for treatment of MDR/RR-TB are categorised into Groups A, B and C based on effectiveness and safety. RR-TB is considered those strains with proven RIF resistance without confirmation of INH resistance. Based on data at the programmatic level all RR present a high likelihood of INH resistance and are considered as such.

After diagnosis, precise baseline tests and actions, similar to DS-TB are necessary before enrolment and during the follow-up during the months under treatment. At the time of this update WHO had recently updated the DR-TB management based on a recent publication giving priority to 6 and 9 months which are explained below.

The selection of regimens suggested:

1. Use first BPaLM or BEAT-TB or End TB regimens (Options 1, 2, & 3)
2. Then use STR Lzd variant (Option 4)
3. Individual long treatment regimen (Option 5)

OPTION 1. BPaL/BPaLM

Candidates:

- Patients aged 14 years and older, and people living with HIV with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular, and disseminated (miliary) TB

Composition and duration:

- 6-9 months daily (7 days per week) altogether (no intensive or continuation phase)
- Bedaquiline, pretomanid, linezolid (600 mg), plus or minus moxifloxacin (BPaLM)

Considerations

- Fluoroquinolones resistance must be ruled out in people with MDR/RR-TB, but DST should not delay the initiation of the BPaLM regimen. In cases with fluoroquinolone resistance (pre-XDR-TB) BPaL without moxifloxacin would be initiated or continued.

- Contraindication for the regimen
 - Previous exposure to any of the drugs in the regimen (or demand that can have crossed resistance with pretomanid) for more than a 1-month.
 - BPaLM and BPaL are not recommended during pregnancy and breastfeeding due to limited evidence on the safety of pretomanid.

Tips in management

- Duration can be extended to 9 months if culture conversion or clinical response (based on the clinical judgement of the treating physician) does not happen at months 4th or 6th.
- Linezolid can be reduced to 300 mg or can be discontinued (and restarted when possible) if there is significant toxicity (depending on the severity of specific adverse events or serious adverse events) associated with linezolid, including optic neuritis, peripheral neuropathy, or myelosuppression. Dose modification of linezolid should be avoided, if possible, in the first 9 weeks of therapy.
- Treatment interruption of up to 1 month can be added to the overall treatment duration if there is a need to make up the missed doses.
- Temporary cessation of the full regimen is allowed for suspected drug-related toxicity. Reintroduction of the full regimen could be considered after cessation of no more than 14 days of consecutive treatment interruption or up to a cumulative 4 weeks of non-consecutive treatment interruption.
- Missed doses need to be made up and added to the treatment duration. Toxicities from Bdq, Mfx, and Pa are considered attainable but the management of Lzd toxicity can be one of the big challenges for BPaLM expansion and mitigation strategies should be considered.

Table 5.1 Dosing of component drugs for adults and adolescents (aged ≥14 years) for BPaLM

Drug	Dose
Bedaquiline (100 mg tablet)	200 mg daily for 8 weeks, then 100 mg daily
Pretomanid (200 mg tablet)	200 mg once daily
Linezolid (600 mg tablet)	600 mg once daily

Moxifloxacin (400 mg tablet)	400 mg once daily
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BOX 5.1 MITIGATION STRATEGIES TO COPE WITH LINEZOLID TOXICITY UNDER BPALM REGIMEN

PERIPHERAL NEUROPATHY GRADE 2

- If after the 9th week, reduce the dose of linezolid to 300 mg per day with a possible drug holiday for 1–2 weeks before dose reduction.

PERIPHERAL NEUROPATHY GRADE 3 OR 4,

- In most cases, permanent suspension of linezolid will be needed.
- in some cases, after a 1–2-week drug holiday and reversion to Grade 2, the linezolid can be restarted and tolerated, provided it does not revert to a Grade 3 or 4 (caution is warranted with this approach because patients can be left with a severe, painful and disabling permanent peripheral neuropathy); and

OPTIC NEURITIS DIAGNOSED AT ANY GRADE:

- permanent discontinuation of linezolid

MYELOSUPPRESSION (EVEN OF GRADE 3 OR 4)

- Often reversible with a short 1-to-2-week drug holiday followed by reducing the dose of linezolid to 300 mg per day;
- Severe anaemia may need to be treated with transfusions or erythropoietin.

Eventually, stop Lzd on the last 8 weeks of the regimen if necessary

OPTION 2. BEAT-TB trial regimens: 6 B-D-L-Lfx-C

Candidates: all patients with MDR/RR-TB who have not had previous exposure to bedaquiline, delamanid and linezolid (defined as >1-month exposure).

Composition and duration: 6-month B-D-L-Lfx-C regimen, composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine

The regimen may be used without either levofloxacin or clofazimine depending on fluoroquinolone DST results:

- **6BDLLfxC** can be initiated without delay in case of unknown FQ-resistance at time of diagnosis of RR-TB (and may be continued

with both levofloxacin and clofazimine if FQ-DST results cannot be obtained);

- **6BDLLfx** is continued for FQ-sensitive TB;
- **6BDLC** for FQ-resistant TB.

The available evidence included children, adolescents, pregnant and breastfeeding women, flagging the possible use of the regimen in these population groups.

OPTION 3. EndTB trial regimens: 9B-L-M-Z, 9B-L-Lfx-C-Z and 9B-D-L-Lfx-Z

Candidates: patients with MDR/RR-TB who have not had previous exposure to bedaquiline, delamanid and linezolid (defined as >1-month exposure) and in whom resistance to fluoroquinolones has been excluded

Composition and duration: 9-month, all-oral regimens (BLMZ, BLLfxCZ and BDLLfxZ).

Amongst these regimens there is a priority on the regimens preferred based in evidence:

- 9BLMZ preferred option
- 9BLLfxCZ next preferred option
- 9BDLLfxZ final option if the others cannot be used.

Consideration: Access to rapid DST for ruling out fluoroquinolone resistance is required before starting a patient on one of these regimens.

OPTION 4. Short treatment regimen, Lzd variant 4–6 Bdq (6m)-Lfx/Mfx-Cfz-Z-E-Hh-Lzd(2m) / 5 Lfx/Mfx-Cfz-Z-E

Candidates: where the previous options are not available or implemented or for patients who are not eligible. without previous exposure to second-line treatment (including bedaquiline), without fluoroquinolone resistance and with no extensive pulmonary TB disease or severe forms of extrapulmonary TB.

Composition and duration: 9-month, all-oral regimens

- Initial phase: **4–6 Bdq (6 months)-Lfx or Mfx-Cfz-Z-E-Hh-Lzd (initial 2m)**
- Continuation phase: **5 Lfx-Cfz-Z-E**
- **Doses: according per body weight as in Annex 3**

Box 5.2. Notes on the STR use:

- Access to rapid DST for ruling out fluoroquinolone resistance is required before starting a patient on one of these regimens.
- Patients with extensive forms of DR-TB (e.g., XDR-TB4) or those who are not eligible for or have failed shorter treatment regimens will benefit from individualised longer (≥ 18 months) regimens designed using the priority grouping of medicines recommended.
- Linezolid is only given for the first 2 months of treatment. Clinical and haematological monitoring are crucial to detect early linezolid-associated adverse events, particularly haematological events (sudden or significant drop in haemoglobin, neutrophils or platelets).
- After the initial 2 months, the remaining six drugs are given for another 2 months (with the possibility of extending by an additional 2 months if the patient's sputum remains bacteriologically positive at the end of the fourth month of treatment).
- High-dose isoniazid is dropped after 4 or 6 months, depending on the decision to extend treatment based on smear status at month 4 of treatment.
- This is followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide.
- Bedaquiline is usually given for 6 months but could be extended to 9 months, particularly if the initial phase is extended from 4 to 6 months due to a positive sputum smear result at month 4.
- All treatment should be delivered under WHO-recommended standards, including patient-centred care and support, informed consent where necessary, principles of good clinical practice, active drug safety monitoring and management, and regular monitoring of patients and drug resistance to assess regimen effectiveness.

OPTION 5. Longer individual regimens

Candidates: individuals with MDR/RR-TB plus further resistance or intolerance to quinolones, bedaquiline, linezolid (XDR-TB), delamanid or pretomanid that make them not candidates for the previous regimens

Composition and duration: 18-24 months using at least 4 drugs of the remaining effective medicines from Groups A, B and C, according to their drug susceptibility profile and other parameters.

TABLE 5.2 GROUPING OF MEDICINES RECOMMENDED FOR USE IN LONGER MDR/RR-TB REGIMENS.

Groups and steps	Medicines	
Group A: Include all three medicines	Levofloxacin <i>OR</i> Moxifloxacin Bedaquiline Linezolid	Lfx, Mfx Bdq Lzd
Group B: Add one or both medicines	Clofazimine Cycloserine <i>OR</i> Terizidone	Cfz Cs, Trd
Group C: Add to complete the regimen, and when medicines from Groups A and B cannot be used	Ethambutol Delamanid Pyrazinamide Imipenem-Cilastatin <i>OR</i> Meropenem Amikacin (<i>OR</i> Streptomycin) Ethionamide <i>OR</i> Prothionamide <i>P</i> -aminosalicylic acid	E Dlm Z Imp- Cln, Mpm Am, (S) Eto, Pto PAS

Find dosage for second-line anti-TB drugs (adults and children) in **Annex 2.**

BOX 5.3 FACTORS TO CONSIDER WHEN CHOOSING INDIVIDUAL MEDICINES FOR LONGER DR-TB REGIMENS

- Results of DST, preferably performed at a laboratory participating in an external quality assurance program.
- Clinical condition of the patient and form of TB (e.g., extrapulmonary TB and its severity, particularly CNS TB).
- History of previous use of first-line or second-line medicines used to treat TB in that patient (if previously treated).
- Prevalence of drug resistance in the region detected through routine or periodic surveillance in the country.
- Known contraindications such as allergy, intolerance to a drug, pregnancy or breastfeeding, critical drug-drug interaction, and presence of comorbidities.
- If the patient is a close or household contact of a bacteriologically confirmed TB case, use the drug-resistance profile of the index case to build up the regimen.
- Operational considerations such as availability of the medicines, ability to monitor for adverse reactions, and availability of necessary tools for follow-up and monitoring.
- Clavulanic acid should only be used in combination with the carbapenems to protect them from the effect of mycobacteria beta-lactamases
- In DR-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 treatment. A treatment duration of 15–17 months after culture conversion is suggested for most patients.


BOX 5.4 SUMMARY TIPS ON SIDE EFFECTS AND DRUG-DRUG INTERACTION PROFILES IN SLDS

	Drug-drug interaction profile	Side effects Profile	Comments/management
Group A:			
Levofloxacin	Low	Low. increase in QTc. Do not	

Moxifloxacin	Low	use it in Marfan and Ehlers-Danlos disease due to risk of tendon and aorta damage.	Stop fluoroquinolones in case of QTc >500 milliseconds
Bedaquiline	Medium	Low. Hepatotoxicity, increase in QTc.	
Linezolid	High,	High. Mitochondrial toxicity able to evolve into pancytopenia, peripheral neuritis, optic neuritis and lactic acidosis	Beware concomitant use with other IMAOs and risk of Serotonergic syndrome. Higher risk of lactic acidosis in combination with Metformin. Lzd mitigation strategies are summarised at Box 7.2
Group B:			
Clofazimine	Low	Medium. Skin dryness and coloration	
Cycloserine	Low	High. Increased risk and worsening of baseline neurologic and psychiatric conditions including suicidal tendencies.	Consider using 50mg of Vitamin B6 in for every 250 mg of Cs. Stop the medication in case of rupture with reality, suffering or suicidal ideation. Consider medication for depression, anxiety or psychotic disease
Group C:			
Delamanid	Low	Low	

Pyrazinamide	Low	Medium. Hepatotoxicity and arthralgia	Management summarised in section 4.3
Imipenem-cilastatin	Low	Medium. Bad tolerance associated with the need to be intravenous several times per day	Consider using a portacath or long-lasting peripheral catheter (PICC). Clavulanic acid should be given orally 30-60 minutes previous to the instillation of carbapenems to avoid the beta-lactamase activity of Mtb
Meropenem	Low		
Amikacin	Low	High. Associated with nephrotoxicity, ototoxicity and teratogenicity	It can be used intramuscular or intravenous
Ethionamide	Low	High. Bad gastrointestinal tolerance. Linked to hypothyroidism. Potential teratogenic	Bad gastrointestinal tolerance associated with treatment interruptions.
P-aminosalicylic acid	Low	High. Bad gastrointestinal tolerance. Linked to hypothyroidism	Bad gastrointestinal tolerance associated with treatment interruptions.
Others			
Pretomanid	Low	Low	Not yet tested in children and pregnancy

Surgery in the treatment of DR-TB



Partial lung resection for patients with MDR/RR-TB is only to be considered when good surgical facilities, staffed by trained and experienced surgeons, are available. In programs with suboptimal surgical facilities and with no trained thoracic surgeons, resection surgery may increase morbidity or mortality.

Consider only in patients who remain sputum smear positive, who have resistance to many drugs, and who have localised pulmonary disease.

CHAPTER 6:

**TB IN CHILDREN
AND ADOLESCENTS**

CHAPTER 6. TB IN CHILDREN AND ADOLESCENTS

6.1 TB DIAGNOSIS IN CHILDREN

Under notification of tuberculosis in children is an important problem in Fiji, especially in children under 5 years of age. See in the box below, the difference between TB in adults and children. The low detection rate in children is due to several factors:

1. Young children have paucibacillary TB and do not excrete enough bacilli to be detectable by available bacteriological tests. Bacteriological confirmation of TB in children is achieved in less than 30-40% even in ideal circumstances
2. The lack of sensitive point-of-care diagnostic tests
3. Difficulties in collecting suitable respiratory samples
4. Misdiagnosis due to the overlap of nonspecific symptoms of TB with other common childhood diseases
5. Paediatric TB services are often highly centralised at secondary or tertiary levels of the health system

Contact and clinical history, symptoms and imaging tests have a massive role in child TB diagnosis. When not diagnosed and consequently not treated, almost 100% of the children die

BOX 6.1 BASIC FACTS ON PAEDIATRIC TB:

- Children account for 13% of the estimated total tuberculosis (TB) mortality globally.
- Access to diagnosis is the biggest gap in childhood TB.
- Due to the immaturity of the immune system, the disease presentation is different than in adults; fewer cavities and more frequent extrapulmonary disease. The smaller the children, the higher the risk of atypical presentation with disseminated and severe disease leading to mortality.
- In field conditions, less than 50% of children with TB can achieve a bacteriological confirmation with smear and culture.
- TB affects families, and household transmission is common.
- Children with TB usually present with the drug-susceptibility pattern of the index case.
- TB presumption and diagnosis in children are not complex.

- Infants and young children, especially those aged under 2 years, are at greatest risk of developing severe disease (miliary TB, meningitis, disseminated TB) weeks or months after exposure.
- First-line and most second-line TB medicines are usually well tolerated by children and dispersible formulations exist.
- Most children dying due to TB are not enrolled in treatment.
- If TB is diagnosed promptly and treated correctly, child survival rates are excellent.
- If TB disease is ruled out, TB preventive treatment (TPT) averts disease development, even in children exposed to drug-resistant TB (DR-TB).

DIAGNOSING TB IN CHILDREN AND ADOLESCENTS RELIES ON A COMBINATION OF

1. Careful history, including any TB contact (especially in the past 12 months), previous TB treatment, and 2. signs and symptoms consistent with TB
3. Clinical examination, including growth assessment
4. Chest x-ray, preferably anteroposterior and lateral in children aged under 5 years and posteroanterior in older children and adolescents)
5. HIV testing if status unknown
6. Bacteriological testing
7. TB infection testing (TST or IGRA)

INVESTIGATIONS RELEVANT TO PRESUMED EPTB IN CHILDREN

- In cases of TB presumption and critical clinical situations, treatment should not be delayed due to diagnostic or confirmation workup.
- The resistance pattern of the index case should lead the treatment regimen.
- If TB disease is ruled out in the context of contact investigation, consider possibilities for TPT. Most children exposed to TB benefit from TPT.

Acknowledging the difficulties and low rates of diagnosis in children <10 y/0, WHO has recently simplified the diagnostic algorithm for pulmonary TB based on clinical history and symptoms with or without the assistance of CXR with a scale, where children with more than 10

points are likely to benefit from a TB regimen based on the susceptibility of the index case (the contact). **See the WHO algorithm A and B at Figures 6.1 and 6.2.**

BOX 6.2 EXPANDING CHILD TUBERCULOSIS DIAGNOSIS: A PROPOSAL IN FIVE STEPS

Step 1: History of contact

- Household contact with TB: often found as the source of child infection.
- Other sources of child infection: close school, neighbourhood or other contacts with lung disease or clinically severe unknown condition.

Step 2: Medical history

- Systemic signs and symptoms: early stages of TB disease may be almost asymptomatic. In advanced and severe stages, children may present with fever (> 2 weeks), swollen lymph nodes, lethargy, failure to thrive, weight loss, night sweats, cough (more than 2 weeks), tachycardia, and tachypnoea.
- Localised signs and symptoms: when TB is spread through blood (frequent in young children), multiple organs may be affected (extrapulmonary TB), including the brain (meningitis, headache, confusion, seizure), bones and joints (anaemia, lytic fracture, inflammation), liver (hepatomegaly, cholestasis), spleen (splenomegaly), and gastrointestinal system (diarrhoea, abdominal pain).
- Respiratory signs and symptoms: persistent cough, haemoptysis, asymmetrical wheeze not responsive to bronchodilators, and atypical pneumonia.
- Duration of symptoms: months in advanced stages of TB disease, but days or weeks in the context of active case finding and contact tracing.

Step 3: Clinical assessment

- Full physical examination: assess for highly specific (gibbus, non-painful enlarged cervical lymphadenopathy) or nonspecific signs and symptoms.
- Malnutrition assessment: look for alterations associated with TB disease.

- Growth curves: length and weight progress stop or are significantly below (bottom third) the percentiles for age and sex. A mid-upper arm circumference of less than 115 mm suggests severe acute malnutrition (over 135 mm is normal).

Step 4: Non-bacteriological test

The following are nonspecific but highly valuable indicators for TB presumption:

· Image tests:

– Chest X-ray: in <10 years old, the presence of enlarged lymph nodes, miliary pattern, effusion, cavity/cavities, and/or opacities is highly suggestive of TB. If adapted to children, artificial intelligence can be helpful.

– Computed tomography (CT) and magnetic resonance imaging (MRI): these are more sensitive but less available. They are used for chest and extrapulmonary TB (e.g., meningitis, tuberculomas, spine, liver).

· TB infection tests – tuberculin skin test (TST), antigen-based skin tests, and interferon-gamma release assay (IGRA): these inform not on disease but on exposure and activation of cellular immunity against TB bacteria. Results may be altered by immunosuppression, lack of immune maturation, malnutrition, the test being done during the window period, inadequate technique, and Bacillus Calmette–Guérin (BCG) vaccination (in TST). A negative test does not rule out TB infection or disease.

· Blood tests: children with TB frequently present with anaemia and increased (ALT), (AST), and C-reactive protein (CRP). These may orient towards a presumption of TB in cases of doubt.

HIV testing if status unknown.

Step 5: Bacteriological test

· TB confirmation (with sputum smear or culture) is achieved in less than 50% of children. However, negative bacteriological tests do not exclude active TB, and new approaches are needed.

Samples: Use the most feasible with the least aggressive procedure:

· Paediatric samples:

– **Stool:** GeneXpert® – sensitivity 50–67%, specificity 98%. Can diagnose rifampicin resistance.

– **Urine:** potential use of TB lipoarabinomannan (TB LF-LAM) assays in children living with HIV and disseminated TB.

–**Gastric aspirate:** lower sensitivity than stool GeneXpert and induced sputum. Needs trained staff. Uncomfortable for children. Nasopharyngeal aspiration is better tolerated, but yield is lower than for stool samples.

· **Sputum samples:** lower sensitivity in children than adults due to paucibacillary nature of the disease in children. Samples are usually difficult to obtain. Induced sputum improves specimen quality and technique yield but needs nebulization and trained staff.

· Extrapulmonary samples (other than stool):

–Lymphadenopathy aspirate or discharge: Xpert® MTB/RIF Ultra.

–Cerebrospinal fluid: Xpert MTB/RIF or MTB/RIF Ultra (reference test for TB meningitis).

–Biopsy: needs surgery.

–Bronchi alveolar lavage: high yield but needs fibro bronchoscopy, which is invasive and not always available.

THE 3 DEGREES OF CERTAINTY OF TB DIAGNOSIS IN CHILDREN

1. Confirmed TB:

At least 1 of the signs and symptoms suggestive of TB disease

Detection of *M. tuberculosis* with genotypic or phenotypic bacteriological test

2. Probable TB:

Signs and symptoms suggestive of TB disease

TB contact (> 78-90 % resistance concordance with adult source)

3. Possible TB:

Signs and symptoms suggestive of TB disease with either

Contact of a source case with TB disease or TB risk factors

WHAT IF I HAVE DOUBTS ABOUT THE DIAGNOSIS?

· Search for consistency in findings and balance the risk of treating versus not treating. This can be critical in very ill children with general danger signs from countries with a high TB burden. If there is a solid clinical presumption, it can be justified to treat TB.

· If community-acquired pneumonia or other respiratory infection is considered more likely than TB, use antibiotics with no action against TB, to avoid delaying the final diagnosis and promoting TB resistance (e.g. do not use fluoroquinolones).



WHAT IF THERE IS NO IMPROVEMENT AFTER INITIATING TB TREATMENT?

Especially in children without bacteriological confirmation and no clinical improvement within the first month after treatment initiation, consider the following:

- Low adherence or malabsorption?
- Incorrect dosage? Use dosing tables (weight bands) and promote the use of child-friendly and dispersible formulations. Training is needed to treat very young children.
- Regimen for drug resistance prescribed
- Added conditions needing management? Consider malnutrition, superinfection and conditions associated with childhood TB (e.g. HIV, pneumonia, parasitosis, malaria).
- Misdiagnosis? The real disease may remain untreated and be evolving. Consider diseases with lymphadenopathies (e.g. lymphoma, Brucella), community-acquired pneumonia, and other disseminated or systemic diseases (e.g. cancers, autoimmune disorders).

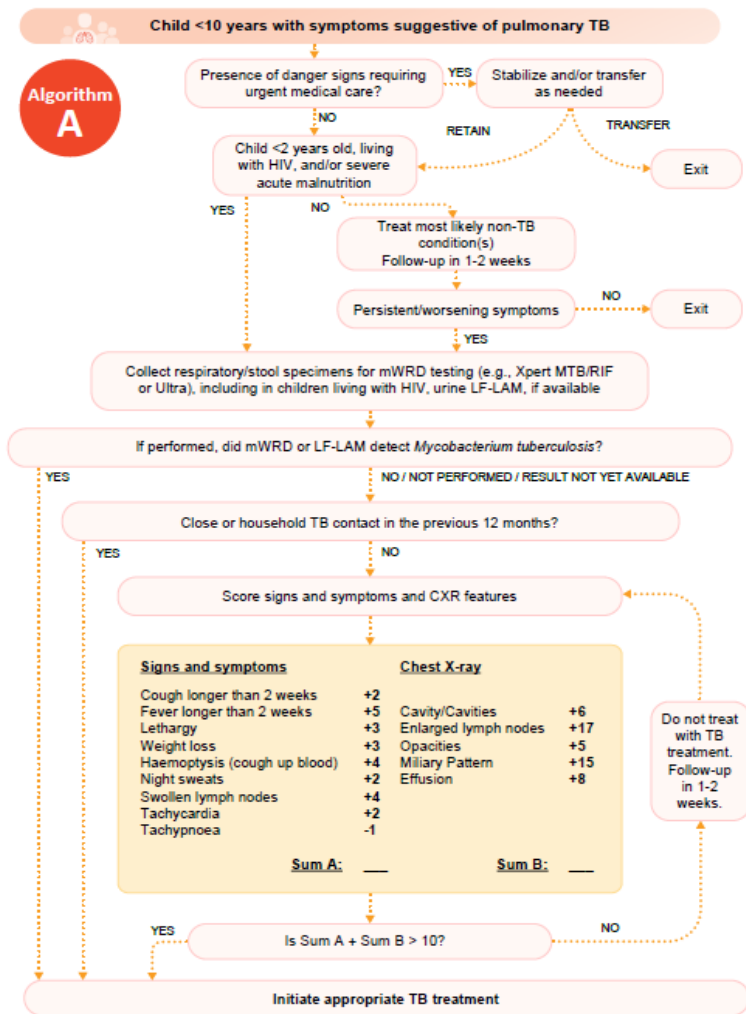


Figure 6.1 WHO algorithm for TB diagnosis in children of less than 10 years old based on contact, clinical presumption and access to CXR (Algorithm A). Source: World Health Organization. (2022). WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents. World Health Organization.

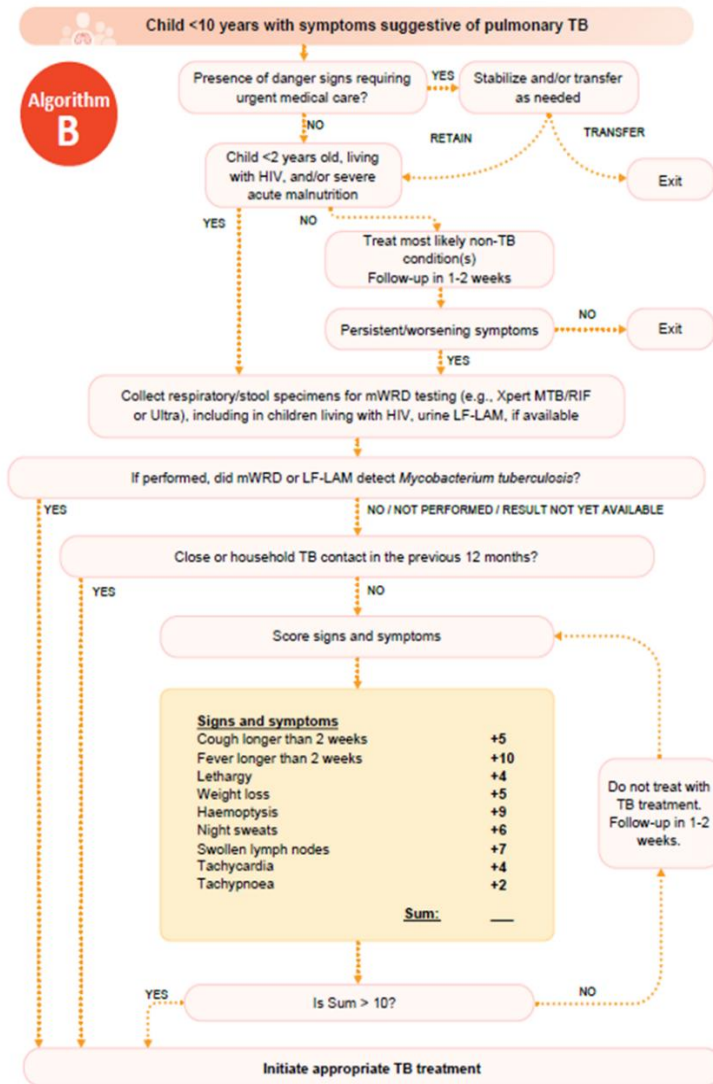


Figure 6.2 WHO algorithm for TB diagnosis in children of less than 10 years old based on contact, clinical presumption (Algorithm B). Source: World Health Organization. (2022). WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents. World Health Organization

6.2 SUSCEPTIBLE TB TREATMENT OPTIONS FOR CHILDREN AND ADOLESCENTS

OPTION 1. 2HRZE/4HR STANDARD CATEGORY I

Candidates: Child and adolescent new patients with pulmonary TB or extrapulmonary TB except TB meningitis, bone and joint or disseminated TB

Composition and duration:

- 2HRZE/4HR: 6 months daily with FDC and preferable in dispersible formulations (child-friendly) in <10 y/o and dose according to body weight bands by tables 3.2 and 3.3.
- In case of premature or low birth weight, management should be based on dose per body weight and under the coordination of a specialist.

TABLE 6.1 NUMBER OF TABLETS DAILY NEEDED TO TREAT TB IN CHILDREN BY WEIGHT BANDS IN FDCs UNDER CATEGORY I REGIMEN.

	Intensive phase (2 months)		Continuation phase (4 months or 2 months in non-severe TB)
	HRZ (50/75/150)	E (100)	HR (50/75)
4-7.9kg	1	1	1
8-11.9kg	2	2	2
12-15.9kg	3	3	3
16-24.9kg	4	4	4
25kg+	Use adult dosages and preparations		

There are now child-friendly, quality-assured formulations of the following first-line medications that can be obtained from the Global Drug Facility: fixed-dose combination of rifampicin (75 mg)/isoniazid (50 mg), and rifampicin (75 mg)/isoniazid (50 mg)/pyrazinamide (150 mg). Similarly, there are available paediatric 2nd line drugs (SLDs): isoniazid, clofazimine, delamanid, bedaquiline, ethambutol, ethionamide, levofloxacin, moxifloxacin, linezolid and pyrazinamide.

TABLE 6.2 RECOMMENDED DAILY DOSES OF FIRST-LINE ANTI-TB DRUGS FOR CHILDREN

Anti-TB drug	Dose and range (mg/kg body weight)	Maximum dose per day (mg)
Isoniazid	10 (7-15) *	300
Rifampicin	15 (10-20)	600
Pyrazinamide	35 (30-40)	-
Ethambutol	20 (15-25)	-
Rifapentine**	10-20 once a week	-

*The higher end of the range for isoniazid dose applies to younger children; as the children grow older, the lower end of the dosing range becomes more appropriate. Remark: As children approach a body weight of 25 kg, clinicians can use adult dosing. ** The usual dose of Rifapentine used for the treatment of LTBI, maximum dose 1200mg.

OPTION 2. 2HRZ(E)/2HR SHORTER REGIMEN

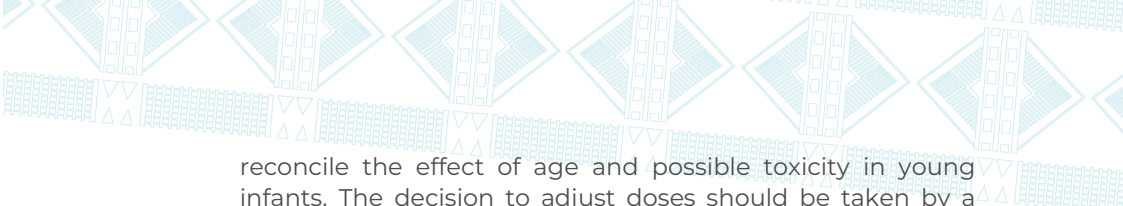
Candidates: children and adolescents between **3 months and 16 years of age with non-severe TB** (without suspicion or evidence of MDR/RR-TB) may benefit from treatment-shortening

Composition and duration: 4-month treatment regimen (2HRZ(E)/2HR)

- fixed-dose combination (FDC) tablets
- The use of ethambutol in the first two months of treatment is recommended in settings with a high prevalence of HIV, or isoniazid resistance.

Recommendations and tips:

- Non-severe TB is defined as peripheral lymph node TB, intrathoracic lymph node TB without airway obstruction, uncomplicated TB, pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern.
- Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be treated with the 6-month treatment regimen (2HRZ(E)/4HR). Treatment may require dose adjustment to



reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing paediatric TB.

OPTION 3. 2HRZE/10HR TB MENINGITIS, BONE, JOINT OR DISSEMINATED

Candidates: Children and adolescents with suspected or confirmed meningitis or osteoarticular TB (without suspicion or evidence of MDR/RR-TB) should be treated with 12 months regimen

Composition and duration: a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months, the total duration of treatment being 12 months.

OPTION 4. 6HRZET TB MENINGITIS

Candidates: For children and adolescents with suspected or confirmed TB meningitis (without suspicion or evidence of MDR/RR-TB) a 6-month intensive regimen (6HRZETo) may be used as an alternative option to the 12-month regimen (2HRZE/10HR). ***Should not be used in children and adolescents living with HIV***

Composition and duration: isoniazid: 20 mg per kg, maximum 400 mg daily, rifampicin: 20 mg per kg, maximum 600 mg daily, pyrazinamide: 40 mg per kg, maximum 2000 mg daily, and ethionamide: 20 mg per kg, maximum 750 mg daily. In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used.

6.3 DR-TB MANAGEMENT IN CHILDREN

The medications and principles used for the treatment of children with MDR-TB are similar to those used to treat adults. Except injectables and Pa (lack of evidence at the time of update), all SLDs can be used safely in children (including Bdq and DIm).

BOX 6.3 SPECIAL CONSIDERATIONS IN THE MANAGEMENT OF DR-TB IN CHILDREN:

- Treatment should be based on the DST pattern of the most likely source case if the child does not have a DST of his or her own.
- It is key to involve family and relatives, education in the disease's features and the need for adherence during the entire treatment, side effects and clinical/bacteriologic evaluations. DOT by a trained relative or HCW is necessary
- Children present an accelerated drug metabolism so usually dosages are higher and slightly different needing special weight bands based on weight and age (available at Annex 2)
- Most SLDs do not have child-friendly formulations (dispersible), this facilitates dosage and intake (including Bdq, Dlm, Lfx, Mfx, and Lzd).
- Obtain baseline weight and height in all children with MDR/RR-TB and measure weight regularly throughout treatment. This will form the basis for dose adjustments of the TB medicines for weight, and allow following of weight gain, an important indicator of clinical response.
- Regularly assess the clinical, radiological, and microbiological (if relevant) response to treatment.
- Avoid unnecessary hospitalisation of children and adolescents with MDR/RR-TB and implement evidence-based infection prevention and control measures when needed.
- Minimise disruption of education by allowing children and adolescents with MDR/RR-TB to go back to school as soon as possible if clinically feasible and no longer infectious.
- Carefully monitor for adverse events and adherence at every visit.
- Offer additional age-appropriate social support for children and adolescents and their families throughout screening, diagnosis, treatment initiation and follow-up.

TABLE 6.3 TREATMENT OPTIONS FOR DR-TB MANAGEMENT IN CHILD AND ADOLESCENTS

DR-TB options	Indications in child and adolescent
OPTION 1. BPaL/BPaLM	Not recommended in <14 y/o (lack of evidence in Pa safety in this group) or weight <35 kg. For adolescent girls, no pregnancy or breastfeeding, and willingness to use effective contraception is necessary. Not recommended in case of severe disease (multiple cavitory disease, disseminated TB, TB meningitis, and bone-joint TB)
OPTION 2. BEAT-TB regimens (6 B-D-L-Lfx-C)	Recommended and tested in children over the other regimens
OPTION 3. EndTB regimens (9B-L-M-Z, 9B-L-Lfx-C-Z and 9B-D-L-Lfx-Z)	Not yet evidence in children
OPTION 4. Short treatment regimen (STR), Lzd variant	Recommended and tested in children. Not recommended in case of severe disease (multiple cavitory disease, disseminated TB, TB meningitis, and bone-joint TB)
OPTION 5. Longer individual regimens	Recommended and tested in children

CHAPTER 7:

**MANAGEMENT OF
TB-HIV IN ADULTS
AND CHILDREN**

CHAPTER 7. MANAGEMENT OF TB-HIV IN ADULTS AND CHILDREN

HIV infection is the greatest risk factor for TB, already known. People living with HIV and TB infection have a 10% annual risk of developing TB disease. A diagnosis of TB in PLHIV is an AIDS defining illness and should always be considered as a clinical emergency.

Worldwide TB is the main cause of death among HIV-infected persons, specially under generalized HIV epidemics in countries with high TB prevalence, like Fiji.

BOX 7.1 KEY FACTS IN TB-HIV

- HIV destroys the first line (macrophages) and the second line (lymphocytes CD4) of defence against TB. The appearance of opportunistic diseases like TB clinically defines the final situation of HIV infection called acquired immunodeficiency syndrome or AIDS.
- The presence of multiple infections and an unhealthy lifestyle accelerate the progression into the AIDS stages
- The lower the CD4, the weaker the response against TB and other opportunistic infections/diseases.
- In severe immune suppression situations (<200 CD4 cells), TB tends to disseminate by blood dissemination, leading to atypical and more severe presentations affecting any organ: lungs (miliary TB), central nervous system (meningitis and tuberculomas), liver (cholestatic hepatitis), bone marrow (suppression), spleen, etc. And this can happen in multiple organs at the same time, a situation called **disseminated TB**, which is the most fatal form of TB. There might be an increased risk of relapse, failure, presentation of resistance patterns, toxicities, and death
- Early TB diagnosis or presumption in the PLHIV is key to survival.
- All TB patients should be screened for HIV, and TB should be on the differential diagnosis of any PLHIV presenting with a localised or systemic disease.

- TB tends to appear in the PLHIV who are not diagnosed or treated, or because of inadequate adherence (ARV failure).
- Current ART is timely diagnosed and, with proper adherence, turns viral load into undetectable. These transform HIV infection into a chronic condition with the same life expectancy as the non-HIV-infected population, limiting the risk of opportunistic disease and limiting HIV transmission to sexual partners
- If timely and properly managed (patient-centred approach), TB and HIV can be treated simultaneously with great chances of survival
- The key to success in TB-HIV management: a high level of presumption, prompt treatment initiation, correct and long enough regimen, use of corticosteroids in severe TB forms, management of malnutrition, considering drug-drug interactions, potential additive toxicities, and other opportunistic diseases

7.1 TB-HIV DIAGNOSIS:

7.1.1 HIV DIAGNOSIS

All TB patients should have an HIV test result as part of the initial screening. The **person infected with HIV presenting TB is on AIDS (Immunosuppression stage 3 or 4)**. Therefore, all TB-HIV patients are severely ill, even if clinical signs are not apparently severe. Knowing the HIV status matters, as if not properly treated, the likelihood of dying is high. The TB HCWs should always offer a routine HIV test, respecting patient privacy without any kind of stigmatising language or attitude.

HIV screening (clinical + test) should be done to all TB patients, and other people with high risk of HIV infection like IDUs, sexual partners of HIV positive couples, children born from mothers who are HIV positive or other

1. HIV Clinical screening.

- **Adults:** among those with risk factors or belonging to HIV high-risk groups, search for the presence of any of the 4 key symptoms: **fever, weight loss, cough, and night sweats.**

In children, consider an HIV test initially if any of the parents is known HIV infected, belongs to any HIV high-risk group, or is under HIV presumption. basic clinical screening is needed to check the necessity of HIV testing, but also to set the clinical staging, which plays a key role when virological testing is delayed or unavailable.

- **Infants and older children** common early signs are: failure to thrive, stunting or wasting (despite adequate nutrition), persistent oral thrush, severe or recurrent pneumonia (particularly *Pneumocystis jirovecii* pneumonia (PJP) TB), generalized lymphadenopathy, chronic diarrhoea (>1 month, often associated with opportunistic infections), recurrent or persistent fever, recurrent bacterial infections, severe or recurrent skin conditions (eczema, seborrheic dermatitis, or extensive molluscum contagiosum), neurological manifestations (delayed milestones, cognitive decline, or HIV encephalopathy), or lymphoid interstitial pneumonitis (LIP)
- **In newborns and infants:** early signs of HIV are often non-specific; hence, testing is essential in <18 months.

2. HIV DIAGNOSIS IN ADULTS

Step	Test	Purpose	Interpretation
1	Rapid Test or ELISA* (1st assay)	Initial screening	If non-reactive → HIV negative If reactive → Proceed to Step 2
2	Different Rapid Test or ELISA* (2nd assay)	Confirmation test	If non-reactive → Inconclusive → Retest in 14 days If reactive → HIV diagnosis confirmed
3 (if needed)	Tie-breaker test (3rd assay)	Resolve discordant results	Used if 1st reactive & 2nd non-reactive

*ELISA in Fiji is only available at tertiary hospitals

Source: UNAIDS. HIV Diagnostic Algorithm, Technical Update, 2020, and HIV Care & Antiretroviral Therapy Guidelines. Third edition 2022. Ministry of Health & Medical Services, Fiji

Notes:

- Use tests from different manufacturers for each assay step.
- Always confirm with a second assay before reporting a diagnosis.
- If indeterminate results persist, → Repeat testing after 14 days or perform viral load testing

3. HIV DIAGNOSIS IN INFANTS AND CHILDREN

In children, maternal antibodies can persist for up to 18 months. Therefore, direct viral load detection (PCR) for HIV RNA or DNA is used starting at 4–6 weeks of age.

Age	Test Used	Reason
4–6 weeks	HIV DNA or RNA PCR [EID]*	Maternal antibodies interfere with antibody tests
≥18 months	Follow the adult algorithm	Maternal antibodies are usually gone

Source: UNAIDS. HIV Diagnostic Algorithm, Technical Update, 2020 and HIV Care & Antiretroviral Therapy Guidelines. Third edition 2022. Ministry of Health & Medical Services, Fiji

* Early Infant Diagnosis

4. OTHER BASELINE TESTS AFTER HIV DIAGNOSIS

The HIV diagnosis should be followed by other minimal markers of disease baseline and progression. The most important are

- **CD4 count:** informing the relative immune status that can be fundamental for clinical decision making. A CD4 count <200 cells/mm³ (or <15% in young children) indicates advanced HIV

or AIDS and is a major risk factor for opportunistic infections like TB.

- **Viral load (VL):** key to monitor the ART effects/goals and to evaluate adherence and risk of resistance.

TABLE 7.1 CD4 COUNT AND IMMUNOLOGICAL STATUS IN ADULTS AND CHILDREN

Age Group	CD4 Count (cells/mm³)	CD4 %*	Immunological Status
Adults (≥19 yrs)	> 500		Normal/Low risk
	200–499		Moderate immunosuppression
	< 200		Severe immunosuppression (AIDS)
Children ≥5 yrs	> 500	> 25%	Normal
	200–499	15–25%	Moderate immunosuppression
	< 200	< 15%	Severe immunosuppression
Children 1–4 yrs	> 1,000	> 30%	Normal
	750–999	25–29%	Mild immunosuppression
	500–749	20–24%	Moderate immunosuppression
	< 500	< 20%	Severe immunosuppression
Infants <1 yr	> 1,500	> 35%	Normal
	1,000–1,499	30–34%	Mild immunosuppression

	750–999	25–29%	Moderate immunosuppression
	< 750	< 25%	Severe immunosuppression

Source: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021.

*In children under 5 years: CD4 percentage is more reliable than absolute count due to normal age-related fluctuations. In older children and adults, absolute CD4 count becomes a more stable marker.

7.1.2 TB diagnosis in the PLHIV

Similarly, to children <10 y/o with TB, the bacteriologic confirmation of TB frequently cannot be achieved in the severely immunosuppressed TB-HIV patient. If there is a consistent clinical TB presumption, provided the high rate of death if untreated, bacteriological confirmation should not delay TB treatment initiation

Most clinical manifestations of TB depend upon the immune system. Therefore, diagnosing TB in the PLHIV may present differently depending on the grade of immunosuppression:

- Patients with **>500 CD4** cells/mm³ usually present **classic TB patterns** (pulmonary TB, cavities).
- Patients with **<50 CD4** cells/mm³ usually present with **disseminated TB** affecting multiple organs at the same time (read more on the section about the critically ill TB patient) in an initially low-symptomatic, but clinically severe situation and with high mortality unless management is timely and adequate.

BASIC DIAGNOSE RECOMMENDATION:

In adults and adolescents who screened positive for TB, or are seriously ill with advanced HIV disease, the following tests should be considered to optimise TB diagnosis:

1. CXR
2. GeneXpert or other mWRD on pulmonary or extrapulmonary samples
3. Others: Urine LF-TB LAM [with CD4 level < 100], CRP in blood, searching for abnormalities compatible with TB

Remarks: Seriously ill individuals include those requiring hospitalisation. Respiratory samples include sputum, early morning gastric lavage, and induced sputum. Advanced HIV disease is defined in people with HIV with a CD4 cell count of <200cells/mm³ or presenting with a WHO Stage 3-4 AIDS-defining illness

Box 7.2 Key considerations in the diagnosis of TB in the PLHIV

1. Clinical presentation and symptom screening: In the HIV-infected person, screening diagnosis for TB considers primarily the 4 systemic symptoms and signs, which are a primary screening tool for TB in HIV-infected persons by WHO: **Fever, weight loss, cough, night sweats.** If all 4 symptoms are absent, with 97% probability, the patient has no TB. But in HIV-infected persons presenting any of these symptoms, TB needs to be ruled out. The presence of lymphadenopathies and signs of other opportunistic diseases should raise concerns of a TB process.

2. CXR: Considered a basic screening tool in the PLHIV. Cavities may appear, but as the capacity to develop granulomas is diminished, finding cavities is unusual at low levels of CD4 counts. Atypical patterns like infiltrates, nodules, pleural effusion, or military TB can appear.

3. GeneXpert: Xpert MTB RIF and Xpert Ultra cartridges with a similar sensitivity to cultures but delivering results in hours can promote a positive impact on the diagnosis capacity. Xpert Ultra should be the diagnosis of choice in these cases. Extrapulmonary samples can be used, like cerebrospinal fluid, lymph node aspirates, stool, and urine.

4. Urine LF-TB LAMs: A simple and cheap way to diagnose TB in HIV infected that increases the yield of diagnosis according to the lower CD4 count. Sensitivity is considered low (rounding 50%), but novel versions of LAMs can potentially increase it. Sensitivity increases to 70% or more in patients with low CD4 counts. Specificity is considered very high (91-95%). These features make it a suitable and cheap option in settings with reduced resources and a high burden of badly immunocompromised patients or those unable to expectorate. It can be used as a point-of-care test due to its simplicity.

5. C-reactive protein (CRP): Basic blood test is starting to be considered by WHO as a screening tool for TB in HIV patients, helpful to orientate towards TB diagnosis under challenging circumstances of disseminated but pauci-symptomatic and bacteriologic negative TB by classic test.

6. AFB smear: The absence of effective granulomas and thus cavities make the bacilli burden in the airway much reduced, and therefore, a low sensitivity test in these conditions. An important proportion of TB-HIV patients tend to be AFB-negative even if they are critically ill.

7. Culture: High sensitivity, cultures might appear positive but usually delay >1 month, and this time can be excessive for a patient in a critical situation.

8. Extra investigations: Different tests can be used, like imaging tests in search of liver or spleen TB infiltration, bone marrow aspiration, ADA in serous liquids, and others.

9. Other useful imaging test: Ultrasound searching for thoracic or abdominal lymphadenopathies or multinodular patterns in liver and spleen. CT or MRI for tuberculomas in the brain.

7.1.3 DIFFERENTIAL DIAGNOSIS OF TB IN THE HIV NEWBORN NOT ON ART

TABLE 7.2 DIFFERENTIAL DIAGNOSIS OF TB IN THE HIV NEWBORN NOT ON ART

Differential diagnosis	Explanation
1. Congenital TB	Rare but possible (transplacental or via amniotic fluid) Symptoms appear within the first weeks of life: hepatosplenomegaly, fever, and respiratory distress
2. Bacterial sepsis (e.g., Group B Streptococcus, E. coli)	Common in neonates. Overlaps with TB: fever, lethargy, respiratory signs Blood cultures are critical for distinction
3. Pneumonia (viral or bacterial)	Cytomegalovirus (CMV) pneumonia is common in HIV-positive neonates

	Requires PCR testing and radiologic differentiation
4. Pneumocystis jirovecii pneumonia (PJP)	Common in HIV-positive infants not on cotrimoxazole Presents with hypoxia, dry cough, and interstitial infiltrates
5. Disseminated Bacillus Calmette–Guérin (BCG) disease	In infants who received BCG vaccination May present with disseminated TB in immunosuppressed neonates
6. Fungal infections (e.g., candidiasis, histoplasmosis)	Especially in severely immunosuppressed infants Need fungal cultures or antigen detection
7. HIV-related lymphocytic interstitial pneumonitis (LIP)*	More common in older infants, but should be considered Radiologically may resemble TB
8. Malignancies (rare)	E.g., congenital leukemia; may present with fever, hepatosplenomegaly, cytopenias

BOX 7.3 KEY NOTES IN LYMPHOCYTIC INTERSTITIAL PNEUMONITIS (LIP)

- **Etiology and clinical presentation:** Benign lymphoproliferative disorder with diffuse infiltration of the lung interstitium by lymphocytes and plasma cells. Common in children with perinatally acquired HIV, especially those not yet on ART. It is frequent in countries with generalized epidemics and resource-limited settings (10–40% of HIV-infected children)
- **Clinical Presentation:** Often asymptomatic initially, progressive chronic cough, tachypnea, clubbing of fingers in advanced stages, mild to moderate hypoxia, failure to thrive, recurrent lower respiratory tract infections.

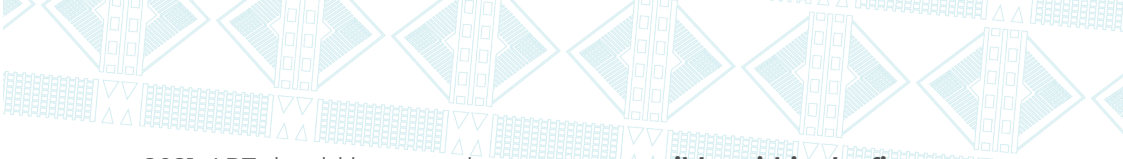
- **Radiological Findings:** Chest X-ray: Bilateral, symmetrical reticulonodular or interstitial infiltrates, often mistaken for TB. High resolution CT: Ground-glass opacities, interlobular septal thickening, and peribronchial cuffing. Hilar lymphadenopathy may be present.
- **Differential Diagnosis:** Pulmonary TB, Pneumocystis jirovecii pneumonia (PJP), Cytomegalovirus (CMV) pneumonitis, Other interstitial lung diseases. Lipoid pneumonia
- **Diagnosis:** Based on clinical and radiological findings in a HIV-infected child. Exclusion of TB and other infections is key. Others: Lung biopsy confirms diagnosis (rarely needed in children). Elevated CD8+ lymphocytes may be seen in bronchoalveolar lavage
- **Management:** Initiation of ART is the cornerstone of treatment resolution. Corticosteroids for severe or symptomatic cases (cough, hypoxia, tachypnea), e.g., Prednisone 1–2 mg/kg/day, 4-8 weeks gradual taper. Monitor for oxygen need and progression to chronic lung disease

7.2 TB-HIV CO-INFECTION TREATMENT

7.2.1 TIMING FOR CO-TREATMENT

Treating opportunistic infections reduces the chances for complications (especially immune reconstitution inflammatory syndrome or IRIS) by the time ARVs are initiated. Conversely, if the ARV treatment is too delayed, the patient will not recover the immune capacity or suffer other opportunistic diseases. Therefore, balance is necessary.

1. **Opportunistic diseases** like TB, PJP, or others should be treated immediately as these diseases are the ones killing the patient, and if left untreated, precipitate the decline of the immune system and the increase in VL.
2. **Antiretroviral therapy (ART).** WHO recommendations on the timing of ART for children and adolescents with TB were updated in



2021. ART should be started **as soon as possible, within the first two weeks [14 days] of initiating TB treatment**, regardless of CD4 count, among adults, adolescents, and children living with HIV. The exception to this rule is patients presenting with TB meningitis or those likely to die due to IRIS, mainly affecting the brain.

3. In case of TB meningitis: ART should be delayed and **initiated 4–8 weeks** after starting TB meningitis treatment. Adjuvant corticosteroid therapy for adults, adolescents, and children with dexamethasone or prednisolone (tapered over 6–8 weeks) might be necessary to increase the survival chances.

7.2.2 TREATING TB AND HIV CONCOMITANTLY

1. TB treatment in the co-infected: daily 2RHZE/4RH using FDCs.

Considerations: due to severe immunosuppression, TB-HIV may present disseminated or TB meningitis needing regimens 2RHZE/10RH and the use of higher doses of RIF or medication with high blood-brain barrier penetration. Quite commonly, TB-HIV presents baseline hepatitis needing fine adjustments towards liver-friendly regimens during the initial phases. See Annex 1 for key tips in the management of complicated cases. For the DR-TB, there are no major changes, as even DR-TB regimens (BPaLM, BEAT-TB or EndTB regimens) had been satisfactorily tested in PLHIV.

2. HIV treatment in the TB patient:

First line ART in Fiji in 2025 is: Dolutegravir (DTG) – Lamivudine (3TC) – Tenofovir (TDF)

The key complication in the HIV regimen in the TB patient is mainly the RIF interaction with some ARVs (see drug-drug interactions). The most commonly used HIV regimen in Fiji is based on DTG (or EFV), which presents better tolerability. In regimens using DTG as the core drug, this needs to be used at 50mg /12 hours (double dose).

EFV-based regimens present no major interaction with RIF, and there is no need for dose adjustment.

Consider potential drug-drug interactions in the standard of HIV care proposed by the HIV/AIDS program in Fiji in future guidelines.

3. Cotrimoxazole preventive therapy (CPT). Cotrimoxazole is an FDC of antibiotics (trimethoprim TMP, sulfamethoxazole SMX), which prevents many common infections highly prevalent in the immunosuppressed patient. The easiest and most recommended dose is 160/800mg daily or 3 times/week. Use CPT in TB-HIV patients regardless of CD4 count and at least for the whole duration of TB treatment and later until an increase of CD4 >350 as per national HIV guidelines.

4. Basic care: All patients with TB-HIV are considered at the AIDS stage and basic health preventive measures are needed. To prevent further opportunistic diseases, it is important to provide a safe environment in terms of water, sanitation, and food, jointly with a healthy lifestyle, including regular population vaccination and others like flu, SARS-CoV-2 and pneumococcal if available. Patient-centred and integrative approaches are highly needed to reduce TB-HIV mortality. Settings where there is integrated TB-HIV care in the form of one - stop shop model (TB-HIV clinics) with psycho-social and nutritional support tend to achieve better outcomes.

Treatment adherence (TB and HIV) is key to avoiding resistance and recovery. Counselling, training and involving the co-infected patient on the clinical decision is fundamental to achieving adherence and long-term survival. Nurses and figures to support adherence are fundamental. TB-HIV critically ill patients with malnourishment and other clinical and social complications are often better managed as inpatients until the short-term risk of death has been reduced

7.2.3 IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS):

IRIS is an exaggerated inflammatory reaction against antigens or living pathogens in the organs of the patient. It tends to happen 1 month after the introduction of ART. When the CD4 count increases, and the HIV viral load decreases, the immune capacity is recovered, creating an inflammatory response at multiple sites, which may put the life of the patient at risk.

There are 2 major types of IRIS.

1. Paradoxical TB-IRIS:

- Characteristics: a patient on TB treatment that nearly 1 month after ART introduction and an initial improvement develops fever, lymphadenopathy, pulmonary infiltrates, worsening of previous symptoms, meningitis, and hepatitis.
- Prevalence: at least in 10% of TB-HIV patients.
- Risk factors for paradoxical TB-IRIS are low initial CD4, high severity of HIV disease (high bacterial load and disseminated disease), and short time between TB treatment and ART
- Diagnosis: There is no test available, and diagnosis is based on clinical presumption and response to treatment.
- Differential diagnosis: needs to be done always to ascertain potential reasons for worsening, which are not IRIS but additional infections, TB resistance, irregular drug intake, etc.
- Treatment:
 - **IRIS prevention in TB-HIV patients at risk**: consider the use of Prednisone 40mg/d for two weeks, followed by another 2 weeks 20mg/d. Use with care, as it may increase the risk of herpes reactivation and other diseases like Kaposi's sarcoma.
 - **IRIS treatment in moderate to severe cases**: consider treating symptoms (i.e., abscesses or secretions: aspiration, anti-inflammatories including NAIDS and corticosteroids (low and high dose see Box below)
 - **Stop ARVs only in life-threatening situations**: prioritise treatments of opportunistic diseases. Situations of concern may concern severe neurological involvement like TB meningitis and cryptococcal meningitis, which may lead to brain herniation, hydrocephalus, and other complications linked to morbidity and mortality.
- Clinical considerations in corticosteroid use:
 - Rule out treatment failure or new opportunistic infections before initiating steroids
 - Monitor closely for corticosteroid adverse effects: hyperglycemia, secondary infections, or interactions with ART

- o In special forms of TB (e.g., **TB meningitis**), corticosteroid use and dosage may differ. IRIS in the brain can be lethal, and doses needed are higher and for a longer time.

Box 7.4 Use of Corticosteroids for IRIS Prevention and Treatment in TB-HIV Patients


	Indication:	Recommended corticosteroid and dose
IRIS Prevention	HIV-positive patients with active pulmonary TB and CD4 count <100 cells/mm ³ initiating antiretroviral therapy (ART).	First 2 weeks after ART initiation: Prednisone 40 mg daily Following 2 weeks: 20 mg daily for the Total duration: 4 weeks
IRIS Treatment	Moderate to severe paradoxical IRIS in patients already on TB treatment and ART. Reduce inflammation and improve symptoms without compromising TB control.	Prednisone (or equivalent such as prednisolone or methylprednisolone). <u>Initial dosage:</u> 1–1.5 mg/kg/day of prednisone (e.g., 60–80 mg/day in adults). <u>After 1–2 weeks</u> at full dose, gradual tapering is recommended over 4–6 weeks, depending on clinical response.

* Seek Specialist advice prior to use

2. Unmasked TB-IRIS:

- Characteristics: This is a completely different complication that appears in patients who are started on ART and suddenly develop TB symptoms (cough, infiltrates, lymphadenopathies, meningitis, respiratory failure). These are patients suffering from TB, but who were not diagnosed before starting ARVs, due to initially paucisymptomatic, or not suspected, and therefore not receiving treatment.

- Risk factors: robust immune recovery in individuals with advanced immunosuppression, often with CD4 counts <50 cells/ μ L.
- Diagnosis:
 - Clinical: severe or atypical presentations of TB (e.g., lymphadenitis, high fever, respiratory distress) soon after ART initiation
 - TB confirmed microbiologically or clinically after ART initiation.
 - Temporal association with ART (<3 months).
 - Absence of alternative explanation. Differential diagnosis may comprise paradoxical TB-IRIS, ART toxicity, drug-resistant TB, and other opportunistic infections
- Management:
 - Prompt initiation of standard **first-line TB treatment** upon diagnosis is critical or based on the pattern of resistance of the index case if known. Delays are associated with poor outcomes due to rapid progression in the context of immune recovery
 - ART should generally **not be interrupted** unless TB-IRIS is life-threatening (e.g., presentation of TB meningitis).
 - Corticosteroid therapy: Indicated in moderate-to-severe cases of unmasked TB-IRIS with life-threatening inflammation (e.g., airway compression, CNS TB).
 - Prednisone 1.5 mg/kg/day for 1–2 weeks, tapering over 4–6 weeks, has shown benefit in paradoxical IRIS and is extrapolated to unmasked forms.
 - Supportive care: Management of respiratory distress, sepsis, or organ dysfunction is crucial.
 - Hospital admission may be needed in severe cases.
- **Prognosis: Frequent and important cause of early mortality of HIV patients after ART initiation** (1-3 months). particularly with central nervous system involvement or severe disseminated disease. This is one of the reasons why HIV hubs should have the



capacity to rule out active pauci-symptomatic TB. Early diagnosis and integrated TB-HIV management are critical to reduce risk.

Other complications in TB-HIV management:

With a TB-HIV patient, many different health problems can be ongoing at the same time:

- Clinical complications TB-HIV, leading to disability or being critically ill
- Simultaneous opportunistic infections and their treatment
- Important pill burden, overlapping toxicities, and drug-drug interactions
- Socio-economic problems (poverty), stigma, mental suffering, depression, anxiety, alcoholism, or IDU
- TB or HIV Resistance

Due to all these complications, TB-HIV patients especially need support and follow up by HCWs, peers, families and communities to achieve the necessary adherence for cure. The lack of health and social support mechanisms impose a massive challenge to patients to cope with both diseases. The need for patient-centred approaches is particularly critical in people suffering from both diseases.

CHAPTER 8:

**SPECIAL
SITUATIONS:
TB-DM,
TB-PREGNANCY**

CHAPTER 8. SPECIAL SITUATIONS: TB-DM, TB-PREGNANCY

8.1 TB-DM

Brief definition of DM and its impact in Fiji

Diabetes mellitus is defined as a metabolic disorder of multiple aetiology, characterised by chronic hyperglycaemia with disturbance of carbohydrate, protein, and fat metabolism resulting from defects in insulin secretion, insulin action, or both. However, while the insulin defects mentioned are critical abnormalities, several other factors contribute to the hyperglycaemic state.

The major types of diabetes mellitus are:

1. Type 1 Diabetes
2. Type 2 Diabetes
3. Gestational Diabetes

Fueled by obesity, urbanization, and lifestyle changes (including nutrition/exercise habits), DM is exponentially growing in Fiji in recent years. DM triples the risk of developing active TB by weakening the immune response. The degree of immunosuppression is not comparable to that of HIV, but given the very high number of DM, this may be a leading factor in the DS and DR-TB epidemic.

People with both TB and DM are twice as likely to die during TB treatment and present twice the risk of TB relapse after treatment completion.

Bidirectional screening (similar to HIV)

- **Screening for TB among people with diabetes:** provided the relative state of immunosuppression, like in children and PLHIV, TB presents frequently with systemic symptoms and extrapulmonary form. For these reasons, TB in DM patients is frequently a delayed diagnosis
- **Screening for diabetes during TB treatment:** see box 8.1

BOX. 8.1 DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

Methods of diagnosis	Glucose tolerance	Hyperglycemia	
	Normal	Pre-diabetes	Diabetes
Fasting Blood sugar*	3.9 - 5.6 mmol/L (70 - 100 mg/dL)	5.7 – 6.9 mmol/L (100 - 125 mg/dL)	≥7.0mmol/L (≥126 mg/dL)
HbA1C	< 5.7%	5.7 - 6.4%	≥ 6.5% (≥48mmol/mol)
2 hour Post load venous glucose	<7.8 mmol/L (<140 mg/dL)	7.8 – 11.0 mmol/L (140 – 199 mg/dL)	≥11.1 mmol/L (≥200 mg/dL)
Random plasma glucose (to be used only in the presence of symptoms)			≥11.1 mmol/L (≥200 mg/dL)

*Overnight fast of 8–14 hours. *The values above do not apply to pregnant mothers.

Source: MOHMS. *Diabetes Management Guidelines, 4th Edition, 2024.*

* Two positive results on two different days are recommended. A single positive result is significant if there is unequivocal hyperglycaemia with metabolic decompensation or is accompanied with symptoms of diabetes e.g. polydipsia, polyuria, polyphagia and overweight.

Co-management of TB-DM

- Prompt diagnosis and initiation of adequate therapy for TB and DM
- DM management with basic glycaemia targets, preferably HbA1C (target HbA1C <7). This maximizes TB cure rates and limits relapse risk

- Counselling and support in lifestyle modification (smoking, diet, sedentarism/exercise) is necessary.
- Active case finding in households or families exposed to TB: other family members can also be diabetic and be exposed to TB from the index case.

Drug Interactions in TB-DM

- Monitor drug interactions between TB - DM. DM patients tend to have other comorbidities:
 - Peripheral neuropathy might worsen with INH and Lzd use
 - Metformin given together with Linezolid increases the risk of Lactic Acidosis. Use with caution.
 - Fluoroquinolones: all may alter glycaemia
 - RIF may reduce the levels of some medications, especially sulfonylureas (eg, Glipizide). Recommend switching to other classes, such as:
 - Insulin therapy
 - Biguanides, e.g., Metformin
 - Renal insufficiency: may require dose adjustments of TB and DM medications

Programmatic management

Similarly to TB-HIV integrated programs in countries with a high burden of both diabetes and tuberculosis, programming models have been considered, among which we can highlight:

1. One-stop shop: where TB and DM care is done in the same facility, and HCWs, with joint planning. Bidirectionally screening and care delivery are provided and are usually integrated within the primary health care network or TB facility.

2. Co-located services: where TB is done in one facility and diabetes care in a different one, but close in space with simple referral systems and intensive coordination between programs and HCWs. This is less convenient but reduces indirect costs for the patient.


3. Separated services: no integration, but there is at least a basic reference system and communication. These models are relatively easy to create since they mainly depend upon internal coordination. But they are associated with higher LTFU, overall worse monitoring, and an increase in cost and patient impoverishment.

BOX 8.2 TB AND KIDNEY DISEASE:

- Chronic kidney disease, defined as $eGFR < 60 \text{ ml/min/1.73m}^2$. Drug dosing is often adjusted based on creatinine clearance (CrCl) which is calculated with Cockcroft-Gault equation using gender, age, weight and serum creatinine.
- Patients with kidney failure are immunocompromised and many of them can also have diabetes.
- Category I regimen (2RHZE/4RH) treatment does not need to be adjusted as toxicity is mainly hepatic, except for ethambutol, which is predominantly eliminated renally, and drug accumulation in the presence of kidney disease can lead to irreversible ocular toxicity.
- In mild renal impairment (CrCl 30 -60ml/min), should be individualised using standard drugs in dose ranges in the lower range of usual recommendations for patients with normal renal function, with careful monitoring of side effects.
- In moderate to severe renal impairment cases (CrCl $< 30 \text{ ml/min}$), an individual approach is recommended with an alternate day regimen, instead of daily treatment. Doses recommended for pyrazinamide are 25 mg/kg, and for ethambutol 15 mg/kg.
- In DR-TB regimens under kidney failure treatments, every-other-day treatment is the common approach, but dosing should be discussed with a nephrologist.
- In severe renal impairment (e.g. $eGFR < 15 \text{ ml/min/1.73m}^2$), TB therapy should be coordinated with a nephrologist, especially if the patient receives chronic dialysis. Haemodialysis often leads to the elimination of most TB drugs, and medications are usually given **after dialysis, not before**. In such patients, ocular toxicity is a significant concern, and ophthalmological reviews are recommended.
- Important infection control measures are needed in haemodialysis centres if a TB patient accesses them.

8.2 TB and pregnancy

- Pregnancy induces a state of relative immunosuppression, increasing the risk of TB disease, including atypical and extrapulmonary forms such as disseminated TB, which carry high maternal and perinatal mortality risk. Globally, it contributes to 6–15% of all maternal mortality and puts neonates born to mothers with TB at higher risk of the disease.
- TB during pregnancy is associated with increased risk of:
 - ✓ Low birth weight
 - ✓ Premature births
 - ✓ Foetal loss
 - ✓ Vertical transmission through the placenta (disseminated TB)
 - ✓ Maternal mortality
- Treatment of TB during pregnancy significantly reduces these risks and limits dissemination to critical organs and the placenta. Treatment should not be deferred; it should be initiated as soon as TB is suspected or confirmed, especially in HIV-infected women.
- All first-line anti-TB drugs and many second-line drugs are considered safe during pregnancy except Amikacin, Kanamycin, and Ethionamide/Prothionamide.
- Pyridoxine (25–50 mg daily) is recommended for all pregnant or breastfeeding women on isoniazid (INH) throughout TB treatment. The dose should not exceed 150 mg daily to prevent withdrawal syndrome in newborns and interference with drug absorption.
- **Symptomatic screening for TB** should be offered to **ALL** pregnant women during their ANC visits.
- All women of childbearing age **should** undergo pregnancy screening once enrolled for TB treatment initiation, and counselling on family planning should be provided IF the



pregnancy test is negative. It is important to note that rifampicin can reduce the efficacy of hormonal contraceptives; therefore, barrier methods should be recommended.

- Thyroid function should be monitored regularly, especially when using ethionamide (Eth) or Prothionamide, due to potential hypothyroidism risks. Eth + PAS may create a decrease in thyroid hormones that are crucial for the neurological development of the foetus.
- Neonates born to Pulmonary bacteriologically confirmed TB [PTB BC] mothers should be screened for active TB disease. Once ruled out, they are offered TPT in consultation with the Paediatrician and TB medical team. BCG should be delayed after TPT and not be provided while on treatment, as the anti-TB drugs also destroy the vaccine (attenuated *M. bovis*).
- Breastfeeding is generally safe in pregnancy if not contraindicated by other medical conditions. Women taking first-line antituberculosis drugs may continue to breastfeed their newborns safely, as the concentrations of these drugs in breast milk are too small to produce toxicity in the nursing newborn. Infection control measures, such as mask-wearing and breastfeeding in well-ventilated areas to minimize neonatal exposure, are essential.
- Contact screening for all household members is critical; undiagnosed TB cases in the household can infect neonates rapidly. Studies suggest that in TB-affected households, > 15% of neonates may become infected with TB (DS or DR-TB) within three weeks of life.
- Do not use aminoglycosides (Sm, Km, Amk) as they are linked to ototoxicity in the foetus. It is assumed that 10-20% of the foetus exposed to aminoglycosides, especially during the first trimester of pregnancy, develops permanent deafness. Capreomycin is a polypeptide and not an aminoglycoside, with a much safer profile, to be considered in case of need.

CHAPTER 9:

**TB PREVENTION:
BCG, INFECTION
CONTROL & TPT**

CHAPTER 9. TB PREVENTION: BCG, INFECTION CONTROL AND TPT

9.1 BACILLUS CALMETTE-GUÉRIN (BCG) VACCINATION

The BCG vaccine contains a live attenuated *Mycobacterium bovis* strain. While it has limited efficacy in preventing TB disease, it is highly effective in reducing severe forms of TB in children like meningitis and disseminated TB. It also has a role in leprosy prevention

Usage: Administered as a single dose to neonates at birth or as soon as possible thereafter. Delays in vaccination increase the risk of exposure to TB or leprosy.

Special Considerations: Safe to co-administer with the hepatitis B vaccine at birth. If missed at birth, catch-up vaccination for unvaccinated infants and children is beneficial and should be done promptly. In settings with low TB incidence (e.g., future Fiji), vaccination may target neonates with known risk factors (e.g., close contacts with a history of TB or leprosy).

HIV Considerations: All well newborn babies will get BCG vaccine, regardless of the mother's serological status at birth. BCG should be delayed if the baby is critically ill and on the advice of the paediatricians only.

Operational Notes: To maximize coverage, open multi-dose vials even if vaccine wastage occurs. BCG vaccination is critical to reducing mortality in children under 5 years old in high TB-burden settings. New TB vaccines more effective in TB prevention are on the pipeline and are expected to be introduced in the market within the next 5-10 years.

9.2 INFECTION CONTROL (IC)

Specific populations and specific sites have a higher risk of TB transmission and progressing to disease once infected. As mentioned in the previous chapters, these groups include people living with HIV infection, health workers, children, and others in settings with a high

risk of transmission of *M. tuberculosis*. Community transmission of drug-resistant bacteria (as opposed to acquired resistance secondary to inadequate treatment) is the dominant mechanism sustaining the global transmission of DR-TB.

Interrupting the transmission is key to achieving global targets for TB elimination. This is mainly based on quick identification of TB sources, treatment of them and limiting person-to-person transmission by reducing exposition and concentration of infectious particles in the air of households and health facilities

Effective infection and prevention control measures are a critical part of the quality of health services. Infection and prevention control measures are divided into three complementary categories:

TABLE 9.1 MAIN GROUPS OF IC MEASURES SORTED BY PRIORITIES.

LEVEL OF PRIORITY	KIND OF MEASURE	OBJECTIVE
FIRST	Administrative control	Reduce exposure of staff and patients to <i>Mtb</i> A set of administrative controls is the first and most important component of any infection prevention and control strategy. These key measures comprise specific interventions aimed at reducing exposure and therefore reducing transmission of <i>Mtb</i> . They include triage, patient separation systems, and prompt initiation of effective treatment. The key and most basic administrative controls are: 1. Triage of people with TB signs and symptoms, or with TB disease, is recommended to reduce <i>M. tuberculosis</i> transmission to health workers (including community health workers (CHW), persons

		<p>attending healthcare facilities or other persons in settings with a high risk of transmission.</p> <p>2. Respiratory separation/isolation of people with presumed or demonstrated infectious TB is recommended to reduce M. tuberculosis transmission to health workers or other persons attending healthcare facilities.</p> <p>3. Prompt initiation of effective TB treatment of people with TB disease is recommended to reduce M. tuberculosis transmission to relatives, health workers, persons attending health care facilities or other persons in settings with a high risk of transmission. Delays in the initiation of effective TB treatment increase the probability of onward transmission of the disease in the community.</p> <p>4. Active case finding among contact exposed to TB (e.g. household) and TPT</p> <p>5. Existence of basic Infection Control plans in health care facilities with allocated tasks and staff in charge.</p>
SECOND	Environmental control	<p>Reduce concentration of infectious particles in closed environments. The air presents less Mtb concentration by the use of three principles: dilution, filtration, and disinfection. This is achieved by using special ventilation systems to maximise airflow rates or filtration, and by using germicidal ultraviolet (GUV) systems to disinfect the air. The current WHO recommendations for environmental controls are:</p> <p>1. Enhance ventilation systems (including natural, mixed-mode,</p>

		<p>mechanical ventilation like fans, and recirculated air through high-efficiency particulate air (HEPA) filters) are recommended</p> <p>2. Upper-room germicidal ultraviolet (GUV) systems are recommended to reduce Mtb transmission to health workers, in sites with limited ventilation and high risk of exposure like laboratories.</p>
THIRD	Personal respiratory protection	<p>Protect health care workers and relatives in environments where infectious particles cannot be reduced Within the framework of a respiratory protection program, N95 and FFP3 and FFP5 respirators are recommended to reduce Mtb to health workers, persons attending health care facilities, or other persons in settings with a high risk of transmission.</p>

9.3 TUBERCULOSIS PREVENTIVE THERAPY (TPT)

TPT is an antibiotic regimen that destroys TB bacteria that may be dormant inside the body of an exposed person. By eliminating them, the risk of progression to disease is greatly diminished. In fact, with TPT, the risk of progression to tuberculosis is reduced by 90%. The benefits of preventing TB with TPT include simpler treatments and regimens, and limits transmission of TB in the community. This is a key intervention towards TB elimination.

9.3.1 RISK GROUPS, DIAGNOSIS OF TB INFECTION AND BASIC INTERVENTIONS

BOX 9.1 PRIORITY POPULATIONS THAT WOULD BE CONSIDERED ELIGIBLE CANDIDATES FOR TPT, ONCE ACTIVE TB HAS BEEN RULED OUT ARE:

1. People living with HIV (PLHIV). HIV infection in recent years has become one of the key factors influencing TB dynamics in Fiji, being the main cause of death in this group. In the case of PLHIV, if active TB is ruled out, the risk of developing TB is considered so high that

starting TPT is justified whether you have been exposed or not to a known source of TB, and with no need for IGRAs or TST according to international recommendations.

2. Children <15 years exposed to susceptible or resistant TB in the family or close environment. Active search is prioritised in children exposed to TB (contacts of patients) to make a diagnosis in the early stages of the disease or as possible candidates for TPT with no need for IGRAs or TST according to international recommendations.

3. Pregnant women exposed to susceptible or resistant TB in the family or close environment. This population should be considered as TPT candidates in case of known exposure to TB, and presenting TST or IGRAs is recommended whenever possible

4. Other immunosuppressed people due to medications (e.g., biological therapy) or diseases (cancer, previous transplant, kidney failure on dialysis, etc.). In the rest of immunosuppressed patients due to medication or diseases, diagnosis of tuberculosis infection by TST or IGRAs is recommended whenever possible.

5. Others. people and groups with greater exposure or vulnerability who could individually be candidates for TPT:

- a. High exposure to TB: health workers and prison workers, people deprived of liberty, migrants, and homeless people
- b. High risk of TB for other reasons: pneumoconiosis, silica workers, fibrotic lesions on the CXR.

These higher-risk cases or situations will be assessed individually in accordance with the regulations of each centre, national occupational risk regulations, and the availability of resources. they could be considered directly as eligible candidates for TPT after ruling out disease. To rule out active disease, in addition to screening for signs and symptoms, a chest X-ray (Rx) is recommended.

Diagnosis of TB infection

- TB infection could be screened using TST and IGRAs. Generally, both tests present similar sensitivity. IGRAs are more expensive but are more specific in the case of BCG vaccination and need only 1 visit for obtaining a result. TPT could also be directly provided in PLHIV and children in Fiji without the necessity of TB

infection (TBI) confirmation due to the high risk of infection in this population and the high mortality among those presenting TB-HIV.

- The critical point before TPT is **ruling out active TB disease** before initiation, including clinical assessment, CXR, and sometimes other tests like GeneXpert. Rule out active TB disease can be challenging in the badly immunosuppressed patient (e.g., <100 CD4) and children <5 y/o, due to extrapulmonary and systemic presentation, sometimes low symptomatic. If TB disease is effectively ruled out, the chances of creating resistance while on TPT are marginal.
- WHO has recently endorsed new antigen-based tuberculin skin tests for TB infection detection using Mtb-specific antigens (ESAT6 and CFP10). There are 3 types: C-Tb (India), C-TST (China) and Dia skintest (Russian Federation). All have a similar requirement as regular TST but similar specificity as IGRAs at a reduced price.

TABLE 9.2_COMPARISON OF THE 2 INDIRECT TYPES OF TESTS FOR TB INFECTION DIAGNOSIS

Test	TST (Mantoux)	IGRA
Technique	Intradermal injection of Tuberculin	Blood is drawn for testing
Mechanism	Delayed-type hypersensitivity reaction if the person has been infected with Mtb	measures the immune response to the TB bacteria in whole blood
N. of visits	The person needs to return for reading	No need for the person to return to complete the test
Time to results	48-72hrs	24hrs
Results	Subject to reader variability. Reported in mm. 0 mm: negative. 5 mm: positive in PLHIV, children, people with	Absolute result but can have indeterminate or

	silicosis and other immunosuppressed. >10mm: Positive	borderline results
BCG	Can be affected by BCG (false positive)	No effect from BCG
Infrastructure requirements	Minimal. Intradermal injection, no laboratory requirements	Moderate. Venous blood sample and laboratory
Can differentiate between TB infection and disease?	NO	NO
Does a negative result exclude TB infection?	NO	NO

9.3.2 REGIMENS FOR TB PREVENTIVE THERAPY [TPT]

There are several regimens with high effectiveness for preventing TB recently documented, being shortened and better accepted by the people exposed to TB (including DR-TB contacts). In Fiji, the first line regimen to TPT is 3HP with other regimens recommended in specific circumstances.

OPTION 1: 3HP ONCE PER WEEK REGIMEN (12 DOSES)

- Composition: 3 months with Isoniazid + Rifapentine (3HP) once a week:
- if possible, **on an empty stomach**, for 3 months and with directly observed treatment (DOT).
- Indications and justification:
 - Adults and children >2 years exposed to TB, PLHIV and other immunosuppressed individuals with no specific contraindication.
 - Simple treatment in 12 total doses, useful in a significant number of the population with good tolerance, lower toxicity and a better rate of completed treatments (8). In

PLHIV on ART, there is no need to adjust the dose of dolutegravir (DTG, first-line antiretroviral) (9, 10). In comparative studies in all the above populations, 3HP obtains better adherence rates, fewer serious adverse events and less hepatotoxicity than 6H regimens.

- Pyridoxine (Vitamin B6):
 - Children >2 years: A pyridoxine supplement containing isoniazid (5-10 mg/day in children under 5 years and 25 mg/day in children over 5 years) may be added during TPT.
 - Adults: Generally, not necessary except in situations of malnutrition, PLHIV, pregnancy/breastfeeding, renal failure, DM, or alcohol abuse. The recommended dose is 25–50 mg/day.
- Dosage:
 - Adults and >13 years: H 900 mg and P 900 mg
 - Children 2-15 years: See weight range in Table 9.3.
 - ***In children <2 years, the 3HP regimen, at the time of writing this manual, is not studied and cannot be recommended.***
- Formulations:
 - Fixed dose combinations (FDC) of HP (300mg + 300mg): These are tablets containing H and P. Whenever possible, use combination medications as this reduces the total number of tablets and makes it easier to take. There is a dispersible formulation of HP (150mg + 150mg) under study, but not on the market at the time of writing this manual.
 - Loose drugs: Necessary if there are no combinations.
 - Dispersible combination medication: At the time of writing this manual, there is a dispersible combination formulation under study but still on the market. If there is no contraindication, it would be considered the standard for small children due to ease of taking.
- Missed doses: Since this is a weekly treatment, if you notice any failures, inform the person being treated so that they can come and take the dose as soon as possible. See tables below for suggested actions in this and other circumstances.

TABLE 9.3 RECOMMENDED WEEKLY DOSE BY WEIGHT RANGE FOR TPT WITH 3HP REGIMEN (ISONIAZID AND RIFAPENTINE WEEKLY) USING COMBINED MEDICATIONS OR, FAILING THAT, SINGLE MEDICATIONS (1, 7)

	Drug formulation	10-15kg	16-23kg	24-30kg	>31kg	>13 years old
Fixed dose combinations	HP (150mg/150mg) td*	2	3	4	--	--
	HP (300mg/300mg)	1	1.5	2	3	3
Loose drugs	H 100mg td	3	5	6	7	9
	H 300 mg	---	---	2	3	3
	P 150 mg	2	3	4	5	6
	P 300 mg	1	1.5	2	2.5	3

Source: WHO operational handbook on tuberculosis. Module 1: prevention - tuberculosis preventive treatment, second edition. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO. H: isoniazid P: Rifapentine; DT: dispersible Tablet * Fixed dose combination HP 150/150 dispersible: not available at the time of guideline publication.

TABLE 9.4 MANAGEMENT OF POSSIBLE ADVERSE REACTIONS AFTER TREATMENT WITH 3HP

Side effect	Stop and consider reintroduction with prudence	Stop and do not reintroduce
Flu-like syndrome, attacks of fever, chills and malaise, sometimes with	If it is mild and does not increase, continue treatment and observe closely	If moderate to severe symptoms, consider alternatives

Side effect	Stop and consider reintroduction with prudence	Stop and do not reintroduce
headache, dizziness or bone pain		Non-rifamycin TPT options (such as 6H)
Isolated fever without other symptoms/signs, associated with medications	Consider reintroduction if fever is less than 39°C, but permanently discontinue if fever recurs	If fever >39°C with previous episodes of drug fever
Nausea or vomiting, frequent and/or persistent or episodes of watery stools	Administer antiemetics or antidiarrheal medication Consider reintroducing 3HP with caution once symptoms have resolved	If there is nausea, vomiting, or diarrhoea that requires aggressive rehydration
Skin reactions	Diffuse rash (without vesicles) Diffuse rash with few vesicles	If there are extensive blisters, lesions or ulceration of the mucous membranes there is a high risk of Stevens Johnson syndrome or toxic epidermal necrolysis. Contact a specialist immediately and use steroids
Other hypersensitivity reactions Hypotension, acute bronchospasm, conjunctivitis, Thrombocytopenia	Assess clinical severity of symptoms and if severe consider alternative TPT options without rifamycins	

Side effect	Stop and consider reintroduction with prudence	Stop and do not reintroduce
HEPATITIS, initial symptoms weakness, fatigue, loss of appetite, persistent nausea	Alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) returns to baseline or <2times the upper limits of normal and absence of symptoms	<ul style="list-style-type: none"> · ALT/AST is $\geq 5x$ the upper limit of normal in the absence of symptoms · ALT/AST is $\geq 3x$ the upper limit of normal in the presence of symptoms
PSYCHOSIS, break with reality	Psychiatric evaluation, antipsychotic therapy, pyridoxine	If it is attributable to isoniazid
CONVULSIONS	Discontinue isoniazid pending resolution of seizures, evaluate possible causes of seizures	If it is attributable to isoniazid

Source: Adapted from “WHO operational handbook on tuberculosis. Module 1: prevention - tuberculosis preventive treatment. 2020.”

TABLE 9.5 RELEVANT DRUG INTERACTIONS OF DRUGS USED IN TPT

Rifampicin (R or RIF) and Rifapentine (P or RFP): HIGH drug interaction profile. Potent inducers of Cytochrome P450 and other metabolic pathways. Significant decrease in blood levels of certain drugs that may be rendered inactive. At least 225 major drug interactions described. Plasma concentrations of rifamycins are not usually affected by other drugs. If in doubt, consult online for possible interactions.	
Commonly used drugs:	Reduces blood levels of contraceptives (birth control pills, injections, implants, skin patches and vaginal rings), statins, old and new oral anticoagulants, polyantihypertensives, polyantidepressants and anxiolytics, methadone, oxycodone, phenytoin.

Drugs frequently used in PLHIV	Reduces blood levels of protease inhibitors, dolutegravir, raltegravir, elvitegravir, NVP, etravirine, rilpivirine, maraviroc, cotrimoxazole, azoles
Anti-TB drugs	Reduces blood levels of bedaquiline, pretomanid, fluoroquinolones, ethionamide/protonamide
Isoniazid (H or INH): LOW drug interaction profile. May increase concentration of certain cytochrome P450 enzyme substrates such as phenytoin (increased concentration) and carbamazepine (risk of hepatotoxicity). Alcohol consumption may increase risk of hepatotoxicity or seizures.	
Levofloxacin (Lfx): LOW drug interaction profile. Concomitant use of steroids may increase risk of tendon rupture. Products containing multivalent cations, including antacids, metal cations may decrease absorption. May increase the action of oral anticoagulants (monitor INR). May increase blood glucose levels, monitor blood glucose and need to increase doses of antidiabetics. Avoid concomitant use with Class IA antiarrhythmics (such as quinidine, ajmaline, disopyramide) and Class III (such as amiodarone, dronedarone, sotalol): the proarrhythmic effect may be potentiated by increasing the QT segment (Mfx more than Lfx).	

Source: adapted from Source: WHO operational handbook on tuberculosis. Module 1: prevention - tuberculosis preventive treatment, second edition. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO

OPTION 2: 3HR DAILY FOR SMALL CHILDREN (<2 Y/O) AND PREGNANT WOMEN

- Composition: 3 months with Rifampicin + Isoniazid (3RH) daily
 - Indications and justification:
 - Children under 2 years: Simple daily treatment available in dispersible formulation and with good results in its use. Its usefulness has been demonstrated even in cases where the child's situation is not clear (contact vs. initial minimal TB). Good tolerance. Check that there are no drug interactions with RIF: requires dose adjustment of antiretrovirals or other possible medications that may be induced by cytochrome p450.
 - Pregnant women: Extensive experience of use, considered the standard TPT regimen.
- Included medications and administration method: rifampicin (RIF or R) and isoniazid (INH or H) taken once a day on an empty stomach, for

3 months and with directly observed treatment (DOT) by a health worker or through a family member. In both children and pregnant women, preferably use fixed doses combination (FDC) and in children FDC dispersible formulation.

- **Dosage:**

Children: preferably use dispersible combination drugs. See dose by weight range with combination drugs in Table 9.6.

H or INH: children <2 years, 10 mg/kg/d (range 7-15 mg/d); R or RIF: children <2 years 15 mg/kg/d (range 10–20 mg/kg).

Pregnant women: usual adult dose by weight range according to Table 9.6. H or INH: 5 mg/kg/d; R or RIF: 10 mg/kg/d

- **Pyridoxine (Vitamin B6):** recommended in both groups

Children: associate 5 mg/day of pyridoxine in all children under 2 years of age in TPT that includes H.

Pregnant women: associate 25–50 mg/day.

· **Missed doses:** If you notice any missed doses, tell the person on treatment to take the medication if it is still the same day. If the day has already passed, skip the dose that the person missed and administer the next dose according to the schedule, but do not administer 2 doses at the same time. See Table 8 for suggested actions.

OPTION 3. 1HP ULTRASHORT REGIMEN

- **Composition:** 1 months of daily Rifampentine + Isoniazid (1HP) daily for 28 days
- **Indications and justification:** adults and children >13 y/o regardless of HIV status
- **Dosage:** See dose by weight range with combination drugs in table 9.6. Children: preferably use dispersible combination drugs.

OPTION 4. 4R

- **Composition:** 4 months of daily Rifampicin
- **Indications and justification:** Only use when the other previous regimens cannot be used for any reason (e.g. intolerance). Adults and children >2 y/o regardless of HIV status
- **Dosage:** See dose by weight range with combination drugs in table 9.6. Children: preferably use dispersible combination drugs.

- Consideration: lengthy regimen usually linked to worst adherence and completion.

OPTION 5. 6H

- Composition: 6 months of daily Isoniazid
- Indications and justification: Only use when the other previous regimens cannot be used for any reason (e.g. intolerance). Adults and children >2 y/o regardless of HIV status
- Dosage: See dose by weight range with combination drugs in Table 9.6. Children: preferably use dispersible combination drugs.
- Consideration: Lengthy regimen usually linked to worst adherence and completion. Higher toxicity than the other regimens (isoniazid monotherapy linked to higher hepatotoxicity than in combination to rifamycins)

TABLE 9.6 SUMMARY OF TPT REGIMENS AND DAILY DOSING BY WEIGHT RANGE

	4- <8kg	8- <12kg	12- <16kg	16- <25kg	25- <30kg	31- <45kg	≥45 kg
1HP**							
H 300mg	---	---	---	---	1	1	1
P 150mg	---	---	---	---	4	4	4
P 300mg					2	2	2
3RH							
RH (75/50) dt*	1	2	3	4	----		
RH (150/75)				2	2	3	4
6H							
H 100mg dt*	0.5	1	1.5	2	3		
H 300mg	---	---	---	---	1	1	1

4R							
RH (75/50) dt*	1	2	3	4	---	---	---

Source: WHO operational handbook on tuberculosis. Module 1: prevention - tuberculosis preventive treatment, second edition. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO dt: dispersible tablet *In children <16 kg, since there are no R dispersible tablets, use RH (75/50) dispersible tablets **1HP only indicated for >13 years. Daily HP dose (300/600) regardless of weight.

OPTION 6. 6LFX TPT REGIMEN FOR PEOPLE EXPOSED TO DR-TB

There is 1 regimen quinolone-based to prevent the development of the disease in people exposed to TB with resistance to Rifampicin. This is highly effective in eliminating resistant bacteria that may be in a metabolically inactive state within the body of the exposed person. These are regimens where levofloxacin (Lfx) is administered daily in DOT for 6 months. Therefore, it is essential to know if the index case with DR-TB is sensitive to quinolones. If the case is resistant to quinolones, these regimens are not valid, and an expert physician should assess the possibility of an alternative regimen.

- Priority populations: PLHIV, children <15 years old and pregnant people and other immunosuppressed people exposed to resistant TB.
- Regimen: 6 months of daily Lfx
- Doses

Children: 15-20 mg/kg/d. For easier dosing use Table 9.7 for doses by weight range. Preferential use of dispersible medication, 100 mg tablet that dissolves in water according to the weight range. The highest standard dose limit is 1000 mg/day

Adults: 750-1000 mg/d. The highest standard dose limit is 1000 mg/day.

Formulations: There are 250 mg, 500 mg and 750 mg tablets. Use the formulation with the least number of tablets possible. In small children, preferably use 100 mg dispersible forms. Dilute the dispersible medication in 10 ml of water per tablet. Using adult tablets (non-dispersible), dilute in water also in 10 mg. Note that when using adult tablets, the number of millilitres is lower, as the tablets have a higher medication content.

Storage: Lfx can be kept at 15-25°C; at higher ambient temperatures, it is better to keep them in the refrigerator. Dispersible medications, once diluted, can be kept at 15-25°C for 3 days without losing their properties or in the refrigerator for 2 weeks. It can also be kept frozen for up to 6 months.

TABLE 9.7 DAILY DOSING BY WEIGHT RANGE FOR TPT WITH 6LFX OR 6MFX REGIMEN IN CONTACTS EXPOSED TO DR-TB

TPT regimens and drug formulations	No. of tablets or quantity of suspension by body weight band												
	3-5.9 kg (< 3 months)	3-5.9 kg (≥ 3 months)	6-9.9 kg (< 6 months)	6-9.9 kg (≥ 6 months)	10-14.9 kg	15-19.9 kg	20-24.9 kg	25-29.9 kg	30-34.9 kg	35-39.9 kg	40-44.9 kg	45-49.9 kg	≥ 50 kg
Six months of daily levofloxacin (6Lfx)													
Lfx 100 mg dt	0.5	1	1	1.5	2	2.5	3	3.5	-	-	-	-	-
Lfx 250 mg tab	0.25 (2.5 mL ^d)	0.5 (5 mL ^d)	0.5 (5 mL ^d)	1 (10 mL ^d)	1	1.5	1.5	2	2	2	2	2	3
Lfx 500 mg tab	-	-	-	-	-	-	-	1	1	1	1	1	1.5

dt: dispersible tablet. Source: WHO operational handbook on tuberculosis. Module 1: prevention - tuberculosis preventive treatment, second edition. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.

9.3.3 PRACTICAL TIPS IN TPT MANAGEMENT INTERRUPTIONS AND COMPLETION CRITERIA

Follow-up and surveillance after TPT. Record TPT start/stop dates and outcome in the TPT register and link to the index TB case number. Schedule post-TPT symptom checks at 6, 12, 18 and 24 months to detect incident TB early; if TB is diagnosed, classify as “TPT failure” and manage per TB disease guidelines. Use these data to

monitor program performance (e.g., initiation, completion, and post-TPT TB rates).

Management of interruptions and completion criteria: see tables below

TABLE 9.8 MANAGEMENT OF INTERRUPTIONS BY DURATION FOR DIFFERENT TPT REGIMENS

TPT regimen	Duration of treatment interruption	Next step
3HP	1 weekly dose missed	<p>If the missed dose is remembered within the next 2 days, continue to take remaining doses according to the original schedule.</p> <p>If the missed dose is remembered > 2 days later, take the missed dose immediately, and change the schedule for weekly intake to the day the missed dose was taken, until treatment completion. This will avoid 2 weekly doses being taken fewer than 4 days apart.</p>
	> 1 weekly dose missed	<p>If treatment interruption occurred after at least 9 doses were taken within 12 weeks of starting, continue and complete the remaining doses, thus prolonging the total treatment duration to a maximum of 112 days.</p> <p>If ≥ 4 weekly doses are missed, consider re-starting the full TPT course.</p> <p>If an individual has difficulty in adhering to a weekly routine, consider discontinuing 3HP and offering an alternative regimen</p>

		with daily dosing.
3HR, 4R, 6H, 6Lfx	< 2 weeks	<p>Resume TPT and add the number of days of missed doses to the total treatment duration.</p> <p>Do not change the scheduled date of the next follow-up visit, but postpone the last follow-up visit by the number of extra days to compensate for missed doses. For example, if a child on 3HR misses 3 days of treatment, continue TPT for a total of 3 months + 3 days from the date of start.</p>
	≥ 2 weeks	<p>If treatment interruption occurred after more than 80% of doses in the regimen had been taken, continue and complete the remaining treatment as per the original plan.</p> <p>If less than 80% of doses in the regimen were taken, and the treatment course can still be completed within the expected treatment duration + 33% additional time, continue and complete the remaining treatment as per the original plan. For example, if an adult on 6H had taken only 120 doses by month 6, the remaining 62 doses can be taken in the next 2 months, without exceeding the 239-day limit.</p> <p>If < 80% of doses in the</p>

		regimen were taken, and the treatment course cannot be completed within the expected time, consider re-starting the full TPT course. A shorter regimen would be preferable.
IHP	≤ 7 doses missed	Continue and complete the remaining doses, thus prolonging the total treatment duration to a maximum of 6 weeks (42 days from starting TPT).
	> 7 doses missed	If < 7 consecutive doses were missed, consider re-starting the complete course of IHP regimen.

Source: WHO operational handbook on tuberculosis. Module 1: prevention - tuberculosis preventive treatment, second edition. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.

TPT outcomes criteria:

- **Treatment completed:** should be assessed based on the consumption of at least 80% of doses of each regimen as per the criteria listed in the table below
- **Failed:** development of TB disease any time while on TPT;
- **Died:** death from any cause while on TPT;
- **Lost to follow-up:** interruption of TPT for a duration that precludes completion of treatment in the maximal time possible (at thresholds in the previous Table); TPT discontinued by a health-care worker: due to toxicity, other adverse events or drug-drug interactions, with or without re-starting or switching the regimen; and
- **Not evaluated:** such as records lost, transfer to another health facility with record of TPT completion.

In future, when TPT would be fully scaled up in Fiji with multiple cases, a specific and adapted TPT R&R system will be considered

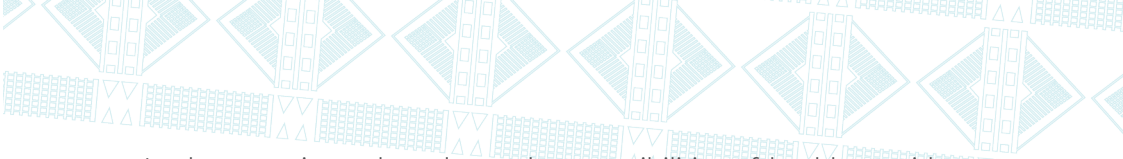
TABLE 9.9 CRITERIA FOR DETERMINING COMPLETION OF DIFFERENT TPT REGIMENS

TPT regimen	Total duration (months)	Expected number of doses	80% of recommended doses (days)	Extended time for treatment completion (days) (treatment duration +33% additional time)
6H (daily)	6	182	146	239
3HR (daily)	3	84	68	120
3HP (weekly)	3	12	10	112
4R (daily)	4	120	96	160
1HP (daily)	1	28	23	40
6Lfx (daily)	6	182	146	239

Source: WHO operational handbook on tuberculosis. Module 1: prevention - tuberculosis preventive treatment, second edition. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.

Organising the package of interventions for the delivery of TPT:

For TB prevention to become a national reality, TB prevention services must be offered in an integrated and coordinated manner with relevant service delivery sites such as TB treatment centres, maternal and child health services centres, or community health centres. Sometimes TPT services may be offered in malnutrition centres, prisons, or refugee camps (formal or informal).



In these settings, the roles and responsibilities of health providers, community health workers, and key stakeholders in the assessment of exposed contacts, eligibility, and initiation of TPT need to be determined.

During the process of TPT expansion, the capacity and availability of health workers should be assessed and additional needs for the national scale-up of TPT services should be considered. Community health workers and other networks (such as former TB patients, the index case themselves, or religious associations) who could contribute to the provision of TPT services and support to individuals.

TABLE 9.10 ACTIONS FOR ACTIVE TB CASE FINDING AND IDENTIFICATION OF TPT CANDIDATES: THE 4 STEPS TO PREVENT TB IN THE COMMUNITY

STEPS	ACTIONS AND DETAILS
1. Active or passive search for TB cases or TPT candidates	<ul style="list-style-type: none"> • Interview with the TB patient: Contact census and prioritisation • Initial assessment of contacts or PLHIV in the SAI: Risk group, signs or symptoms • Outcome: Candidate for TPT, presumed TB, not a candidate for TPT or presumed TB • Filling out the active search and TPT control card
2. Medical assessment and selection of TPT candidates	<ul style="list-style-type: none"> • Physician rules out TB disease and confirms eligibility for TPT at the UNAP or home • If there is a presumption of TB (signs/symptoms/examination): complete diagnostic study and re-evaluation
3. Prescription of TPT and First Visit	<ul style="list-style-type: none"> • Selection of the regimen and dose by weight and category. Record on the active search and TPT control card • Medical history and concomitant medication • Patient counselling and adherence options, including DOT • Scheduling for DOT and follow-up medical visits, including the end of treatment
4. Follow-up of the Person on TPT	<ul style="list-style-type: none"> • DOT: weekly or daily depending on the type of regimen • At each visit: Counselling, appearance of TB symptoms, weight and dose adjustment, adverse effects, adherence, comorbidities • Follow-up visit and final visit (3rd visit): Treatment outcome • Record the outcome on the TPT control card and post-treatment follow-up.

Source: Adapted from WHO operational handbook on tuberculosis. Module 1: prevention - tuberculosis preventive treatment, second edition. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO

REFERENCES

REFERENCES

- Broger, T., Koepfel, L., Huerga, H., Miller, P., Gupta-Wright, A., Blanc, F. X., ... Fielding, K. (2023). Diagnostic yield of urine lipoarabinomannan and sputum tuberculosis tests in people living with HIV: A systematic review and meta-analysis of individual participant data. *The Lancet Global Health*, 11(6), e903–e916. [https://doi.org/10.1016/S2214-109X\(23\)00123-7](https://doi.org/10.1016/S2214-109X(23)00123-7)
- Chiang, S., Graham, S., Schaaf, H., Marais, B., Sant'Anna, C., Sharma, S., ... et al. (2023). Clinical standards for drug-susceptible TB in children and adolescents. *The International Journal of Tuberculosis and Lung Disease*, 27(8), 584–598. <https://doi.org/10.5588/ijtld.23.0017>
- Conradie, F., Badat, T., Poswa, A., Rajaram, S., Kooverjee, S., Maartens, G., ... Phillips, P. (2025). BEAT Tuberculosis: A randomized controlled trial of a 6-month strategy for rifampicin-resistant tuberculosis. *medRxiv*. <https://doi.org/10.1101/2025.05.14.24307141>
- Conradie, F., Bagdasaryan, T. R., Borisov, S., Howell, P., Mikiashvili, L., Ngubane, N., ... et al. (2022). Bedaquiline–pretomanid–linezolid regimens for drug-resistant tuberculosis. *New England Journal of Medicine*, 387(9), 810–823. <https://doi.org/10.1056/NEJMoa2117764>
- Davies, P. D., & Pai, M. (2008). The diagnosis and misdiagnosis of tuberculosis. *The International Journal of Tuberculosis and Lung Disease*, 12(11), 1226–1234.
- Dooley, K. E., Chaisson, R. E., & Tuberculosis and Diabetes Working Group. (2009). Tuberculosis and diabetes mellitus: Convergence of two epidemics. *The Lancet Infectious Diseases*, 9(12), 737–746. [https://doi.org/10.1016/S1473-3099\(09\)70282-8](https://doi.org/10.1016/S1473-3099(09)70282-8)
- Dodd, P. J., Yuen, C. M., Becerra, M. C., Revill, P., Jenkins, H. E., & Seddon, J. A. (2018). Potential effect of household contact management on childhood tuberculosis: A mathematical modelling study. *The Lancet Global Health*, 6(12), e1329–e1338. [https://doi.org/10.1016/S2214-109X\(18\)30401-7](https://doi.org/10.1016/S2214-109X(18)30401-7)
- Drain, P. K., Bajema, K. L., Dowdy, D., Dheda, K., Naidoo, K., Schumacher, S. G., ... et al. (2018). Incipient and subclinical tuberculosis: A clinical review of early stages and progression of infection. *Clinical Microbiology Reviews*, 31(4), e00021-18. <https://doi.org/10.1128/CMR.00021-18>

Framework for collaborative action on tuberculosis and comorbidities. (2022). Geneva: World Health Organization. <https://www.who.int/publications/i/item/9789240055056>

Golub, J. E., Mohan, C. I., Comstock, G. W., & Chaisson, R. E. (2005). Active case finding of tuberculosis: Historical perspective and future prospects. *The International Journal of Tuberculosis and Lung Disease*, 9(11), 1183–1203.

Harries, A. D., Satyanarayana, S., Kumar, A. M. V., Nagaraja, S. B., Isaakidis, P., Malhotra, S., ... et al. (2011). The looming epidemic of diabetes-associated tuberculosis: Learning lessons from HIV-associated tuberculosis. *The International Journal of Tuberculosis and Lung Disease*, 15(11), 1436–1445.

Hesseling, A. C., Johnson, L. F., Jaspan, H., Cotton, M. F., Whitelaw, A., Schaaf, H. S., ... et al. (2006). Bacille Calmette-Guérin vaccine-induced disease in HIV-infected and HIV-uninfected children. *Clinical Infectious Diseases*, 42(4), 548–558. <https://doi.org/10.1086/499953>

Hesseling, A. C., et al. (2008). Consensus statement on the revised World Health Organization recommendations for BCG vaccination in HIV-infected infants: Submitted on behalf of the BCG Working Group, Child Lung Health Section, International Union Against Tuberculosis and Lung Disease, 38th Union World Conference on Lung Health, Cape Town, 8–12 November 2007. *The International Journal of Tuberculosis and Lung Disease*, 12(12), 1376–1379.

Koroituku, T., Finau, E., & Mataika, R. (2023). *Tuberculosis epidemiology in Fiji, 2014–2022: Trends, treatment outcomes, and mortality*. *Fiji Journal of Public Health*, 5(2), 45–56. <https://doi.org/10.xxxx/fjph.2023.05.02>

Krutikov, M., Faust, L., Nikolayevskyy, V., & others. (2022). The diagnostic performance of novel skin-based in-vivo tests for tuberculosis infection compared with purified protein derivative tuberculin skin tests and blood-based in vitro interferon- γ release assays: A systematic review and meta-analysis. *The Lancet Infectious Diseases*, 22(2), 250–264. [https://doi.org/10.1016/S1473-3099\(21\)00495-4](https://doi.org/10.1016/S1473-3099(21)00495-4)

Mave, V., Paradkar, M., Conradie, F., Gupta, A., Avihingsanon, A., Meintjes, G., & Chaisson, R. E. (2025). Tuberculosis disease among people with HIV: Therapeutic advances. *The Lancet HIV*. [https://doi.org/10.1016/S2352-3018\(25\)00123-4](https://doi.org/10.1016/S2352-3018(25)00123-4)

Meintjes, G., Brust, J. C., Nuttall, J., & Maartens, G. (2019). Management of active tuberculosis in adults with HIV. *The Lancet HIV*, 6(7), e463–e474. [https://doi.org/10.1016/S2352-3018\(19\)30128-5](https://doi.org/10.1016/S2352-3018(19)30128-5)

Meintjes, G., Lawn, S. D., Scano, F., Maartens, G., French, M. A., Worodria, W., & Colebunders, R. (2008). Tuberculosis-associated immune reconstitution inflammatory syndrome: Case definitions for use in resource-limited settings. *The Lancet Infectious Diseases*, 8(8), 516–523. [https://doi.org/10.1016/S1473-3099\(08\)70184-1](https://doi.org/10.1016/S1473-3099(08)70184-1)

Mitchison, D. A., & Davies, P. D. (1978). Bactericidal mechanisms in short-course chemotherapy. *Bulletin of the International Union Against Tuberculosis*, 53, 254–259.

Nyang'wa, B.-T., Berry, C., Kazounis, E., Motta, I., Parpieva, N., Tigay, Z., & others. (2022). A 24-week, all-oral regimen for rifampin-resistant tuberculosis. *New England Journal of Medicine*, 387(25), 2331–2343. <https://doi.org/10.1056/NEJMoa2201128>

Odone, A., Roberts, B., Dara, M., Van Den Boom, M., Kluge, H., & McKee, M. (2018). People- and patient-centred care for tuberculosis: Models of care for tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 22(2), 133–138.

Pai, M., Behr, M. A., Dowdy, D., Dheda, K., Divangahi, M., Boehme, C. C., & others. (2016). Tuberculosis. *Nature Reviews Disease Primers*, 2, 16076. <https://doi.org/10.1038/nrdp.2016.76>

Pai, M., Dewan, P. K., & Swaminathan, S. (2023). Transforming tuberculosis diagnosis. *Nature Microbiology*, 8(5), 756–759. <https://doi.org/10.1038/s41564-023-01345-y>

Pooranagangadevi, N., & Padmapriyadarsini, C. (2022). Treatment of tuberculosis and the drug interactions associated with HIV-TB co-infection treatment. *Frontiers in Tropical Diseases*, 3, 834013. <https://doi.org/10.3389/ftd.2022.834013>

Qin, Z. Z., Sander, M. S., Rai, B., Titahong, C. N., Sudrungrot, S., Laah, S. N., & others. (2019). Using artificial intelligence to read chest radiographs for tuberculosis detection: A multi-site evaluation of the diagnostic accuracy of three deep learning systems. *Scientific Reports*, 9(1), 15000. <https://doi.org/10.1038/s41598-019-51503-3>

Raftery, A., Tudor, C., True, L., & Navarro, C. (2018). Nursing guide for managing side effects to drug-resistant TB treatment. *International*

Council of Nurses (ICN) & Curry International Tuberculosis Center (CITC).

Rabie, H., & Taljaard, J. (2024). Improving tuberculosis diagnosis in adults with HIV through Urine-Xpert Ultra. *The Lancet Global Health*, 12(12), e1917–e1918. [https://doi.org/10.1016/S2214-109X\(24\)00356-2](https://doi.org/10.1016/S2214-109X(24)00356-2)

Richards, A. S., Sossen, B., Emery, J. C., Horton, K. C., Heinsohn, T., Frascella, B., & others. (2023). Quantifying progression and regression across the spectrum of pulmonary tuberculosis: A data synthesis study. *The Lancet Global Health*, 11(5), e684–e692. [https://doi.org/10.1016/S2214-109X\(23\)00123-7](https://doi.org/10.1016/S2214-109X(23)00123-7)

Sharma, S. K., Mohan, A., & Kohli, M. (2021). Extrapulmonary tuberculosis. *Expert Review of Respiratory Medicine*, 15(7), 931–948. <https://doi.org/10.1080/17476348.2021.1915780>

TAG. (2024). An activist's guide to rifapentine TB preventive treatment: 3HP and 1HP. Treatment Action Group.

Tuberculosis and diabetes: Invest for impact (2023). World Health Organization.

Turkova, A., Wills, G. H., Wobudeya, E., Chabala, C., Palmer, M., Kinikar, A., & others. (2022). Shorter treatment for nonsevere tuberculosis in African and Indian children. *New England Journal of Medicine*, 386(10), 911–922. <https://doi.org/10.1056/NEJMoa2109867>

UNAIDS. (2020). HIV diagnostic algorithm: Technical update.

Van Deun, A., Decroo, T., Piubello, A., De Jong, B., Lynen, L., & Rieder, H. (2018). Principles for constructing a tuberculosis treatment regimen: The role and definition of core and companion drugs. *International Journal of Tuberculosis and Lung Disease*, 22(3), 239–245.

WHO. (2013). Definitions and reporting framework for tuberculosis – 2013 revision: Updated December 2014 and January 2020. World Health Organization.

WHO. (2018). BCG vaccine: WHO position paper – February 2018. *Relevé Épidémiologique Hebdomadaire*, 93(8), 73.

WHO. (2019). WHO guidelines on tuberculosis infection prevention and control: 2019 update. World Health Organization.

WHO. (2021). WHO consolidated guidelines on tuberculosis. Module 3: Diagnosis – Rapid diagnostics for tuberculosis detection, 2021 update. World Health Organization.

WHO. (2022a). *Primary health care measurement framework and indicators: Monitoring health systems through a primary health care lens*. World Health Organization. <https://www.who.int/publications/i/item/9789240062684>

WHO. (2022b). WHO consolidated guidelines on tuberculosis. Module 4: Treatment – Drug-resistant tuberculosis treatment, 2022 update. World Health Organization.

WHO. (2022c). WHO operational handbook on tuberculosis. Module 5: Management of tuberculosis in children and adolescents. World Health Organization.

WHO. (2022d). Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations. World Health Organization.

WHO. (2022e). Rapid communication: TB antigen-based skin tests for the diagnosis of TB infection. World Health Organization.

WHO. (2022f). Management of drug-resistant tuberculosis in pregnant and peripartum people: A field guide. The Sentinel Project for Pediatric Drug-Resistant Tuberculosis.

WHO. (2023a). Tuberculosis and diabetes: Invest for impact (Information note). World Health Organization.

WHO. (2023b). *Asia Pacific Health Security Action Framework II: 2023–2027*. World Health Organization Regional Office for the Western Pacific. <https://www.who.int/westernpacific/publications>

WHO. (2023c). WHO consolidated guidelines on tuberculosis. Module 1: Prevention – Tuberculosis preventive treatment, second edition. World Health Organization.

WHO. (2024a). Key updates to the treatment of drug-resistant tuberculosis: Rapid communication, June 2024. World Health Organization. <https://doi.org/10.2471/B091232024>

WHO. (2024b). BCG vaccine: WHO position paper, February 2018 – Recommendations. *Vaccine*, 36(24), 3408–3410.

ANNEXES

Annex 1. Tips on the management of patients with high complexity

TB meningitis and TB drugs penetration in the central nervous system

In general, the therapeutic regimen is similar to pulmonary TB. Disseminated, CNS and osteoarticular TB tend to need 12 months. When there is TB in the Central nervous system (CNS), the blood-brain barrier blocks the entrance of many drugs and substances. Frequently treatment needs to be individualised to improve survival and limit disability. Steroids, drugs at high dose, use of iv medication and use of drugs with high blood-brain barrier penetration might be needed to select an intensive phase to assure patients survival:

- **HIGH** CNS Penetration: Linezolid, Moxifloxacin, Levofloxacin, Cycloserine, Ethionamide, Bedaquiline, Imipenem–Cilastatin, Pyrazinamide
- **VARIABLE** CNS Penetration depending on meningeal inflammation: Amikacin, high dose Isoniazid, high dose Rifampicin, Streptomycin
- **LOW** CNS Penetration: Ethambutol, Clofazimine, Clavulanic acid
- **UNKNOWN** CNS Penetration: Delamanid and Pretomanid. There are no current formal studies but with limited patient experiences apparently both might have a role in CNS TB.

The critically ill TB patient

A. Organ location:

- Central nervous system, miliary, pericarditis. Disseminated TB is the presentation of TB in multiple organs at the same time with blood dissemination. In case of TB affects the central nervous system and being critically ill consider an individual management comprising drugs with high penetration of the blood-brain barrier like FQ, Lzd, Cs, Eth, carbapenems and Bdq. Intravenous medication can be considered and the use of high doses of INH and RIF.
- Advanced TB stages with important organ destruction: e.g. big and multiple cavities with patterns of lung destruction leading to respiratory failure
- Advanced disease with wasting syndrome, anaemia, and malnutrition

B. Complicated by the bacilli pattern of resistance

- Amplified patterns of resistance that might reduce the patient prognosis or capacity to be treated

C. Host conditions

- Due to low immunity (HIV infection, children, malnutrition).
- Co-infections: TB-HIV with opportunistic diseases (on top of low immunity), TB with pneumonia or other Mycobacteria superinfections, TB-COVID-19, hepatitis B or C or other parasitic diseases.
- Co-morbid conditions: TB-Diabetes with renal failure, TB in the elderly, alcohol and/or drug use, mental disease

Complications after TB treatment

- Associated with delayed diagnosis; patients diagnosed in advanced stages of disease present higher risk of complications, side effects, development of resistance and dying.
- Eventually even cured, after important levels of lung destruction, patients will permanently live with lung disability. Early diagnosis and treatment are important not only to avoid community transmission but to prevent disability and long-term sequela.
- Pulmonary impairment after tuberculosis is responsible for an important burden of disease and disability.

1. Patients with big cavities or emphysema patterns after cure:

a. Will present different levels of respiratory failure limiting their activity and should be managed permanently as a chronic bronchitis patient including B2 agonist (long and short activity), Ipratropium bromide, nebulized corticoids or long-term home oxygen, etc

b. The reduced vascularity of damaged tissues, cavities, scars or destroyed lungs is a suitable environment where multiple infections can thrive: atypical mycobacteria, fungus, and other bacteria. Community pneumonia and Aspergillus infections are very frequent and more complicated to be treated than in the regular population. In patients with lobes or lung collapse, present an increased risk of TB relapse, provided that these are environments where drugs do not penetrate as well as in normal tissues: bacilli can remain alive. TB re-infection is a possibility, especially in household outbreaks. Patients with previous lung damage are more vulnerable.

2. Extrapulmonary cases can present as well important disability depending on the location and severity of the damage. Typical examples are:

- a. TB meningitis if not treated on time, may present important and variable neurological deficits
- b. Lymph node TB, especially if affecting the neck and mediastinum may be problematic if, during the healing process, fistula and tunnelling were created. These abnormal spaces tend to become infected by common skin pathogens (like *Staphylococcus aureus*) if there is communication with the exterior.
- c. TB affecting bone and joints may present long-term sequelae if there are patterns of destruction or lytic lesions. The most typical one is hyperkyphosis or hump, sometimes needing stabilisation and multiple surgeries.

ANNEX 2. WEIGHT-BASED DOSING OF MEDICINES USED IN MULTIDRUG-RESISTANT TB REGIMENS, ADULTS AND CHILDREN

Group A medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	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	≥70 kg	Comments
		kg	kg	kg	kg	kg	kg	kg	kg	kg	kg	
Levofloxacin (Lfx)	100 mg dt (10 mg/mL)	5 mL (0.5 dt)	1	1.5	2	3	–					
	250 mg tab (25 mg/mL)	2 mL ^b 5 mL (0.5 tab) ^b		1	1.5	2	3	4	–			
	500 mg tab	–		–	1	1.5	2	3	4	–		
	750 mg tab	–		–	–	1	1.5	2	3	4	–	
Moxifloxacin (M or Mfx)	100 mg dt (10 mg/mL)	4 mL	8 mL	1.5	2	3	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	1					
	Standard dose	–		–	–	–	1 or 1.5	1.5	1.5 or 2	2	–	
	400 mg tab high dose ^c	–		–	–	–	1 or 1.5	1.5	1.5 or 2	2	–	

<p>Bedaquiline (B or Bda)</p>	<p>20 mg dt</p>	<p>0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F</p> <p>3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F</p> <p>≥ 6 months: 3 od for 2 weeks; then 1 od M/W/F</p> <p>≥ 6 months: 4 od for 2 weeks; then 2 od M/W/F</p>	<p>3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F</p> <p>≥ 6 months: 6 od for 2 weeks; then 3 od M/W/F</p>	<p>10 od for 2 weeks; then 5 od M/W/F</p>	<p>20 od for 2 weeks; then 10 od M/W/F</p>	<p>-</p>
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Group A medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	Weight (kg)						Comments
		3–<5 kg	5–<7 kg	7–<10 kg	10–<16 kg	16–<24 kg	24–<30 kg	
Bedaquiline (B or Bdq)	100 mg tab (10 mg/mL) ^d	0 to <3 months: 3 mL od for 2 weeks; 3 mL od for 2 weeks; then 1 mL od M/W/F ^b	0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F ^b	0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F ^b	3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F ^b	3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F ^b	3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F ^b	
		≥3 months: 2 mL od for 2 weeks; then 2 mL od M/W/F ^b	≥3 months: 2 mL od for 2 weeks; then 2 mL od M/W/F ^b	≥3 months: 2 mL od for 2 weeks; then 2 mL od M/W/F ^b	≥6 months: 12 mL od for 2 weeks; then 6 mL od M/W/F ^b	2 od for 2 weeks; then 1 od M/W/F	2 od for 2 weeks; then 1 od M/W/F	2 od for 2 weeks; then 1 od M/W/F

Group B medicines	Formulation	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
		1 M/F	1 M/W/F	1 M/F	1 M/W/F	1	1	1	1	1	1	1	
Clofazimine (C or Cfz)	50 mg cap or tab ^f	1 M/F	1 M/W/F		1				2				For children <24 kg, the use of the 50 mg tab is preferred.
	100 mg cap or tab ^f	-	1 M/F		1 M/W/F				1				
	125 mg mini cap (Cs) (12.5 mg/mL)	2 mL ^b , g	4 mL ^b	1	2	3	4					-	Pyridoxine is usually given to limit Cs toxicity.
Cycloserine or terizidone (Cs/Trd)	250 mg cap (25 mg/mL)	1 mL ^b , g	2 mL ^b	5 mL ^b	1	2					3		-
	Formulation	3-5 kg ^a	5-7 kg ^a	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 C medicines	100 mg dt (10 mg/mL)	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			

Delamanid (D or DIm)	25 mg dt	1 od	<3 months: 1 od ≥3 months: 1 bd	1 bd	2 morning 1 evening	2 bd	-	-
	50 mg tab ^h (5 mg/mL)	5 mL (0.5 tab) od ^b	<3 months: 5 mL (0.5 tab) od ^b ≥3 months: 5 mL (0.5 tab) bd ^b	5 mL (0.5 tab) bd ^b	10 mL (1 tab) 5 mL morning 5 mL (0.5 tab) evening	1 bd	2 bd	-
Pyrazinamide (Z or PZA)	150 mg dt (15 mg/mL)	5 mL (0.5 dt)	1 2	3 5	-	-	-	-
	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	3 4	5	-
	500 mg tab (50 mg/mL)	2 mL ^b	5 mL (5 mL) ^b	1 1.5	2 2.5	3 4	5	-
Imipenem-cilastatin (Ipm/Cln)	500 mg + 500 mg powder for injection, vial (10 mL)	Not used in patients aged <15 years (use meropenem)		2 vials (1 g + 1 g) bd		Only to be used with clavulanic acid.		

Meropenem (Mpm)	1 g powder for injection, vial (20 mL)	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	Only to be used with clavulanic acid.
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Group C medicines	Formulation	3- <5	5- <7	7- <10	10- <16	16- <24	24- <30	30- <36	36- <46	46- <56	56- <70	≥70	Comments
		kg ^a	kg ^a	kg	kg	kg	kg	kg	kg	kg	kg	kg	
Amikacin (Am)	500 mg/2 mL solution for injection, ampoule				j					3-4 mL	4 mL		Recommended only in adults aged >18 years.
					j					Calculate according to the dilution used			Recommended only in adults aged >18 years.
Streptomycin (S)	1 g powder for injection, vial												
	125 mg dt (Eto) (12.5 mg/mL)	3 mL ^b	7 mL ^b	1	2	3	4				-		Although once daily dose advised, two divided doses can be also given to improve tolerance.
Ethionamide or Prothionamide (Eto/Pto)	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	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. Fully dose may be given once daily if tolerated.
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Other medicines	Formulation	3-5	5-7	7-10	10-16	16-24	24-30	30-36	36-46	46-56	56-70	Comments
		<5 kg	<7 kg	<10 kg	<16 kg	<24 kg	<30 kg	<36 kg	<46 kg	<56 kg	<70 kg	
Isoniazidⁱ (INH or H) (high dose)	50 mg/5 mL soln	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	4.5	-			
	300 mg tab	-	-	1	1.5	2	-					
Clavulanic acidⁱ (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	2 mL	3 mL	5 mL	8 mL	10 mL	10 mL	10 mL	10 mL	10 mL	Only available in combination with amoxicillin. To be given with each dose of imipenem/cilastatin (bd) or meropenem (tid).
		tid	tid	tid	tid	tid	tid	or tid	bd	-	-	

	125 mg clavulanic acid as amoxicillin/clavulanate (500/125 mg) tab	-	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; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid 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-TB: multidrug-resistant TB; MDR/RR-TB: multidrug- or rifampicin-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.

^a Dosing guidance is based on currently available data and may be revised once additional data are available. Dosages were established by the GDGs for the WHO guidelines on DR-TB treatment (2018 and 2020 updates), the WHO Global Task Force on the Pharmacokinetics and Pharmacodynamics (PK/PD) of TB medicines and the expert consultation on dosing convened by WHO in October 2021, following the GDG meeting on child and adolescent TB in June 2021. Doses for children and young adolescents weighing <46 kg were revised according to Annex 6 of the 2022 *WHO operational handbook on tuberculosis – Module 5: Management of tuberculosis in children and adolescents (153)*, which was informed by an expert consultation on dosing convened by WHO in October 2021 (154). They are based on the most recent reviews and best practices in the treatment of (paediatric) MDR/RR-TB. For certain medicines the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling and maturation (155). Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the mg/kg/day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient. The guidance for the 3–<5 kg weight band and for bedaquiline and delamanid is based on currently available data and may be revised when new data become available.

^b 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 fractioning solid formulations, although bioavailability of the dissolved, crushed adult tablets is uncertain (use of dispersible tablets is preferred).

^c 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.

^d 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.

^e 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.

^f Clofazimine tablets are technically not dispersible, but they do dissolve slowly (this takes approximately 5 minutes) 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 50 mg and 100 mg soft gel capsules are difficult to swallow for young children and therefore countries are strongly encouraged to make the 50 mg tablet formulation available.

^g In children weighing 3 to <7 kg doses are lower than previously recommended. This is because of high exposures associated with risk of neuropsychiatric adverse events, which is especially concerning when co-administering cycloserine with delamanid.

^h Delamanid adult tablets (50 mg) crushed and suspended in water have been shown to be bioequivalent to tablets swallowed whole.

ⁱ 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).

^j 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-TB regimens in adults (isoniazid).


Specific comments on dosing children with medicines used in second-line MDR-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.

Source: WHO operational handbook on tuberculosis. Module 4: treatment and care. Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA 3.0 IGO.

ANNEX 3. SPUTUM COLLECTION


1 CLEAR YOUR MOUTH



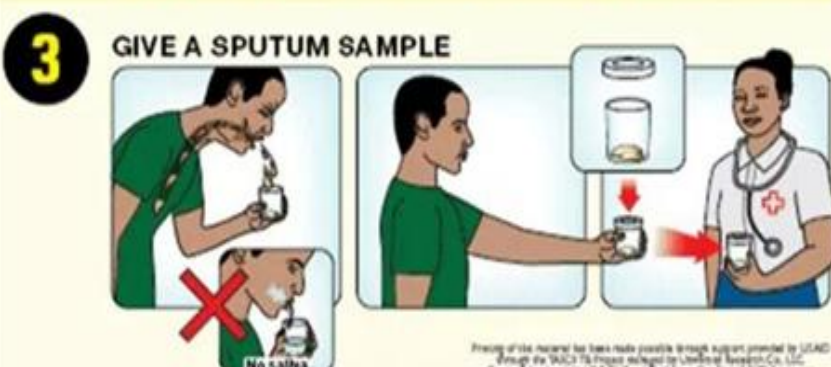
Rinse with water

Empty your mouth

2 BREATH IN AND OUT 3 TIMES



3 GIVE A SPUTUM SAMPLE



No saliva

Privacy of the Patient has been made possible through support provided by USAID through the WAC2 TB program managed by Unifone Research Co., LLC. Content developed by USAID and Unifone. Copyright © 2013 Unifone

Source: [HTTPS://www.aidsmap.com/](https://www.aidsmap.com/)

ANNEX 4. Possible components of a multifaceted, patient-centered treatment strategy

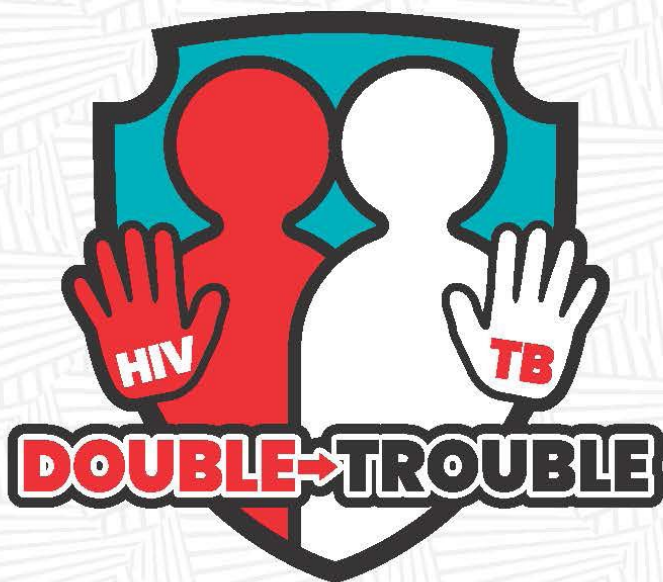
Enablers: Interventions to assist the patient in completing therapy	Incentives: Interventions to motivate the patient, tailored to individual patient wishes and needs, and, thus, meaningful to the patient
Transportation vouchers	Food stamps or snacks and meals
Convenient clinic hours and locations	Restaurant and grocery store coupons
Clinic personnel who speak the languages of the populations served	Assistance in finding or provision of housing
Reminder systems and follow-up of missed appointments	Clothing or other personal products
Social service assistance (referrals for substance abuse treatment and counselling, housing, and other services)	Books
Outreach workers (bilingual/bicultural as needed; can provide many services related to maintaining patient adherence, including provision of directly observed therapy, follow-up on missed appointments, monthly monitoring, transportation, sputum collection, social service assistance, and educational reinforcement)	Stipends
Integration of care for tuberculosis with care for other conditions	Patient contract

END→TB

PROTECT YOUR HEALTH

DO YOU
KNOW?

People living with **HIV** have
a higher risk of developing
TB disease.



Seek Early Care & Get
Tested. Treatment is Free.

TB is CURABLE

EARLY TESTING PROTECTS YOU & YOUR FAMILY.