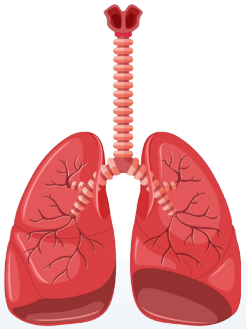
KINGDOM OF ESWATINI

MINISTRY OF HEALTH

NATIONAL INTEGRATED TUBERCULOSIS MANAGEMENT GUIDELINES 2025



World Health Organization

NTCP
National Tuberculosis Control Programme

PEPFAR
U.S. President's Emergency Plan for AIDS Relief

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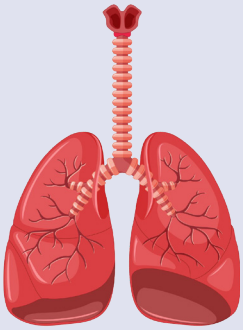

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FOREWORD

Eswatini has made significant strides in decreasing tuberculosis (TB) incidence and mortality. TB incidence declined from 648/100,000 population in 2015 to 350/100,000 population in 2023. Similarly, TB mortality rate dropped from 35/100,000 population in 2015 to 24/100,000 population in 2023. These achievements translate to 46% and 31% decrease in TB incidence and mortality respectively compared to 2015 baseline and surpassed the End-TB milestone one target to achieve the reduction of 20% TB incidence. However, the COVID-19 pandemic hampered further progress in decreasing TB incidence and mortality which are slightly off-track, but achievable against the global End-TB milestone two targets of reducing TB incidence by 50% and TB mortality by 75% by 2025 compared to 2015 baseline. TB preventive treatment coverage among household contacts of persons with bacteriologically confirmed TB increased from 2.3% to 17% of estimated total household contacts. More effort is needed to catch-up achieving the end TB milestone two targets which will in the end contribute to achieving National TB strategic Plan (2024-2028) Vision of TB Free Eswatini by 2035.

TB/HIV collaborative activities also resulted consistent achievement of 98% of people with TB knowing their HIV status and 98% ART coverage among TB/HIV coinfected. These achievements reflect the country's continuing effort of integrated TB/HIV and HIV/TB services. The expansion of integrating with non-communicable diseases (NCDs) management, especially diabetes mellitus, hypertension, lung cancer and mental health screening and treatment among persons with TB are currently ongoing within the country. This effort will provide a comprehensive care to persons with TB at one health service delivery point.

As the global health landscape changes coupled with the country's steps towards achieving the end TB strategy targets, it is very important to ensure that the gains attained so far are accelerated using innovative approaches and new tools as well as building resilient health systems for emergency preparedness (e.g. pandemic, natural disaster, etc.). Therefore, the recommendations made in the National Integrated TB Management Guidelines include the most updated international recommendations. Additionally, healthcare workers across all cadres should maintain up-to-date understanding of these innovative approaches, incorporating them into daily practice.

These guidelines provide the standards and recommendations for the Government of the Kingdom of Eswatini's vision of an Eswatini Free of TB. To achieve this vision, we need continued concerted effort from all stakeholders at all levels of service delivery to translate these guidelines into action.

Meaningful engagement of recipient of care, people/community affected by TB and civil society/faith-based organizations is also vital in achieving this vision.

I would like to take this opportunity to thank the Ministry of Health program leads, technical working group members, recipients of care, key stakeholders, implementing and development partners for their contribution and support in developing and implementing these guidelines.

Dr Bongiwe Malinga
Acting Director of Health Services, Ministry of Health

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The following professionals and country teams are appreciated for their input and review:

Name	Affiliation
Dr. Violet Mwanjali	Mental Health Unit
Dr. Shili Kundhunda	Mental Health Unit
N/S Penuel Fakudze	Mental Health Unit-MOH
S/N Phutile Nkwanyana	TB Centre-MOH
S/N Raymond Vusi Shabangu	NCD-MOH
Zinhle Shabangu	NCD-MOH
Dr Njeri Nyanja	NCD-MOH
Bheki Mabuza	HPU-MOH
Muzie Yende	ASPIRE Project
Fannie Khumalo	ASPIRE Project

Name	Affiliation
Dr Cleophas d'Auvergne	USAID-HQ
Sabine Verkuijl	WHO-HQ
Saskia den Boon	WHO-HQ
Avinash Kanchar	WHO-HQ
Billy	WHO-HQ
Dr. Nomthandazo Dlamini	WHO-Eswatini
Mlandvo Dlamini	MOH
Dr. Debrah Vambe	Baylor
Dr. Lindokuhle Dlamini	National TB Centre
Dr. Tafadzwa Mazuruse	Good Shepherd Hospital

Name	Affiliation
Dr. Deo Kabantu	ASPIRE Project
Ntokozo Gama	ASPIRE Project
Dr. Elisha Nyandoro	Georgetown University
Gugu Mchunu	Georgetown University
Dr. Arnold Mafukidze	Georgetown University
Neliswa Bhembe	Georgetown University
Vuyani Dlamini	Georgetown University
Siphesihle Nhlabatsi	NPC-MOH
Mangaliso Ziyane	Baylor/NTRL
Badanile Shiba	EHSL-MOH
Menzi Mhlanga	ICAP
Nokwethu Mkhumane	NCCU-MOH
Gugulethu Madonsela	ENAP-MOH
Nomsa Kunene	IPC-MOH
Simangele Msibi	GHSC
Welcome Mdluli	Regional Coordination - Shiselweni
Cynthia Dlamini	NTCP-MOH
Sipholesihle Mthethwa	NTCP-MOH
Mlungisi Nkambule	NTCP-MOH
Tumiso Mutumba	NTCP-MOH
Lindokuhle Dlamini	NTCP-MOH
Sanelisiwe Tsela	NTCP-MOH

Name	Affiliation
Dr. Tafadzwa Mazuruse	Good Shepherd Hospital
Sidwell Msibi	Mbabane Government Hospital
Simphiwe Mngometulu	Hlathikhulu Government Hospital
Bonsile Gama	Nhlangano Health Centre
Kayise Dlamini	AHF Matsapha
Lamlile Vilakati	National TB Centre
Zinhle Mbatha	RFM Community
Thabani Mdluli	Dvokolwako Health Centre
Mbutfo Magagula	Emkhuzweni Health Centre
Majaha Mtshali	Pigg's Peak Government Hospital
Bongiwe Dlamini	Mankayane Government Hospital
Sonto Shabangu	Regional TB Coordination - Hhohho
Ernest Nhlengetfwa	Regional TB Coordination - Manzini
Thabo Kunene	Regional TB Coordination - Lubombo
Nozipho Dlamini	Regional Information Office-Manzini
Tiyandza Mabuza	Regional Information Office-Hhohho
Nomfundo Maphalala	Regional Information Office-Shiselweni
Siphiwe Dube	Regional Information Office-Lubombo
Thando Mabuza	NTCP-MOH
Similo Simelane	NTCP-MOH
Nkosingiphile Mndzelebe	NTCP-MOH
Wandile Zwane	MOH

ABBREVIATIONS

ACSM	Advocacy, Communication and Social Mobilization
AHD	Advanced HIV Disease
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Treatment
aTB	Asymptomatic Tuberculosis
aTB-C	Asymptomatic Tuberculosis Bacteriologically Confirmed
aTB-U	Asymptomatic Tuberculosis Bacteriologically Unconfirmed
ATS	American Thoracic Society
BC-TB	Bacteriologically Confirmed Tuberculosis
Bdq/B	Bedaquiline
BMI	Body Mass Index
CBC	Complete Blood Cell Count
CDC	United States Centers for Disease Control and Prevention
CD-TB	Clinically Diagnosed Tuberculosis
Cfz	Clofazimine
CrCl	Creatinine Clearance
Cs	Cycloserine
DAT	Digital Adherence Technology
Dlm	Delamanid
DOT	Directly Observed Treatment
DST	Drug Susceptibility Test
EMB or E	Ethambutol
FDC	Fixed-Dose Combination
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTB	Global TB Program
HHC	Household Contacts
HIV	Human Immunodeficiency Virus
Hr-TB	Isoniazid Resistant Tuberculosis
IDSA	Infectious Diseases Society of America
IGAR	Interferon-Gamma Release Assay
Imp/Cln	Imipenem/Cilastatin
INH or H	Isoniazid
IPC	Infection Prevention and Control

IRIS	Immune Reconstitution Inflammatory Syndrome
KNCV	Royal Dutch Tuberculosis Foundation
LF-LAM	Lateral Flow Urine Lipoarabinomannan Assay
LFT	Liver Function Test
Lzd/L	Linezolid
MDR-TB	Multidrug-Resistant Tuberculosis
Mfx/M	Moxifloxacin
MUSIC	Mid-Upper Arm Circumference
mWRD	WHO Recommended Rapid Molecular Diagnostic Tests?
NAAT	Nucleic Acid Amplification Test
NGO	Non-Governmental Organization
Pa	Pretomanid
PDR-TB	Poly-Drug Resistant Tuberculosis
PMDT	Programmatic Management of Multi-drug-resistant Tuberculosis
PZA or Z	Pyrazinamide
RIF or R	Rifampicin
RFP	Rifapentine
RFT	Renal Function Test
RR-TB	Rifampicin Resistant Tuberculosis
SAT	Self-Administered Treatment or Unsupervised Treatment
SMS	Short Message Service or Text Message
TB	Tuberculosis
TBI	TB Infection
tNGS	Targeted Next-Generation Sequencing
TPT	TB Preventive Treatment
Trd	Terizidone
TSH	Thyroid-Stimulating Hormone
TEST	Tuberculin Skin Test
The Union	International Union Against Tuberculosis and Lung Disease
ULN	The Upper Limit of Normal
USAID	United States Agency for International Development
VOT	Video-observed Treatment
WHO	World Health Organization
WRD	WHO Recommended Rapid Diagnostic Tests?
XDR-TB	Extensively Drug-Resistant Tuberculosis

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DEFINITION OF TERMS

Asymptomatic TB Bacteriological Confirmed (aTB-C): refers to a person with bacteriologically confirmed TB who did not report symptoms suggestive of TB during screening.

Asymptomatic TB Bacteriologically Unconfirmed (aTB-U): refers to a person with bacteriologically un-confirmed TB who did not report symptoms suggestive of TB during screening.

Household Contact: refers to any person who was exposed to a person with TB.

Close Contact: refers to a person who does not live in the same household as a person with TB but who has shared an enclosed space, such as a social gathering place, workplace or facility, with the index patient for extended periods during the day during the 3 months before the current disease episode commenced.

Contact Investigation (or evaluation): refers to a systematic process for identifying previously undiagnosed people with TB among the contacts of an index case or presumed source persons with TB if the index person with TB is a child (i.e. reverse contact investigation). Contact investigation consists of identification, prioritization and clinical evaluation. It also includes identifying candidates for TB preventive treatment.

Household Contact: refers to a person who has shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods in the 3 months before TB disease was identified in the index case.

Index Patient (index case) of TB: refers to the initially identified person with TB disease in a specific household or other comparable setting in which others may have been exposed. An index patient is a person on whom a contact investigation is centred but who is not necessarily the source of an outbreak of TB.

Patient-Initiated Care: refers to a patient-initiated pathway to TB diagnosis that involves: (1) a person with TB disease experiencing symptoms that they recognize as serious; (2) the person having access to and seeking care, and presenting spontaneously at an appropriate health facility; (3) a health worker correctly assessing that the person fulfils the criteria for presumptive TB; and (4) the successful use of a diagnostic algorithm with sufficient sensitivity and specificity to diagnose TB.

A person with presumptive TB: refers to a person with symptoms or signs suggestive of TB disease.

Risk group: refers to any group of people at increased risk of TB infection, or progression from TB infection to TB disease, or TB-associated mortality, compared with the general population.

Provider-initiated care: refers to screening and testing initiated by health care providers. This can be done in health facilities or communities by mobile teams, often using a mobile X-ray machine and rapid molecular tests.

Screening: refers to the systematic identification of people at risk for TB disease in a predetermined target group by clinical examination, assessing symptoms and using tests (sputum-smear microscopy, LF-LAM, C-reactive protein), or other procedures (e.g. chest radiography). For those who screen positive, diagnosis should be established by one or more diagnostic tests (e.g. mWRD, culture). This term is sometimes used interchangeably with "active tuberculosis case-finding". It should be distinguished from testing for TB infection (using a TB skin test or interferon-gamma release assay).

TB Infection: refers to a state of persistent immune response to stimulation by M. tuberculosis antigens with no evidence of the clinical manifestations of TB disease. This is also at times referred to as "latent TB infection". There is no gold standard test for direct identification of M. tuberculosis infection in humans. Most infected people have no signs or symptoms of TB but are at risk for progression to active TB disease.

TB Preventive Treatment (TPT): refers to treatment offered to individuals who are considered at risk of progression from TB infection to TB disease. Also referred to as treatment of TB infection, treatment for latent TB infection or TB preventive therapy.

TB Disease: refers to a person with disease caused by the M. tuberculosis complex. The M. tuberculosis complex comprises nine distinct but closely related organisms. The complex includes M. africanum, M. bovis, M. canetti, M. caprae, M. microti, M. mungi, M. orygis, M. pinnipedii, and M.tuberculosis.

TB Case: refers to the occurrence of TB disease in a person. The term should be reserved for use in the context of registration or reporting of the clinical condition and not during the provision of care. This definition also includes the identification of TB disease through post-mortem examination. All TB cases should be notified to public health authorities, regardless of whether TB treatment was started. People with TB who died or were lost to follow-up before TB treatment started should also be notified to public health authorities; this is because they are important from the perspective of both surveillance and public health (they may have contacts that require tracing and follow-up).

TB Patient: refers to a person who is receiving care for TB disease.

Bacteriologically confirmed TB: refers to a person from whom a biological specimen is positive by a WHO-recommended rapid TB diagnostic test including molecular test and biomarker test (i.e. LF-LAM), culture, or smear microscopy.

WHO-recommended rapid diagnostic test (WRD): refers to a test approved by WHO that employs molecular (e.g. Xpert Ultra®) or biomarker-based techniques (e.g. urinary lipoarabinomannan assays (U-LAM) for the diagnosis of TB. Throughout this publication, the term "WRD" refers to molecular WRDs unless otherwise specified.

Clinically diagnosed TB: refers to a person who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with TB disease by a medical practitioner who has decided to give the person a full course of TB treatment. This definition includes pulmonary cases diagnosed based on radiographic abnormalities and extrapulmonary cases diagnosed based on suggestive clinical presentation or histology. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Pulmonary TB: refers to a person with TB disease involving the lung parenchyma or the tracheobronchial tree. A case with both pulmonary and extrapulmonary TB should be recorded and counted as a pulmonary TB case for surveillance purposes. Miliary TB is classified as pulmonary TB.

Extrapulmonary TB: refers to a person with TB disease involving organs other than the lung parenchyma or tracheobronchial tree (e.g. pleura, lymph nodes, digestive tract, genitourinary tract, skin, joints and bones, meninges).

New Case: refers to a person with TB disease who has never been treated for TB or has only ever taken TB drugs for less than 1 month.

Recurrent Case: refers to a person with TB disease who has previously been treated for TB, was declared cured or treatment completed at the end of their most recent course of TB treatment and is now diagnosed with a new episode of TB.

Re-registered Case: refers to A person with TB disease who has been notified previously as a TB case, who started treatment and took TB drugs for at least 1 month but who was not declared cured, or treatment completed and is now being started on a new course of TB treatment. Examples of re-registered cases include:

- A person who declared treatment failed during or at the end of their most recent course of TB treatment and who is starting a new course of TB treatment (normally using a different drug regimen);
- A person who was declared lost to follow-up before, during or at the end of their most recent course of TB treatment and who has returned to start a new course of TB treatment; and
- A person whose outcome after their most recent course of TB treatment is undocumented and who has returned to start a new course of TB treatment.

Unknown previous treatment history refers to A person with TB disease who has no documented history of TB treatment.

New episode: refers to a person with TB disease who is classified as a new case, a recurrent case or a case with unknown previous treatment history (i.e. any case apart from a re-registered case).
A previously treated case refers to a person with TB disease who is either a recurrent or a re-registered case.

Drug Susceptibility Testing (DST): refers to In vitro testing of a strain of M. tuberculosis complex using either: 1) molecular, genotypic techniques to detect resistance-conferring mutations; or 2) phenotypic methods to determine susceptibility to a medicine.

Drug-resistant TB (DR-TB): refers to a person with TB disease who is infected with a strain of M. tuberculosis complex that is resistant to any TB medicines tested. When available, DST results for individual drugs should be recorded.

Drug-susceptible TB (DS-TB): refers to a person with TB disease for whom there is no evidence of infection with a strain of M. tuberculosis complex that is resistant to rifampicin or isoniazid. (This definition should only be used for initiation of treatment for drug-susceptible TB and the recording of treatment outcomes. Wherever available DST results for individual drugs should be recorded and used to define a person's drug susceptibility status. When DST results are not available for individual drugs, their absence should be recorded.)

Isoniazid-resistant, Rifampicin-susceptible TB (Hr-TB): refers to a person with TB disease who is infected with a strain of M. tuberculosis complex that is resistant to isoniazid but susceptible to rifampicin.

Rifampicin-Resistant TB (RR-TB): refers to a person with TB disease who is infected with a strain of M. tuberculosis complex that is resistant to rifampicin. Note: These strains may be either susceptible or resistant to isoniazid (i.e. MDR-TB) or resistant to other first-line or second-line TB medicines.

Multidrug-resistant TB (MDR-TB): refers to a person with TB disease who is infected with a strain of M. tuberculosis complex that is resistant to both rifampicin and isoniazid.

MDR/RR-TB: refers to MDR-TB as a subset of RR-TB, and the two are often grouped using the term MDR/RR-TB.

Pre-extensively drug-resistant TB (pre-XDR-TB): refers to a person with TB disease who is infected with a strain of M. tuberculosis complex that is resistant to rifampicin (which may also be resistant to isoniazid), and which is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin).

Extensively Drug-Resistant TB (XDR-TB): refers to a person with TB disease who is infected with a strain of M. tuberculosis complex that is resistant to rifampicin (and which may also be resistant to isoniazid) as well as resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and at least one other "Group A" drug (bedaquiline or linezolid).

HIV-positive: refers to a person with TB disease who has documented positive results from HIV testing before, at the time of TB diagnosis or during the TB episode.

HIV-negative: refers to a person with TB disease who has a negative result from HIV testing conducted at the time of TB diagnosis. If the person is subsequently found to be HIV-positive during their TB treatment, they should be reclassified as an HIV-positive TB case.

HIV status unknown: refers to a person with TB disease who has no result from HIV testing and no documented evidence of receiving treatment for HIV. If the person's HIV status is subsequently determined, they should be reclassified as an HIV-positive TB case or an HIV-negative TB case, as appropriate.

First-line TB medicine (or drug): refers to an agent used to treat a person with drug susceptible TB disease.

Second-line TB medicine (or drug): refers to an agent used to treat a person with drug-resistant TB disease.

Treatment initiation: refers to the initiation of an appropriate treatment regimen for a person with TB disease. Note: It is recommended to monitor this step in the pathway of care because diagnosis of TB disease does not necessarily mean that a person will be offered or accepted to take treatment.

Treatment Outcomes Definition

Cured: refers to a pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy with evidence of bacteriological response and no evidence of failure.

Treatment completed: refers to a person with TB disease who completed treatment as recommended by the national policy whose outcome does not meet the definition for cure or treatment failure.

Treatment successful: refers to a person with TB disease who was either cured or who completed treatment as defined above.

Treatment failed: refers to a person with TB disease whose treatment regimen needed to be terminated or permanently changed to a new regimen option or treatment strategy.

Died: refers to a person with TB disease who died for any reason before starting (for case outcomes), or during, treatment (for both case and treatment outcomes).

Lost follow-up: refers to a person with TB disease who did not start treatment (for case outcomes) or whose treatment was interrupted for two consecutive months or more (for both case and treatment outcomes).

Not evaluated: refers to a person with TB disease to whom no treatment outcome was assigned, excluding those lost to follow-up.

CHAPTER 1
INTRODUCTION AND COUNTRY BACKGROUND

1.1 Introduction

The development of new tools, medicines, and regimen across the tuberculosis (TB) care and prevention cascade has been faster than ever in the past decade. With this development, the World Health Organization (WHO) has updated and released new recommendations including many operational handbooks to guide the countries since 2021. The Kingdom of Eswatini through the Ministry of Health (MOH) has adopted most of the WHO's new recommendations and implemented them. These National Tuberculosis Management Guidelines, 2024 are the consolidation of all the previous manuals, guidelines, SOP and memoranda. Significant changes featured in these guidelines are briefly summarized below in Table 1.

Table 1: Summary of Changes and New Recommendations in the Guidelines

Definitions and terms use	Adapted as in the new WHO TB surveillance guidelines, 2024 includes the change of LF-LAM diagnosed TB cases to bacteriologically confirmed TB instead of clinically diagnosed TB.
TB Screening	New screening tool: CXR and CAD use both in health facilities and community, CRP for PLHIV, revised symptom screening tool to increase presumption index on lung cancer Approaches: Bidirectional screening of TB and COVID, Integrated Screening in the Community Strategies to ensure optimal screening coverage: • Checking the copy of the screening tool that is given out to the client (recording in the CMIS) by the screening officer/any community cadre by the attending clinicians. • Using a stamp strategy (i.e. giving a stamped slip to the client and checking by attending clinicians if screening is done or not) • Repeated screening at the multi-service delivery points • Cascade analysis and continuous quality improvement using the data of screening activities
TB Diagnosis	Children: Stool sample used for TB diagnosis with GeneXpert, Treatment decision algorithms. Drug-resistant-TB: Xpert XDR and Sequencing tests.
Drug-susceptible TB treatment	Four-month regimen for children 3-15 years old with non-severe pulmonary TB, 6-month (6RHZ+Eto) TB meningitis treatment regimen for children, COVID-19 vaccination for TB patients, post-TB lung disease assessment and referral Treatment support: Nutritional support for clinically indicated clients (i.e. based on BMI/MUAC), Digital adherence technology use (Smart pillbox in addition to VOT)

Drug-resistant TB treatment (DR-TB)	Use of BPaLM regimen for RR/MDR TB, guidance for empirical treatment approach, especially for initially diagnosed as Hr-TB before tNGS result. Use of 6-month Bdq-Dlm-Lzd-Lfx-Cfz regimen for individuals not eligible for BPaLM regimen, especially for children, pregnant and lactating women Use of 9-month regimens for individuals not eligible for 6-month long BPaLM and Bdq-Dlm-Lzd-Lfx-Cfz regimens. These regimens include: 9 Bdq-Mfz-Cfz-Z, 9 Bdq-Lzd-Lfz-Cfz-Z, 9 Bdq-Dlm-Lzd-LfX-Z
Collaborative TB and HIV activities and advanced HIV disease	Synchronized the updates from National Integrated HIV Management Guidelines, 2022 including HIV prevention in presumptive TB and TB clients
TB Preventive Treatment (TPT)	Use of new TPT regimens among household contacts (3HP, 3 HR as preferred regimen) Use of Levofloxacin for all DR-TB household contacts regardless of age Community-based TPT for household TB contacts
Integrated TB/HIV and non-communicable diseases including mental health (New Chapter)	A New Chapter
Zoonotic TB and Leprosy Management	A New Chapter

1.2 Geographic and Socio-demographic

The Kingdom of Eswatini is a landlocked country situated in southern Africa bordered by South Africa and Mozambique. The country has a land surface area of about 17,364 square km. It is divided into four administrative regions; Hhohho, Manzini, Lubombo and Shiselweni, and further subdivided into 59 Tinkhundla (constituencies) and 385 chiefdoms.

In 2022, the World Bank estimated the Eswatini population to be 1,201,670 people, (and population density of 63 people per sq. km), with a 9.02% growth in population since the inception of the past NSP. The current population is distributed as 596,167 (48.58%) males and 605,504 (51.42%) females. At least 43% of the total population are children and adolescents. The largest population is in Manzini (32.6%), 29.3% Hhohho, 19.4% Lubombo, and 18.7% Shiselweni. Approximately 25% of the population resides in urban areas and most of the population resides in rural areas.

1.3 Health System and Health Service Delivery

The health systems of Eswatini are under the auspices of the Ministry of Health, which provides leadership and ensures the existence of strategic policy frameworks. The National TB Control Program (NTCP) is under the Department of Public Health. The Ministry of Health through the NTCP is responsible for coordinating and overseeing the implementation of TB in the country. The National TB Control Program is responsible for planning, implementing, monitoring, and evaluating all TB control response activities. The NTCP is accountable for all deliverables for TB response in Eswatini. The National TB Control Program is under the immediate supervision of the Director of Public Health, who subsequently is under the responsibility of the Principal Secretary. The Honourable Minister of Health provides political guidance on the implementation of the UN declarations and global commitments towards ending TB.

The country has a healthcare delivery system consisting of both formal and informal sectors. The Ministry of Health is driving the agenda of providing health services that are comprehensive by providing preventative and curative services that are high-quality, affordable, and socially acceptable. The health delivery system with a total of 327 health facilities consists of four tiers:

Community Level: Is made up of a network of community-based services provided by community-based Health Care Workers, comprising Rural Health Motivators (RHMs), TB Champions, Faith Based Organizations, Community Health Workers, Traditional Healers, Traditional Birth Attendants (TBAs) and other volunteers providing home-based care, support and treatment.

Primary Health Care Facility: This is made of primary health care (PHC) facilities, consisting of clinics and Public Health Units (PHUs), as well as outreach services.

Health Centres and Regional Referral Hospitals: Consists of Health Centres (HCs) and regional referral hospitals (RRHs) providing basic inpatient, outpatient, maternity, dental, minor surgery, some speciality, staffed by regional medical officers, some specialists, and nurses.

National Referral Hospital: This is made up of national referral hospitals (NRHs), two of which are classified as speciality hospitals as they offer specialized care for non-communicable disease (NCD) and psychiatric services.

1.4 National Tuberculosis Control Program

The NTCP is structured at four levels, namely the national, regional, facility, and community levels. At the national level, the Program Manager is supported by the national TB/HIV focal, Child & Adolescent TB/HIV focal, Advocacy Communication and Social Mobilization Coordinator, National Community Services Coordinator, Laboratory focal, National Monitoring & Evaluation Officer, Community Monitoring Evaluation Officer, Monitoring and Evaluation Advisor, PMDT Focal, TB and Research Technical Advisor, IT Officer, M&E Technical Advisor, National Information Officer and IPC National Coordinator.

Each region is supported by a TB/HIV Coordinator responsible for the programmatic management of TB and TB/HIV services, supported by Regional Information Officers, TB doctors and nurses. The TB/HIV Coordinators are part of the Regional Health Management Teams (RHMT) in their respective regions.

At the facility level, there are health care workers who are tasked with providing TB services in each of the 149 TB BMUs. These include TB nurses, laboratory personnel, TB screening officers, TB expert clients, HTS counsellors, and TB/HIV adherence officers. At the community level provision of TB, is through TB Champions (previously known as Active Case Finders), working in collaboration with Rural Health Motivators, TB treatment supporters, Community-Based Organizations, Faith-based organizations, Non-Governmental Organizations and Civil Society Organizations.

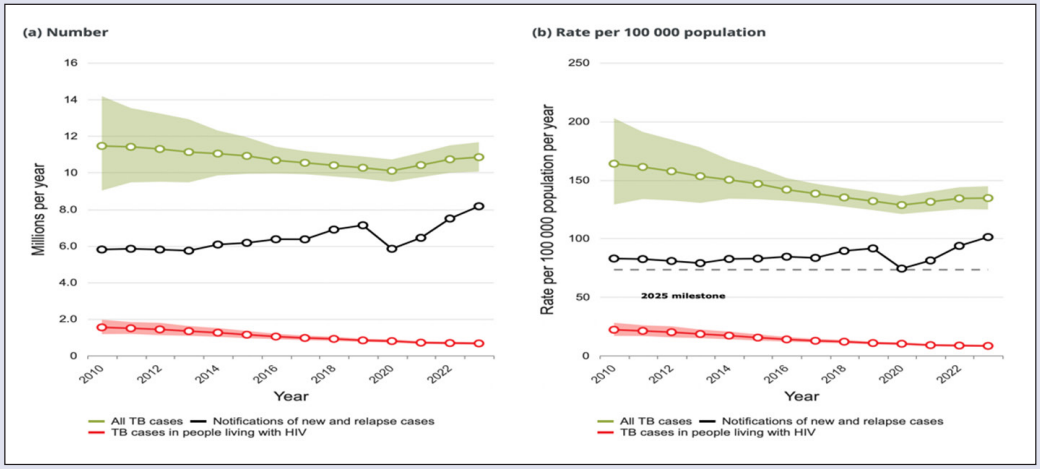
1.5 Epidemiology of Tuberculosis

Tuberculosis (TB) is an infectious disease caused by Mycobacteria tuberculosis and affects mainly the lungs. It is transmitted through the air when a person with TB in the lungs coughs or sneezes. People infected by TB have a 5-10% chance of developing TB disease in their lifetime. However, people with immune-suppressive conditions are at higher risk of developing TB disease once they have contracted TB infection. People living with HIV have a 16 times higher risk of TB disease than non-HIV infected. People with diabetes are 3 times more at risk of TB disease. Malnutrition, two extremes of age (elderly more than 60 years old and children younger than 5 years old) and other social-behavior factors such as smoking, alcohol and substance misuse are also risk factors for developing TB disease. Additionally, TB is associated with climate change by exacerbating the TB risk factors including undernutrition, diabetes, HIV, mass displacement, poverty and overcrowding. Globally males are more affected than females with a ratio of 1.3:1 (5.8 million vs 3.5 million).

Though tuberculosis is a preventable and curable disease, it remains a global public health issue and the second deadliest killer after COVID-19. Approximately 25% of the world's population is infected by TB. An estimated 10.8 million people fall ill due to TB including 1.3 million children and 6.8% were people living with HIV (PLHIV) in 2023. TB caused approximately 1.1 million deaths in 2023 (see Figure 1 below the global trend of TB incidence and mortality). Drug-resistant TB is also a global public health threat causing an estimated 400,000 people to fall ill in 2023.

1.5.1 Global trend in TB incidence

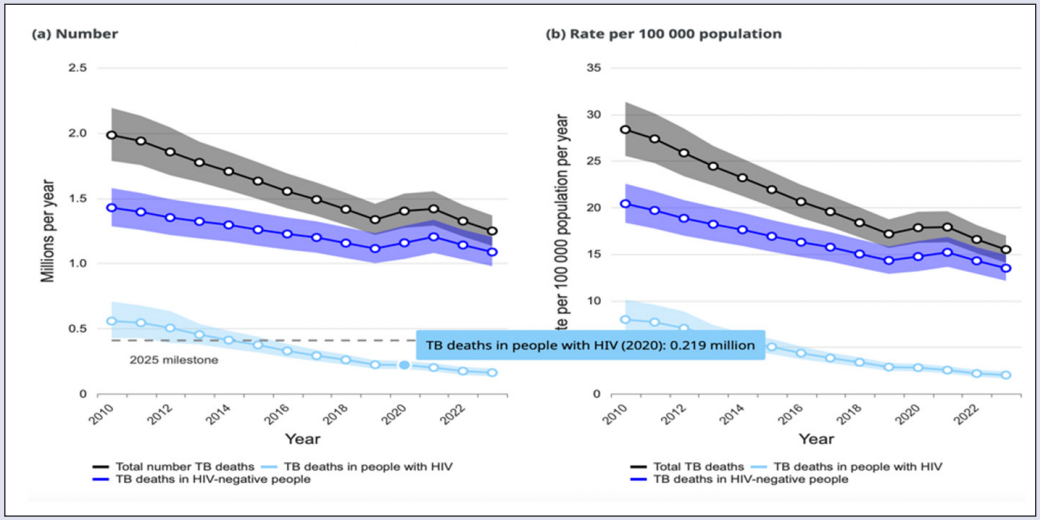
Figure 1: Global TB Incidence Trends, 2024



(Source: WHO Global TB Report, 2024)

1.5.2 Global trend of TB mortality

Figure 2: Global TB Mortality Trends, 2024



(Source: WHO Global TB Report, 2024)

To combat the global TB threat, both the United Nations (UN) through its Sustainable Development Goals (SDGs) and the WHO with its End TB Strategy have set the target date for ending the TB epidemic as of 2030. The End TB strategies encompass the following three pillars underpinned by four key principles. The summary of the End TB milestones and targets is in Table 2.

Table 2: End TB Strategy Milestones

Pillars of The End TB Strategy	Key Principles of the End TB Strategy
1. Integrated, patient-centred TB care and prevention. **2. Bold policies and supportive systems.** **3. Intensified research and innovation**	1. Government stewardship and accountability, with monitoring and evaluation. 2. Strong coalition with civil society organizations and communities. 3. Protection and promotion of human rights, and ethics. 4. Adaptation of the strategy and targets at the country level, with global collaboration.

Vision

A World Free of TB (Zero deaths, disease, suffering due to TB)

Goal

End The Global TB epidemic

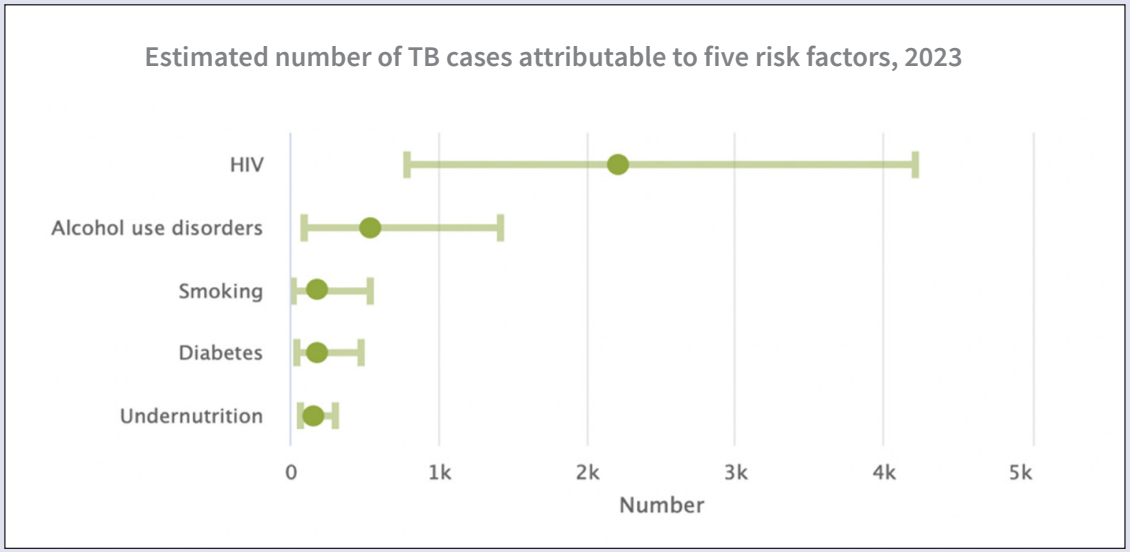
	MILESTONES		TARGETS	
			SDG*	END TB
	2020	2025	2030	2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20%	50%	80%	90%
TB-affected families facing catastrophic costs due to TB (%)	0%	0%	0%	0%

*The United Nations Sustainable Development Goals (SDGs) include ending the TB epidemic by 2030 under Goal 3.

Many countries have embraced this vision and pledged their commitment to achieving these strategic goals and objectives. To achieve these goals, a decline of at least 5% in TB incidence per year is required and many countries, especially in African regions achieved this rate of decline in TB incidence. However, the COVID-19 pandemic in 2019 offset and reversed these gains in many countries. Post-COVID-19, many countries have already recovered from this reversal and are working towards maximizing the reduction in TB incidence.

Tuberculosis is a major public health issue in Eswatini. The country also joined the pledge to achieve the SDG and end-TB strategy goal. TB predominantly affects males in Eswatini like elsewhere and the ratio of male and female TB incidence was 1.3 in 2022 and 55% of notified cases were male in 2022. HIV remains the main driver of TB since HIV prevalence in the country was high at 24.7% in 2021 according to the Swaziland HIV Incidence Measurement Survey (SHIMS 3, 2021). However other determinants such as undernourishment, diabetes, alcohol and smoking are emerging key drivers (see Figure 3).

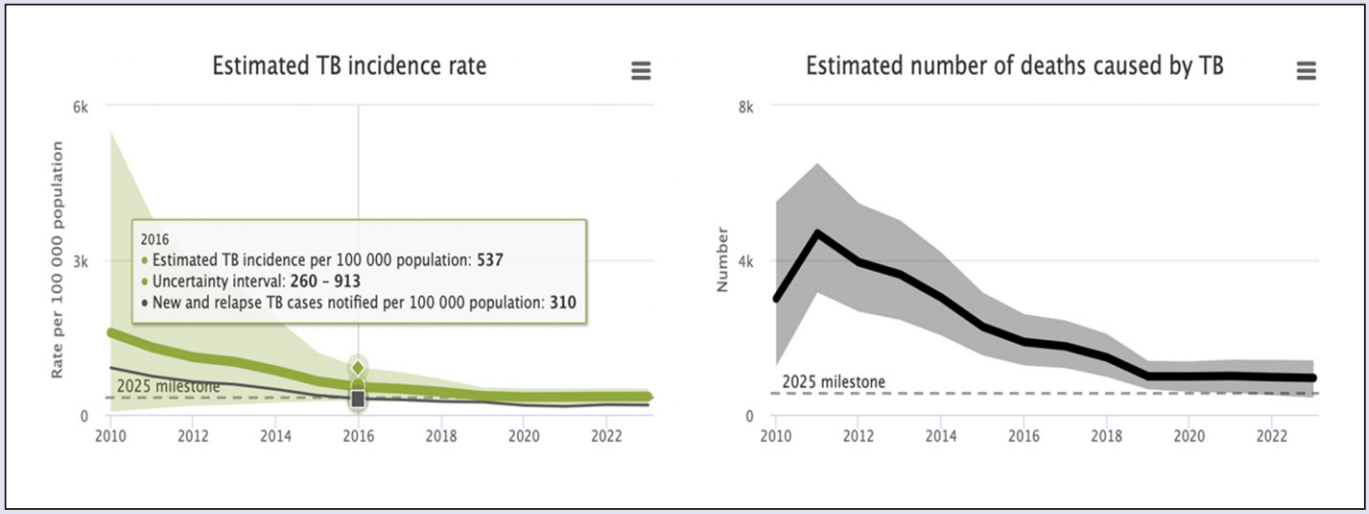
Figure 3: Drivers of TB in the Kingdom of Eswatini



(Source: WHO Global TB Report, 2024)

Due to the concerted efforts of the national tuberculosis control program, the national HIV/AIDS program and their stakeholders, there was an accelerated decline in TB incidence from 1590/100000 population in 2010 to 335/100,000 population in 2020. TB Mortality rate in HIV-negative individuals declined from 56/100,000 in 2010 to 24/100,000 population in 2020. However, this momentum was interrupted due to the COVID-19 pandemic (see Figure 4 below) and remains one of the 30 highest TB/HIV countries in the world. In 2023, the TB incidence rate was 350/100,000 with an estimated 4300 people falling ill with TB, of which 53.5% were people living with HIV. Due to the TB/HIV confection rate, Eswatini remains on the list of the 30 highest TB/HIV burden countries in the world. Drug-resistant TB incidence was 18/per 100,000 population in which 230 people fell sick.

Figure 4: Estimated incidence – Eswatini, 2024



(Source: WHO Global TB Report, 2024)

1.6 National TB Strategic Plan

By embracing the End TB strategy, the Ministry of Health of Eswatini develops the National Tuberculosis Strategic Plan (TB-NSP) periodically. The vision, mission and milestones set at each cycle of TB-NSP are aligned with the End TB strategy. The TB-NSP (2020-2023) aimed to achieve 90% treatment coverage including 12% of notified TB cases being children 0-15 years old and a 90% treatment success rate for both drug-susceptible tuberculosis (DS-TB) and drug-resistant tuberculosis (DR-TB). However, due to the impacts COVID-19 pandemic and other challenges, the treatment coverage was 69% in 2022, and the treatment success rate was 81%. The childhood TB notification was 6% overall. To address these gaps, the Ministry of Health of Eswatini through the National Tuberculosis Control program with the support of key stakeholders has been putting more effort into achieving the targets set for TB notification and treatment outcomes that were retained in the new national strategic plan (2024-2028).

The new TB-NSP (2024-2028) is summarized in Table 3 below. The new strategic plan emphasizes the use of new tools for TB screening, diagnosis and treatment to address the gaps in TB prevention and care through accelerated TB case finding in combination with TB preventive treatment provision, quality holistic care to decrease TB mortality, the use of strategic and surveillance data for TB programming and strengthening coordination and collaboration with stakeholders including civil society organization and private sector. The strategy also includes a contingency plan for preparedness and responses at the time of disaster or crisis by having a resilient health system to minimize the impact on the TB service delivery.

Table 3: Summary of the new TB National Strategic Plan

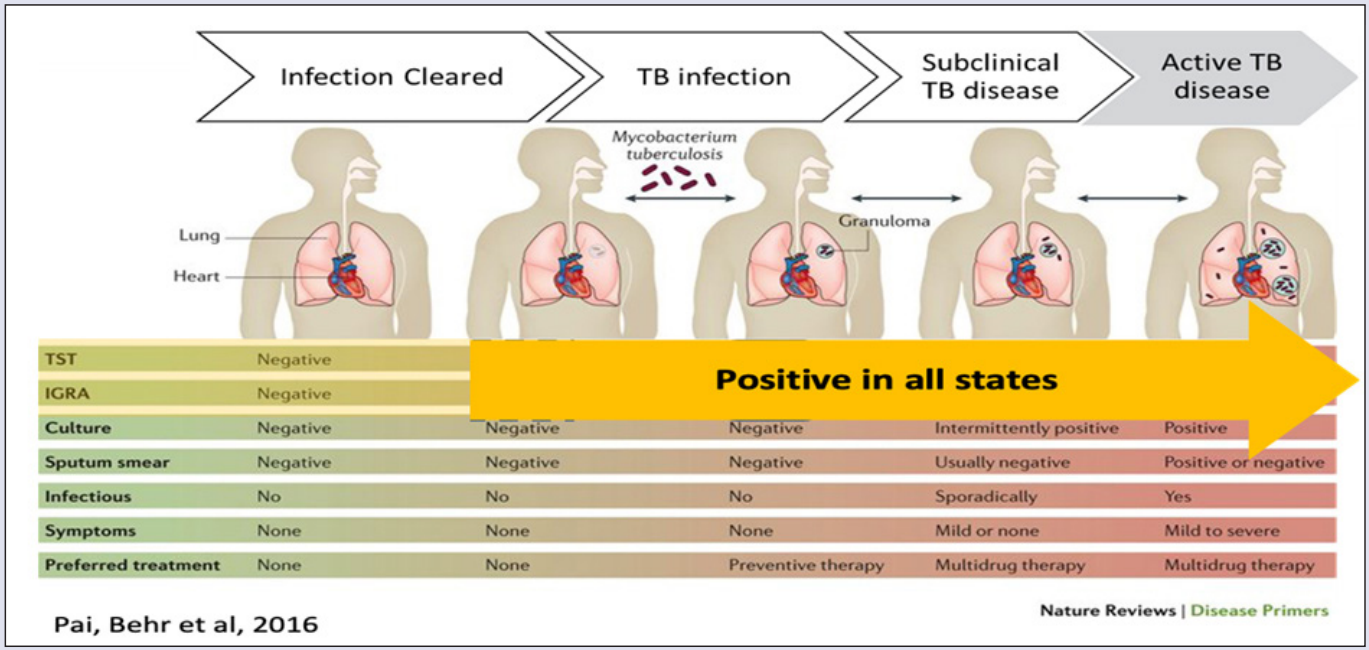
Vision	Eswatini Free of TB by 2035
Mission	To ensure the provision of quality care and prevention services for all people in Eswatini with TB disease and TB infection.
Goal	Reduce TB incidence by 40% relative to the 2022 levels Reduce TB deaths by 50% by 2028 relative to the 2022 levels. Eliminate catastrophic costs (0%) for recipients of care and their household members.
Strategic Objectives	• To achieve 90% TB treatment coverage by 2028. • To strengthen primary and secondary TB prevention services. • To achieve a 90% treatment success rate for all forms of TB including DS-TB and DR-TB. • To improve TB screening, diagnosis, treatment and prevention among children and adolescents. • To improve the quality and utilization of TB Information for decision-making and programmatic actions. • To strengthen governance structures and organizational capacity for optimal program management.

1.7 Natural History of TB

TB infection is acquired by inhalation of infected droplets from an infectious person and affects mainly the lungs in which case it is referred to as pulmonary TB. However, the MTB in the lung may also spread through the bloodstream and the lymphatic system to other body parts, especially in persons with immuno-suppressive conditions, which case it is called Extra-Pulmonary TB (EP-TB).

When a person has acquired TB infection, different immune responses may occur. The various states that may result are demonstrated in the 6 below, from left to right: (1) where the infection is cleared; (2) state that is often called latent TB infection; (3) sub-clinical TB state where asymptomatic but progressing to TB; (4) active TB disease with clinical manifestations.

Figure 5: Natural History of TB Infection



It is estimated that each infectious individual can transmit TB to up to 10-15 people per year until they have been started on treatment and rendered non-infectious. Studies have documented an infection rate of 30 to 50% amongst household contacts of infectious adults with the infection rate in children under 5 as high as 72% overall. People infected with TB have a 5-10% chance of developing TB disease in their lifetime.

1.7.1 Clinical Manifestation of TB

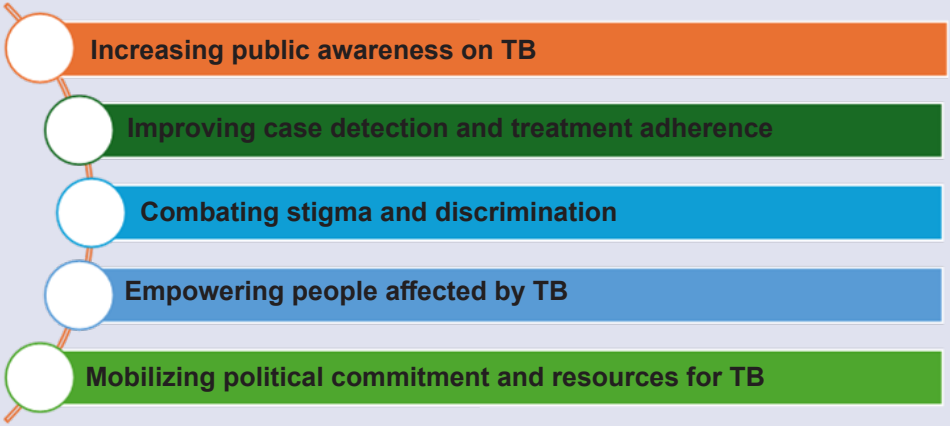
The most common and typical features of pulmonary TB are cough, fever, weight loss, and drenching night sweats, and these signs and symptoms are used as standardized TB symptoms screening tools. Other signs and symptoms of TB are haemoptysis (coughing blood), chest pain, back pain, breathlessness, loss of appetite, generally feeling unwell (malaise), tiredness or reduced activity in children (e.g., reduced playfulness). During a clinical examination, general indicators of infection and systemic disturbance might be observed, including fever, fast heartbeat (tachycardia), and accelerated breathing (tachypnoea). Auscultation with a stethoscope may reveal diminished airflow and atypical respiratory sounds, such as crackling, wheezing, and the distinct sounds of bronchial breathing. The clinical manifestation of EP-TB depends on the sites of TB occurrence (refer to details in the TB diagnosis chapter).

CHAPTER 2
TB ADVOCACY, COMMUNICATION AND SOCIAL MOBILISATION

2.1 Introduction

Advocacy, communication, and social mobilization (ACSM) are key pillars for effective prevention, case finding, testing, treatment and securing resources for both drug-susceptible and drug-resistant TB. These pillars are interwoven in strategic communication aimed at different target audiences for the national TB response. They are also essential for achieving the ambitious vision of a TB-free Eswatini by 2035. ACSM therefore cuts across all aspects of TB control.

Figure 6: ACSM interventions help address five key challenges to TB control[1]



2.2 Advocacy

Advocacy refers to any action of speaking up in support of a specific issue to influence positive change. It is often directed at policymakers, decision-makers and senior government officials. It can be actioned by an individual, group, or organization. An example is taking action to help people living with TB voice their concerns and interests and obtain the health services they need in communities.

At the national level, advocacy seeks to ensure that the government remains strongly committed to implementing TB control policies. Policymakers such as parliamentarians, funders and development partners are pivotal in ensuring adequate allocation of domestic and external resources as well as providing an enabling environment for the national TB response. They also enforce government accountability for fulfilling commitments and reaching global and national TB targets.

[1]Advocacy, communication and social mobilization for TB control, A WHO Guide.
https://www.who.int/publications/i/item/9789241596176

Effective advocacy strategies for healthcare workers and TB advocates include:

- Lobbying
- Networking
- Sensitization /empowerment
- Collaborations
- Campaigns

Other types of advocacies to ignite positive changes regarding identified pertinent issues about TB control:

Policy advocacy – to inform lawmakers and decision-makers how an issue will affect the country and outline actions to take to improve laws and policies. Once informed, policymakers are expected to take action to allocate the necessary resources and improve policies that will enable the best national TB response.

Program advocacy – targets programmers to ensure that TB interventions include the views and aspirations of healthcare workers and communities at all levels.

Media advocacy – prompts the media to cover TB-related topics regularly and responsibly, to raise awareness of underlying problems and solutions. This contributes to generating support from all concerned, including government, donors, and civil society.

Advocacy tactics include:

- Policy briefs
- Formal letters
- Debates
- Peaceful demonstrations and petitions
- Testimonials
- Meetings and workshops

Results of effective advocacy:

- Enabling environment
- Political commitment
- Favourable policies and laws
- Resilient TB advocates
- Sufficient resources e.g. funds, human resources, infrastructure, work equipment, TB drugs

2.3 Communication

Communication aims to convey accurate messages to target audiences using appropriate channels. The main purpose is to influence positive behaviour changes such as persuading people with TB symptoms to seek care early and those diagnosed with TB to adhere to treatment. Communication also seeks to receive feedback to ensure that messages are well understood to achieve the communication objectives.

2.3.1 Communication Strategies

To effectively communicate with different target groups, it is important to engage in different communication strategies that appeal to individual target audiences. These strategies include the following:

(a) Community Engagement: This seeks to ensure that information is distributed correctly and timely across different sub-populations in communities. It provides an opportunity for clarification and dispelling myths and misconceptions to improve TB service uptake. Meaningful community engagement is critical and keeps people at the centre of the TB response. Engagement with communities as equal partners, moving from informing about needs and services related to local issues, to empowering them to be leaders in identifying problems and co-creating solutions as part of the national TB response[2]

(b) Digital Media Engagement: The use of digital and other social media platforms is becoming one of the most effective ways of conveying information to different audiences. These include Facebook, Twitter (X), Instagram, YouTube, Linked-In, TikTok and WhatsApp.

(c) IEC Materials: TB information, education and communication materials remain important in communicating TB messages. Different types of IEC materials (posters, brochures, pamphlets, job aids etc.) should be developed and distributed to various audiences according to their needs.

(d) Traditional Media: Though communication has evolved over the years, the use of traditional media such as radio, television and newspapers remain important in the communication of TB messages. According to recent surveys, radio remains the most effective channel for communicating health messages.

(e) Interpersonal Communication (IPC): One-on-one or door-to-door engagement of communities has proven to be another effective way of communicating health messages, including TB messages. It is important for those involved in mobilizing for the uptake of TB services to be capacitated on interpersonal communication for effective engagement and communication of TB messages.

(f) Stakeholder engagement: The national TB response is driven by various stakeholders including TB patients, TB survivors, public health programmes, other government ministries, development partners, implementing partners, health care workers, civil society organizations, community-based organizations, faith-based organizations, community volunteers, non-governmental organizations, parliamentarians, businesses, academia, media, etc. All the stakeholders must be engaged and empowered so that no one is left behind in actions implemented towards eliminating TB in the country.

[2]WHO guidance on community and civil society engagement to end tuberculosis, 2022

2.3.2 Key Messages, Target audiences and Channels of Communication

Messages should consider the audience, i.e. the key people for whom they are intended.

The message content should:

- Be short and precise
- Be accurate
- Ensure that the message is technically sound
- Emphasize the problem and the best solution
- Provide examples of successes and demonstrate the advantages.

Table 4 below summarises the target audience, various communication channels or modes to reach them and key messages.

Table 4: Target audience, communication channels/modes and key messages

Primary Audience	Communication Channels /Modes
TB patients Key affected populations (household TB contacts, PLHIV, miners/ex-miners and their families, factory workers, inmates, diabetes clients) **TB survivors**	• Health talks at the facility level • One-on-one discussions with HCWs • Support groups • Campaigns • Phone calls • Radio programmes • Television programmes • Newspapers articles • Printed and digital IEC materials (flyers, posters, pamphlets, brochures, promotional materials, newsletters) • Billboards • SMS • Short Educational videos • Facebook posts
Key Messages • Screen for TB when you experience any one TB symptom • Test for TB when screened positive • Get TB treatment for free in all public health facilities • Take and complete your TB treatment as advised by your healthcare provider • Ask your healthcare provider about TB preventive treatment (TPT), if you are eligible, start TPT and take it as advised. • To prevent the spread of TB, cover your mouth when coughing.	

Secondary Audience	Communication Channels / Modes
Health care workers Community-based health volunteers Traditional and faith-based practitioners Caregivers (parents and guardians) Families of TB patients Co-workers of TB patients Civil Society Organizations	Sensitization Meetings Training Workshops WhatsApp Groups Printed and digital IEC materials (posters, desk flipcharts, SOPs, promotional materials, etc.) Social media Emails Websites
Key Messages: Educate all clients about basic TB facts Screen all clients for TB Test all TB presumptive clients Administer correct treatment to TB clients	(a) Monitor all TB clients for treatment adherence (b) Stand-up against stigma and discrimination associated with TB
Tertiary Audience	**Communication Channels /Modes**
Implementing partners Development partners Donors Parliamentarians Journalists	Sensitization meetings Policy briefs Training workshops Media briefings
Key Messages: Support TB campaigns in communities Advocate for sufficient domestic and external resources for the national TB response Provide technical expertise in planning, implementation and evaluation of TB interventions Invest in TB and save lives Convey correct messages about TB	

2.4 Social Mobilization

Social mobilization entails engaging communities and other stakeholders to participate and take ownership of activities and strategies aimed at ending TB in Eswatini. Such activities may include community dialogues, community outreaches, road shows, meetings, door-to-door outreaches, health fairs, debates, sports, drama performances and many more. Community mobilization helps generate a wider participation and involvement of everyone including community leaders and opinion leaders to be at the forefront of activities that will contribute to ending TB in Eswatini.

Table 5 below briefly describes ACSM interventions, desired behaviours and outcomes that will contribute to ending TB in Eswatini.

Table 5: ACSM intervention and desired behaviors and outcomes

Intervention	Desired behaviours	Outcomes
Advocacy	• Government maintains TB control a high priority • Government provides quality TB services • Government ensures an un-interrupted adequate supply of TB diagnostic tests and anti-TB drugs • Policymakers remain active in advocating for TB issues	• Sufficient resources for TB control • Availability of policies that enable access to free TB services regardless of Sex, ethnicity, social status. • Enabling environment for implementing TB services by applying patient-centred care approach
Communication	• Early screening and testing for TB among all people with symptoms • Adherence to TB treatment • Collaboration and action against stigma and discrimination • Provision of quality TB services	• A significant drop in the number of TB cases • Reduction in all forms of stigma and discrimination • Improvement in access to care and quality of TB services
Social Mobilization	• Communities and stakeholders unite and take action to fight TB	• Significant increase in the number of TB-free communities

2.5 Stigma and Discrimination

Stigma is an attitude or belief that results in a negative 'label' that affects the way individuals view themselves or are viewed by others based on certain attributes perceived as socially unacceptable.

Three types of stigma:

(i) Self-stigma – internalized negative views a person holds about themselves, resulting in blame, shame, low self-esteem and self-hatred.
(ii) Social stigma – social disapproval of a person on grounds that distinguish them from others.
(iii) Stigma by association – negative label against individuals who are associated with or related to a marginalized person.

Discrimination - an action or behaviour perpetuated by stigma and often aimed at marginalizing a person and making them feel inferior. It also undermines human rights and opportunities for those perceived as different. Common acts of discrimination include rejection, avoidance, and name-calling.

Effects of stigma and discrimination include stress, depression, loneliness, low self-esteem and poor health-seeking behaviour.

Stigma and discrimination are some of the barriers that hinder access to TB testing, and treatment services and contribute to unfavourable treatment outcomes, which hamper efforts to end the epidemic. Factors and determinants of TB-related stigma and discrimination are summarized in Table 6.

Table 6: Factors and determinants of TB-related stigma and discrimination

Factors	Determinants
The history of TB Associating TB with HIV Fear of contracting TB Fear of dying Lack of exposure to people having TB Myths and misconceptions about TB	Lack of knowledge about TB Poverty Health care system Cultural belief system Sex sensitivity

Strategies to use in addressing issues of stigma and discrimination

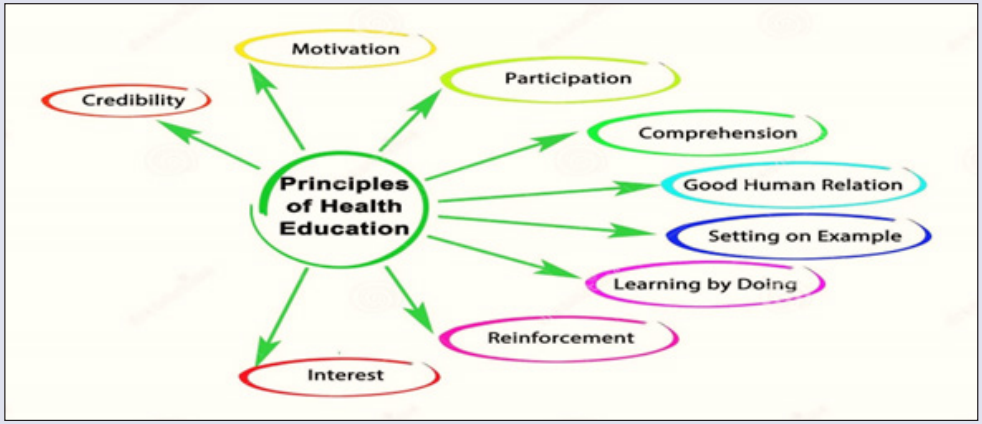
- Health Education
- Support groups (peer-to-peer engagement)
- Counselling (one on one sessions)
- Testimonials (experience sharing by TB survivors)
- Conducive environment – protecting and defending the rights of people infected and affected by TB

2.6 Health Education

Health education is a combination of consciously constructed opportunities for learning, involving some form of communication designed to improve health literacy, knowledge and developing skills which are conducive to individual and community health.

Different approaches are used when conducting health education including an individual approach such as consultation rooms, a group approach such as group discussions or role plays, and a mass approach such as using the media and IEC materials. Figure 7 below summarizes the principles of health education.

Figure 7: Principles of health education



2.6.1 Points to discuss during health education sessions are.

- Transmission of TB
- Differences between latent TB infection (LTBI) and active TB disease
- Progression of LTBI to active TB
- Signs and symptoms of active TB disease
- Diagnosis of TB
- Relationship between TB and HIV
- Relationship between TB and diabetes and other non-communicable diseases
- Treatment duration
- Possible side effects and adverse medication reactions
- Benefits of TB preventive treatment (TPT)
- Importance of treatment adherence
- Treatment monitoring methods (directly observed therapy and digital adherence technologies)
- Importance of regular medical assessments
- Importance of contact investigation
- The right to have access to free diagnosis and treatment regardless of sex, ethnicity and social status

2.6.2 Health Education Intervals for Patients

At screening: Presumptive cases

- Explain basic facts on TB (what is TB, signs & symptoms, transmission, prevention, relationship with HIV)
- Explain the procedure of TB diagnosis
- Explain how to produce a good sputum sample
- Explain to the patient that they will produce sputum at baseline and as needed during consultations

At treatment initiation

- On the day of TB treatment initiation, give emotional support regarding the diagnosis.
- Assess previous knowledge and explain facts on TB disease, including:
  - ✓ What is TB?
  - ✓ What are the signs and symptoms of active TB?
  - ✓ What are the ways of transmission and prevention of TB?
  - ✓ What does the treatment consist of?
  - ✓ How to adhere to treatment?
  - ✓ Possible side effects of treatment
  - ✓ Clinic follow-up
- What is the relationship between TB and HIV?
- What is the difference between drug-sensitive and drug-resistant TB?
- Explain the risks of taking traditional concoctions, drugs and alcohol while on TB treatment
- Explain treatment adherence methods
- In-person treatment adherence support

- Digital adherence technologies (video observed therapy and smart pill boxes)
- Discuss the patient support package, its eligibility criteria and what clients are expected to do.

At the end of the intensive phase

- Evaluate adherence.
- Address any adherence issues identified.
- Explain the change in drug regimen for the continuation phase.
- Explain the importance of continuing treatment throughout the continuation phase, even if the patient might feel better.
- When adherence issues are detected, patients should be referred to for extra patient support, education and counselling sessions.

Other health education sessions (for DRTB patients)

- For patients with pre-XDR or XDR-TB, educate them on pre-XDR and XDR-TB diagnosis, treatment options and palliative care.
- For hospitalized patients, provide one or two sessions before their discharge to prepare them for the ambulatory phase and the importance of maintaining infection control at home.
- Additional sessions can be planned according to patients' needs e.g. poor adherence, depression, mental health etc.

2.7 Risk Communication

Risk communication refers to the real-time exchange of information, advice and opinions between experts or officials and people who face a threat to their survival, health, economic or social well-being[3]. The main purpose is that everyone at risk can make informed decisions to mitigate the effects of the health threat.

For the TB response, a mix of communication approaches should be used in times of crisis to ensure the circulation of accurate information to patients, stakeholders and the general public. This could be during an outbreak of diseases and other situations that may hinder the delivery of TB services or threaten gains made in the country's TB response. Therefore, it is important to start communicating early, as soon as the threat is detected, to warn those at high risk and the general public to establish trust and ensure informed decisions, to save lives.

[3] https://www.who.int/emergencies/risk-communications/guidance

CHAPTER 3
TUBERCULOSIS CASE FINDING

3.1 Importance of TB Case Finding

The National TB Control Program (NTCP) places a strong focus on the early detection of TB cases and the delivery of prompt and effective treatment. The country has made concerted efforts to improve TB case detection, moving from traditional health facility-centric case finding to actively identifying TB cases within community settings. This strategic shift aims to detect any TB cases that might have been overlooked through passive facility-based detection methods, ensuring early diagnosis and effective treatment. Enhancing case finding in the community is crucial for reaching populations at heightened risk of TB and those with restricted access to TB services.

Thorough systematic TB screening should be carried out at every service delivery point through medical history taking and physical examination. This will identify additional presumptive TB cases that are initially missed through systematic TB case finding.

The following principles should be applied in systematic TB screening:

- Before screening is initiated, high-quality TB diagnosis, treatment, care, management and support for patients should be in place.
- Targeting groups at high risk of TB
- TB screening should follow established ethical principles for screening for infectious diseases
- The TB screening approach should be developed and implemented in a way that optimizes synergies
- A screening strategy should be monitored and reassessed continually to inform re-prioritization of risk

3.2 Screening tools for systematic TB screening

The most up-to-date WHO-recommended screening tools are symptom-based screening with 4 classical symptoms of TB, Chest X-ray, C-reactive protein and rapid molecular diagnostic tests (mWRD) for people living with HIV (PLHIV). Among these tools, the latter three will enable identifying asymptomatic TB cases. Aligning with WHO recommendation, the country has adopted 3 screening tools in this guideline (4 classical symptoms of TB, Chest X-ray, and C-reactive protein).

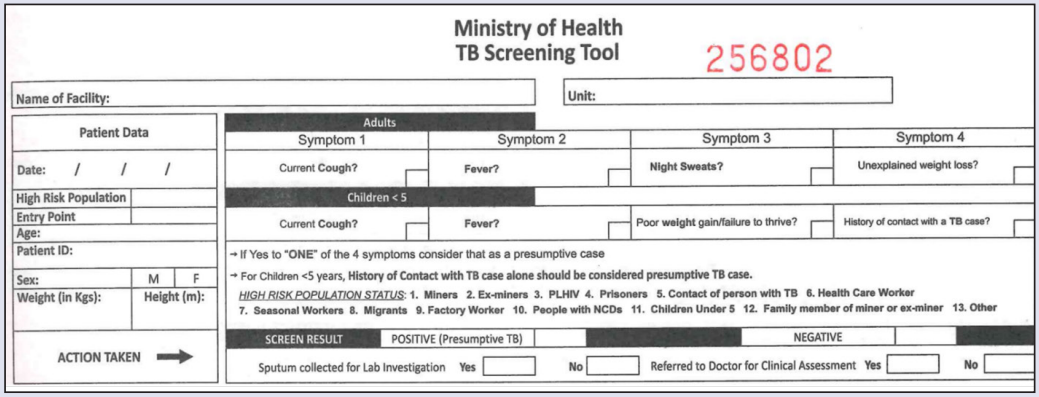
3.2.1 Standard TB Symptoms Screening Tool

The standard TB symptom screening tools include screening with the four clinical signs and symptoms of TB and are structured into two sections: one detailing the signs and symptoms in adults, and the other focusing on children under 10 years of age. The following are the four classical symptoms of TB that are applied in systematic TB screening.

- Cough of any duration
- Fever
- Night sweats
- Unintended weight loss

The presence of at least 1 sign/symptom is defined as presumptive TB. In children younger than 10 years old, having a TB contact history alone regardless of signs and symptoms is defined as presumptive TB (see Figure 8 below for the TB symptoms screening tool).

Figure 8: Standard TB Symptom Screening Tool



Ministry of Health
TB Screening Tool
256802

Name of Facility: Unit:

Patient Data	Adults: Symptom 1	Symptom 2	Symptom 3	Symptom 4
Date: / / /	Current Cough?	Fever?	Night Sweats?	Unexplained weight loss?
High Risk Population	Children < 5			
Entry Point	Current Cough?	Fever?	Poor weight gain/failure to thrive?	History of contact with a TB case?
Age:				
Patient ID:				
Sex: M F				
Weight (in Kgs): Height (m):				

→ If Yes to "ONE" of the 4 symptoms consider that as a presumptive case

→ For Children <5 years, History of Contact with TB case alone should be considered presumptive TB case.

HIGH RISK POPULATION STATUS: 1. Miners 2. Ex-miners 3. PLHIV 4. Prisoners 5. Contact of person with TB 6. Health Care Worker 7. Seasonal Workers 8. Migrants 9. Factory Worker 10. People with NCDs 11. Children Under 5 12. Family member of miner or ex-miner 13. Other

ACTION TAKEN → SCREEN RESULT: POSITIVE (Presumptive TB) / NEGATIVE

Sputum collected for Lab Investigation Yes No Referred to Doctor for Clinical Assessment Yes No

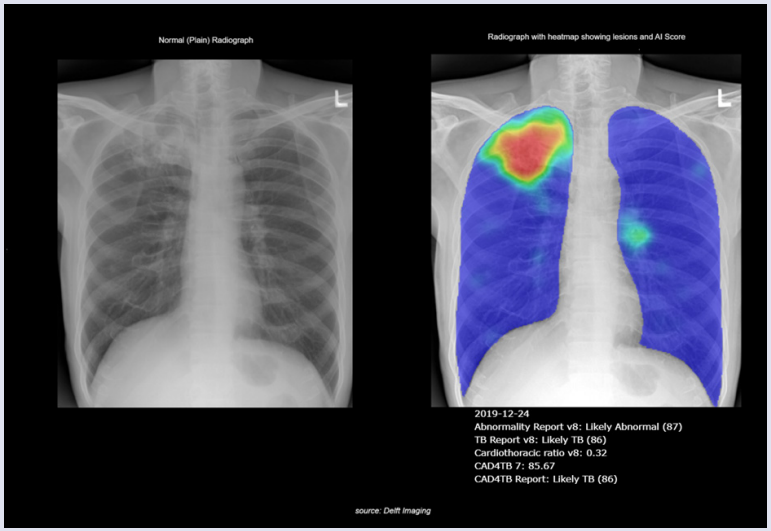
(**Note:** A presumptive TB client with a smoking history who turns out to have a microbiological test negative should have a high index of suspicion for lung cancer and be referred for further evaluation of cancer.)

These signs and symptoms should be evaluated during thorough medical history taking and physical examination.

3.2.2 Chest X-ray and Computer-Aided Detection (CAD)/Artificial Intelligence (AI)

Chest X-ray (CXR) is recommended for TB screening in both children and adults whereas CAD/AI software is to assist in reading the digitized image of CXR to determine the possibility of TB (i.e. presumptive TB/suggestive of TB), but not as the diagnostic tool. The performance of CAD/AI software reading for determining presumptive TB is the same as that of human readers and better than human readers in some studies. Abnormalities analogous to TB can be seen on a heat map by digital chest X-ray with CAD/AI software. A high abnormality score indicates the likelihood of TB which can be signified by a binary classification "TB-related abnormalities present" or TB-related abnormalities absent" as seen in Figure 9.

Figure 9: An example of a CAD/AI reading result



3.2.3 C-Reactive Protein

C-Reactive Protein (CRP) is an indicator of systemic inflammation that can be measured with a blood test. It is recommended for ART-naive PLHIV above 10 years old. Results above the cut-off value of > 5 mg/L is defined as presumptive TB. CRP should be used in conjunction with a national TB screening algorithm.

(a) Defining Presumptive TB

Anyone presenting with one or more of the following should be considered a Presumptive TB client:

Presence of one or more of the key clinical signs and symptoms of TB

- In children under 10 years old, a history of contact with a TB case alone is regarded as presumptive TB even if there are no classical signs and symptoms.
- CAD/AI reading result of chest X-ray is positive (i.e. suggestive of TB)
- CRP result of >5 mg/dl

3.2.4 Systematic TB Case Finding Model

NTCP has laid out 3 systematic TB case-finding models that include 1) Intensified case finding in health facilities, 2) Integrated occupational health screening, and 3) Community-based active case finding of TB.

3.2.5 Intensified case finding in health facilities

Intensified TB Case Finding (ICF) interventions aim to identify individuals with presumptive TB, through systematic screening of TB regardless of their primary medical concern.

All people attending health facilities regardless of their medical concern, except those on TB treatment, should be screened with the standard TB symptom screening tool at every service delivery point. In facilities where CXR and CAD/AI are available, complementary screening with these tools annually should be performed for targeted high-risk TB when they are screened negative by initial symptom screening. CXR screening is recommended only once a year to avoid unnecessary radiation exposure. See screening algorithms in Section 3.7 for systematic TB screening with CXR and CAD for non-PLHIV, PLHIV and screening with CRP for PLHIV respectively in Section 3.7). (For details, refer to the SOP for integrated CXR and CAD/AI use in Systematic TB case finding)

The following are targeted high-risk groups for CXR screening.

- PLHIV
- People with diabetes mellitus
- Household contact with TB
- Miners/ex-miners attending health facilities.
- People with Chronic Obstructive Pulmonary Disease (COPD)
- People with substance use disorders (e.g. alcohol, tobacco etc.).
- Undernourished/malnourished people (MAUC < 24.5 cm or BMI < 18.5 in adults)
- Person with immunosuppressive medical conditions or taking immunosuppressant drugs (e.g. cancer, chronic renal dialysis, prolonged steroid therapy, those having organ and bone marrow transplant, anti-TNF therapy, etc.)
- Correctional inmates visiting a health facility.

NB: All persons presenting to a health facility must be screened for TB at every service delivery point.

(a) Systematic TB screening of PLHIV

The standard symptom screening tool should be used to screen for TB at every visit, whereas CXR and CAD/ screening and CRP (only for ART-naive above 10 years old) should be used in annual screening when symptoms screening is negative. (For details refer to the SOP for integrated CXR and CAD/AI use in Systematic TB case finding)

All persons in the above high-risk population should not be taken for CXR with CAD/AI if they have done it within a year.

All persons screened for TB should be registered in the Client Information Management System (CMIS) and those identified as presumptive TB should be recorded on a "Presumptive TB Register" regardless of sample submission for TB diagnosis.

(b) Consideration for implementation of TB screening with symptoms

Clients should be screened for TB with a symptom-screening tool at every clinic visit unless they are already on TB treatment. For patients who visit the health care facility often i.e. twice within a week, considerations should be made based on the client's clinical condition as well as the result of a recent TB screening event.

3.2.6 TB case finding through Occupational Health Screening

This case-finding strategy targets the specific population that is usually required to undergo annual occupational health screenings, including miners/ex-miners and healthcare workers.

3.2.6.1 Implementing active case finding among miners, ex-miners

While annual occupational screening of miners/ex-miners is conducted in the designated occupational health centre, TB screening should be included. Mobilization of miners/ex-miners and scheduling of screening shall be organized in coordination with the mining association.

Parallel screening with standard TB symptoms screening tools and CXR and CAD/AI should be applied. See the screening algorithm for miners/examiners Figure 13 (page 40).

The presence of at least one TB symptom and/or CXR screening positive is defined as presumptive TB.

Referrals and linkages using the standardized national tool should also be made with accredited Benefit Medical Examination (BME) service providers to conduct full BME for miners who screen positive for silicosis. The BME service providers are the Occupational Health Service Centres (OHSCs), one at RFM Hospital and the other one at Hlatikhulu Government Hospital.

In addition, referral and linkage of Swazi miners working in South Africa, a cross-border standard of care has been established. Miners will be screened for TB at entry to the Kingdom of Eswatini, those already on treatment are linked to the nearest BMUs where they access refills for their medicines and their family contacts are screened, investigated for active TB and initiated on treatment if confirmed to have active TB. The ministry has made efforts to implement the Cross Border Referral System (CBRS) in the SADC member states to refer TB patients across borders for a continuum of care.

Note: Miners/ex-miners who do not undergo annual occupational screening shall be offered annual TB screening in any health facilities where they seek care. Miners working in the local mining sector and surrounding community should be included in the community-based ACF activities.

3.2.6.2 Implementing active case finding among health care workers

Health care workers (HCWs) as frontline soldiers against TB are very vulnerable to infection hence periodic screening is recommended as part of a TB Infection Control Plan and to maintain a healthy workforce in the health delivery system. TB screening programs should include anyone working or volunteering in health-care settings. Persons

(skilled healthcare workers, lay health workers, other health facility staff and support personnel) who are always in face-to-face contact or exposed to TB should be routinely screened for TB. See the algorithm for HCW screening in Figure 14.

TB screening should be done:
- At baseline or upon recruitment
- Bi-annual through their wellness clinics or corners by signs and symptoms
- Annually by CXR and TB signs and symptoms

TB Preventive Therapy (TPT) regimen should be provided once in a lifetime using 3HP to HCWs who screen negative for TB symptoms, regardless of HIV status. HIV testing should, however, be encouraged. Healthcare workers who started TPT should complete TPT as prescribed and report any adverse effects to their provider.

3.2.7 Community-based Active TB Case Finding

To increase TB case detection, active case finding (ACF) initiatives are implemented at the community level. Active case finding requires a special effort by the healthcare system to increase the detection of TB in a given population. These strategies identify and bring to treatment people with TB who have not sought diagnostic services on their initiative.

3.2.7.1 Models of Community-based Case Finding

The following dynamic models are specifically crafted for screening populations at high risk of TB. They are collectively known as "targeted approaches," tailored to address specific needs.

(a) Proactive Screening

Some examples of proactive screening are:
- Targeted screening in hot spot areas or high-risk areas
- Mass screening of children in hot spot areas
- Screening PLHIV under DSD models in communities
- Peer educator model.
- Mobile clinic outreach model

(b) Reactive Screening

Examples of reactive screening are:
Household contact tracing and screening, cluster screening and mass screening in the reported outbreak areas.
Community Education and Awareness Campaigns to prompt earlier care-seeking for TB symptoms at healthcare facilities.

These active case-finding models may be implemented through community outreach activity by community health volunteers in collaboration with other community partners or a team including the provision of integrated mobile clinic services.

Screening tools for community-based TB screening:

- Standard TB symptoms screening tool (mentioned above) is a basic tool to apply in every ACF activity
- CXR and CAD/AI shall be utilized if available.

The following is a contextual selection of key-affected populations who are at high risk of TB in Eswatini. These groups should be targeted for ACF activity.

- Close contacts with TB including household contacts
- PLHIV
- People in congregate settings including correctional facilities, orphanages, institutional accommodation, retail shops, informal traders, religious gatherings, etc
- Individuals with occupational health risks including miners, ex-miners and labour-sending communities, factory workers, public transport operators (in industries such as sugar, textiles, and bottling) and their respective communities
- Individuals with predisposing medical conditions including malnutrition, diabetes, a history of TB, chronic lung disease, or other underlying conditions that increase their risk of TB
- Populations with structural risk factors for TB and limited access to healthcare, such as the urban poor, homeless individuals, refugees, migrants, and other vulnerable or marginalized groups
- Communities where an outbreak occurs.

Mapping should be done to identify hotspots in consideration of factors such as where the targeted population reside and areas with high case notification or under notification.

3.2.7.2 Implementing active case finding in communities through contact investigation

Contact investigation is the process of finding, screening, notifying, and treating people who might have TB infection (previously called latent TB infection-LTBI) or TB disease as a result of recent contact with a person diagnosed with TB disease. This process should be undertaken promptly after a TB patient is identified (index case) regardless of if they are bacteriologically confirmed TB (BC-TB) or clinically diagnosed TB (CD-TB).

(a) Goals of contact investigation

The goals of contact investigation are to identify and treat people with active TB disease as early as possible and to identify contacts who might have been infected with TB and provide them with treatment for TB infection (TBI), which prevents the progression of TB disease.

(b) Identification of TB contacts through index TB case

Contact investigation should be considered for all contacts of index patients who are confirmed as having active TB disease. An investigation is recommended if the index has pulmonary TB regardless of bacteriological confirmation since not all index cases are the source cases. During consultation to initiate TB treatment, the clinician should obtain verbal consent from the index case to visit the household for contact tracing. The extension of contact investigation beyond household contact may be considered (e.g. workplace, boarding

school, orphanage, disabled home, refugee camp, etc.) if resources are available. It is the responsibility of all healthcare workers to facilitate active screening of contacts, sputum collection in contacts with presumptive TB, transportation of samples and referral for further management.

(c) Source Case Investigation

A source case investigation seeks the likely source person with TB disease who might have infected the index case. If the index case is a child, reverse contact tracing/source case investigation is conducted to identify the individual who might have infected the child. TB disease in children aged <5 years typically indicates that the infection must be recent.

(d) Procedures of contact investigation

- Educate index about the importance of contact investigation and obtain consensus on the home visit by community cadres for TB screening of household contacts
- Record the list of contacts as enumerated by the index case including address and contact number in the contact investigation (CI) register
- All contacts should be traced and screened primarily with the TB symptom screening tool mentioned above.
- Upon identification of more household members than listed in the initially registered in the CI register, update the contact list.
- Collect sputum specimens from the people identified as presumptive TB and transport samples to the nearest laboratory
- Refer children less than 10 years old and those who cannot produce symptoms
- Chest X-ray screening should be conducted for TB contacts (both adults and children) attending health facilities with X-ray or in mobile clinic service.
- All presumptive TB identified by TB symptoms screening or by CXR should be evaluated for TB with microbiological tests. Gene X-pert, LF-LAM for PLHIV) as per the national diagnostic algorithm (see the diagnostic algorithm (Figure 16) in the chapter on TB diagnosis).
- TB treatment should be started immediately for those diagnosed with active TB disease.
- After exclusion of active TB disease, TB preventive treatment (TPT) should be provided to all contacts, children and adults, after evaluation of eligibility for TPT (see details in TB Preventive Treatment Chapter)
- Contact investigation for all household contacts of TB should be done every 3 months, spreading over 9-month periods using a symptom screening tool. CXR screening should be performed at the initial screening episode (baseline) or the repeat screening if not done in the baseline screening
- All household contacts and close contacts who have symptoms compatible with active TB should be offered HIV counselling and testing as part of their clinical evaluation.

3.2.7.3 Implementing active case finding in communities through integrated mobile clinics

For the population that is either underserved or without access to health services or residing in a hot spot area or congregate setting, community-based active TB case finding using an integrated mobile clinic (IMC) is an important strategy to improve TB case finding. The IMC is a mobile medical unit

equipped with tools for TB screening and diagnostics (e.g. X-ray, Gene X-pert lab), HIV testing service and non-communicable disease (NCD) including diabetes, hypertension and lung cancer screening. The IMC visit will be prioritized in TB hot-spot areas as identified through artificial intelligence technology-driven hot-spot mapping using epidemiological, socio-demographic and geospatial data. Parallel screening with TB symptoms screening tool and CXR read by CAD/AI should be used. Its advantage is that it provides opportunities for early detection and treatment of TB and other morbidities.

Preparation and community mobilization should be conducted in advance before the IMC activity is conducted in a particular area. The following are activities to be undertaken before the IMC visit.

- Meeting with community leaders/relevant authorities (e.g. community inner-council (bandlancane), correctional facility authorities/factory management) 2-3 weeks in advance once a hot spot/an out-reach area is identified
- Schedule date, venue, designated crowd controller (e.g. community police) for IMC in agreement with community leaders
- Community awareness campaign
- Ensure availability of the dedicated service delivery team (including HR listed above)
- Ensure logistics required (fuel, lab and commodity supply, medical equipment, IEC material, register, generator if required, etc.)

3.2.7.4 Implementing Active Case Finding among People living with HIV (PLHIV) in the community

To strengthen TB and HIV integration community health volunteers (CHVs) are trained using a comprehensive training package included.

- Screening PLHIV for TB and testing presumptive cases for HIV using the self-testing kit.
- Offering assisted HIV self-testing to Presumptive TB cases aged ≥ 16 years with HIV negative or unknown status, and their household members.
- Referring exposed children under two years old 2 years old to the health facility for HIV testing if there is no documented evidence of testing
- Referring those aged between two and sixteen years to community partners, outreach clinics or facilities for testing.
- Refer those who test positive on the self-test kit to the nearest health facility for confirmatory testing.
- Referring to those who test negative and are at high risk of HIV infection for PrEP

Note: Those who refuse assisted testing should not be denied the self-testing kit, but ACF should follow up to discuss the results and write referrals where necessary.

Community healthcare workers must follow up with health facilities to ensure successful referrals and linkages. Several kits distributed, assisted self-testing results, unassisted self-testing results, referrals, linkages, and documented facility confirmation of positive status should be documented in the self-testing logbook and monthly reports submitted to Regional SID. In addition, HIV-negative status, and facility-confirmed HIV-positive status must be documented in the facility presumptive TB register, contact tracing logbook and facility contact tracing register.

3.3 TB Case Finding in Special Circumstances

3.3.1 Implementing Active Case Finding for TB Among Inmates (Correctional Facilities)

The World Health Organization reports that TB incidence among inmates is 100 times higher than that of the general population. There is a need to strengthen case-finding interventions in correctional facilities. To improve the detection of active TB in this target group, continued education and screening is recommended among inmates, warders and other correctional services staff.

People in correctional facilities and other high-risk institutions who are eligible for screening include both inmates and facility staff. When started screening, it is important to ensure that good treatment and case management, as well as effective mechanisms for continuing treatment after transfer or discharge, are in place.

This guideline recommends that all correctional services facilities in the country provide active case finding among inmates and correctional facility officials. Active case finding should be included.

- Provision of TB screening using the national TB screening tools (symptoms and/or CXR and CAD/AI)
- Collection of sputum samples from inmates screening positive.
- Investigating inmates who are presumptive for TB through the Xpert MTB/RIF Ultra test
- Initiating inmates who are confirmed to have active TB on treatment preferably in the correctional clinic or to the nearest BMU.
- Screening in correctional facilities should be combined with efforts to improve living conditions and infection prevention and control. As much as possible, TB screening in correctional institutions should be combined with screening for other diseases and health promotion activities.

Inmates must be screened for TB upon entering the correctional facility and additionally as follows:

(i) Quarterly (Proactively)
Those with a negative TB screen should be provided with TPT if not received in the past regardless of HIV status.

(ii) On every clinic visit.
Cellmates of diagnosed inmates with TB must be screened and provided with appropriate diagnostic and treatment services.
Where TB is ruled out, TPT must be provided for the cellmates.

(iii) Inmates must also be screened on release.

Note: Correctional staff and their dependents need screening periodically (at least twice a year).

3.3.2 Implementing active case finding in schools and training institutions

This category includes childcare centres, pre-schools, primary and high schools, vocational schools, colleges and universities. The NTCP collaborates with the School Health Programme when an investigation is considered in schools.

Moreover, teachers should be trained in the identification of signs and symptoms of TB and infection prevention and control to prevent TB transmission.

Strategies to reach school children and students in tertiary institutions:

- Screen all children in schools in contact with index clients (teacher or students).
- Screen all close and casual contacts from home and community.
- Engage the school health team to incorporate TB screening in their services.
- Advocate for self-screening at the beginning of each term.
- Train peer educators on TB/HIV and ACF strategy.
- Incorporate TB in the training curriculum at all levels of education.

3.3.3 Implementing active case finding in migrants and congregate settings e.g. orphanages; refugee camps and migrants

The ACF strategy targets all institutionalized children in Eswatini to implement TB control activities such as TB screening and infection prevention, to reduce TB transmission among the children and caregivers. Screening should be conducted at least twice a year, and a peer education programme should be conducted for continuity.

The ACF strategy should also include migrants including displaced populations and refugees. ACF activities should be carried out in the refugee camp regularly, reinforced with a continuous surveillance system.

3.3.4 Implementing active case finding among factory workers (Textile workers)

NTCP collaborate with Eswatini Business Health (EBH) in terms of investigating TB among employees in the private sector or business entities. Textile workers should be screened at their workplaces quarterly by trained Peer educators through symptom-based screening. Workers who have presumptive TB should be referred for diagnosis, treatment and care.

3.3.5 Implementing active case finding among people living with non-communicable diseases

The Kingdom of Eswatini has made a tremendous effort to capacitate community healthcare workers (CHWs) and engage stakeholders to integrate community TB activities with NCDs including chronic lung conditions (CLCs) such as asthma etc. CHWs should screen community members for NCDs and CLCs and refer those with risk factors to healthcare facilities using the national referral tool. Integration of community-based TB services with NCDs and CLCs is a holistic community healthcare system where community members identify signs and symptoms of TB and risk factors for NCDs and CLCs for early treatment and to improve quality of life. A syndromic approach will be applied to screen TB and other chronic lung diseases.

3.3.6 Syndromic referral approach to cough and other signs of TB/CLC

The entry point for the integration of TB with CLC is chronic cough as a key symptom of underlying problems. For standardisation, cough of any duration needs to be investigated. If tests for TB are negative but the cough persists, further tests for CLC need to be undertaken.

Chronic cough may be present due to several factors including:

- Asthma
- Bronchiectasis
- COPD
- Left Heart Failure
- Lung Cancer
- Tuberculosis
- Other Conditions

CHWs should normally screen and refer those with signs and symptoms to the Primary Health Care (PHC) clinic as the first step. The PHC should determine whether patients need further diagnosis for conditions that cannot be managed at the PHC and, if so, refer them further to the nearest hospital or specialist facility. Referral and feedback tools should be used at each stage of referral (i.e. CHW to PHC, PHC to hospital/specialist facility).

CHWs are closely linked to PHCs with a formal system of referral that feeds into the national monitoring and reporting system. At PHC level CHWs are provided with information about the diagnostic outcome of each presumptive case referred through a feedback loop. In addition, CHWs need to maintain close follow-up of all those receiving treatment to ensure that those whose symptoms persist despite treatment completion are re-referred to the PHC or more specialized facilities or hospitals. Similarly, PHCs must use referral tools to hospitals or specialized TB/CLC facilities and ensure a feedback loop is also provided to them for onward relay to the CHW in whose area the patient resides for follow-up and support.

Some potentially life-threatening conditions should be treated as “red flag symptoms” (e.g. Chest pain). CHWs are capacitated to recognise such signs and utilize a tool (see Table 7 below) to assist them ask the right questions to ensure such “emergency” cases are rushed to the nearest health facility.

It should be stressed that the enhanced screening of persons with cough by CHWs should not result in the CHW being viewed as a diagnostician either by themselves or by others. Rather, their general awareness of causes of cough should be raised and they should recognise that chronic cough is a sign of a range of possible diseases or conditions.

Table 7: Symptomatic Referral Chart

Signs and Symptoms	Possible Causes	Action by CHW
Current Cough	• Disease (TB, Asthma, COPD, Heart Failure) • Environmental toxins (smoking, silent smoking, dust) • Medications (medications that may cause cough as a side effect e.g., ACE inhibitors as anti-hypertensive) • Allergies (pollen, animals)	Referral to PHC
The cough persists after treatment	Prior misdiagnosis of disease	Re-referral to PHC or nearest hospital with details of persistence noted
Cough continuing with negative TB diagnosis	Possible Cancer or other CLC	Referral to the nearest hospital or back to PHC with details of persistence noted
Wheezing	Asthma	Referral to PHC
Weight Loss	TB	Referral to PHC/TB clinic
Night Sweats	TB	Referral to PHC/TB clinic
Fever	TB	Referral to PHC/TB clinic
Change in voice quality persisting over 1 week	Cancer	Referral to PHC/nearest hospital
Red Flag Symptoms: • Noisy breathing • Swelling of limbs or face/neck • Chest pain • Blood in sputum • Continuous coughing • Confusion • Rapid breathing with palpitation	Potentially life-threatening symptoms for immediate attention and treatment	Urgent and immediate referral to nearest health facility whether PHC or hospital and follow up

3.3.7 Bidirectional screening for TB and COVID-19

Bi-directional screening for TB and COVID-19 should be done simultaneously to identify presumptive and suspects of TB and COVID-19 respectively because the two conditions' clinical manifestations mimic each other. In addition, clients who have a high risk of TB such as persons with diabetes mellitus, elderly (more than 60 years old), immuno-compromised conditions etc are at risk of severe forms of COVID-19 too. Bi-directional screening will help identify both TB and COVID-19 for early and effective management of both diseases. Moreover, both persons with presumptive TB and confirmed TB should be offered COVID-19 vaccination when fever and other COVID-19 symptoms are absent.

3.4 Strategies to ensure optimal TB screening coverage

To ensure optimal coverage of TB screening, the following approaches can be applied.

Ensuring if a client has been screened or not by:

- Checking the copy of the screening tool that is given out to the client (recording in the CMIS) by the screening officer/any community cadre by the attending clinicians
- Using a stamping strategy (i.e. giving stamped paper to the client and checking by attending clinicians if screening is done or not)
- Repeated screening at multi-service delivery points
- Cascade analysis and continuous quality improvement using the data of screening activities

3.4.1 Cascade analysis and continuous quality improvement

It is recommended to conduct analyses of screening data across the cascade regularly. The following indicators across the cascade are to be reviewed (see Table 8) for TB screening in the health facility weekly and within a week after each integrated mobile clinic visit in the community.

A cascade analysis team may be formed in a health facility. The team may be composed of a team lead as designated by the facility manager, a CMIS focal person in a health facility, an ART clinic team lead, a TB clinic team leader, or another outpatient service department team leader. The team will agree to meet on a scheduled day of the week. *CMIS focal will produce a screening cascade dashboard, TB contact investigation dashboard and the list of clients that are missing at each stage of the cascade if any.* This will help the facility team to review the cascade.

At the national and regional levels, the review should be made at least quarterly and monthly when the functionality of an electronic case-based system (i.e., Client Management Information System – CMIS).

Table 8: TB screening cascade

TB symptoms screening positive cascade	Number ()
Total number of clients who attended OPD	
Number of clients screened with TB symptoms	
Number of clients screened positive for TB symptoms	
Number of clients screened positive submitted sputum samples.	
Number of clients screened positive and evaluated for TB by WRD (GeneXpert and/or TB-LAM)	
Number of clients with WRD positive results (i.e. Bacteriologically confirmed TB, BC-TB)	
Number of BC-TB clients put on Anti-TB treatment.	
TB symptoms are negative and CXR screening cascades	
Total number of clients who attended OPD	

Number of clients screened with TB symptoms	
Number of clients screened negative by TB symptom screening	
Number of clients screened by CXR	
Number of clients screened positive by CXR	
Number of clients CXR screened positive and evaluated for TB by WRD (GeneXpert and/or TB-LAM)	
Number of clients with WRD positive results (i.e. Bacteriologically confirmed TB, BC-TB)	
Number of BC-TB clients put on Anti-TB treatment.	
Number of clients put on Anti-TB treatment (both BC-TB and CD-TB)	
TPT Enrolment	
Number of clients eligible for TPT	
Number of clients put on TPT	

Any gaps/leakage identified must be acted upon as quickly as possible. Table 9 below shows an example of some possible gaps and actions to be taken.

Table 9: Example of possible gap identified by cascade analysis and action to be taken

Gap	Action to be taken
Low screening coverage by CXR and CAD/AI	Identify which entry point has the lowest coverage (e.g. PLHIVs at ART clinic, TB contacts at TB clinic, persons with diabetes at NCD clinic, children at MCH clinic)
	Remind the relevant HCWs to identify the missing clients and refer them for CXR
Presumptive TB clients missing sputum submission	Follow-up the presumptive TB clients failing to submit sputum samples through community cadres (rural health motivators/TB champions, expert clients)
	Strengthen training to clients on how to collect a good quality sputum sample
Missing microbiology test results	Follow-up at the laboratory
Missing clients diagnosed with TB to initiate TB treatment	Follow-up on clients not initiated on TB treatment in collaboration with community cadres/CSOs
Missing eligible clients to initiate TPT	Reminder to offer at next visit (e.g. PLHIV, clients with silicosis, etc.,)
	Follow-up through community cadre to return for the TPT initiation (household TB contacts)

3.5 Linking people with presumptive TB for diagnosis and treatment

All presumptive TB identified in any settings (either in health facilities or the community) should be evaluated with microbiological tests (i.e. Xpert MTB/Rif Ultra test, LF-LAM for PLHIV). Two sputum samples should be collected from all people with presumptive TB. In children below 5 years old, a stool sample should be collected. For children 5-15 years old, a stool sample should also be collected when a sputum sample cannot be collected. All health facilities without on-site GeneXpert machines should send samples collected for TB laboratory investigation to the nearest laboratory along the sample referral hub-and-spoke network. The samples collected in the community should be sent to the nearest health facility. All people diagnosed with active disease (both bacteriologically confirmed and clinically diagnosed with TB) should be initiated on TB treatment as early as possible. In the event of any delays in treatment initiation, health facilities should coordinate with CHWs to trace the clients and refer them for TB treatment initiation.

3.5.1 Sputum collection at the community level

Make an appointment to collect two sputa samples within 24 - 48 hours depending on the accessibility of the local facility /National Sample Transportation System schedule and the TB diagnosis capacity of the local facility.

Correctly label the sputum bottles and give them to the person (or guardian of the person) being investigated for TB.

At the time of sputum collection, complete the sputum request form and attach the pink stickers for proactive case finding (door to door) and yellow for contact tracing (reactive).
Remind the patient with presumptive TB to produce the sputa on the day on which it will be transported to the nearest health facility.

3.5.2 Sputum Collection, Labelling, Storage and Transport

At least two sputum specimens should be taken from a person with presumptive TB. This can be done using either of two strategies:

Spot-Spot

At the first encounter with the patient the first specimen, referred to as the “first spot specimen”, is collected on the spot and the patient is provided with a sputum specimen container for the collection of a second specimen, referred to as the “second spot specimen”, at least one hour apart.

Spot – Morning

At the first encounter with the patient the first specimen, referred to as the “spot specimen” is collected on the spot. The patient is then provided with a sputum specimen container for collection of a second sample. Referred to as the “early morning specimen”, on waking up the next morning while at home.

To ensure reliable laboratory test results, it is important to ensure that each sample is macroscopically of good quality and that a minimum of 2ml is served into the specimen container.

3.5.3 Sputum Specimen Collection Procedure

It is important to inform the client of the importance of proper sputum collection (see 3.7.1 for educational message and illustration for proper sputum collection). The healthcare worker should take time to explain the steps fully and make sure that the patient with presumptive TB has comprehended the instructions.

Collection of sputum specimens should be performed in an area with excellent natural ventilation, preferably outside in an open space; try as much as possible to maintain privacy as sputum specimen collection should be viewed as part of clinical consultation.

- Demonstrate a deep cough from the bottom of the chest, beginning with deep breathing.
- The person must be encouraged to produce a specimen after deep coughing.
- The patient should rinse his/her mouth with water first, to remove any residual food particles from the oral cavity.
- Give the patient the specimen container

The patient should be properly instructed on the importance of directing the sputum into the container and not contaminating the outside of the bottle.

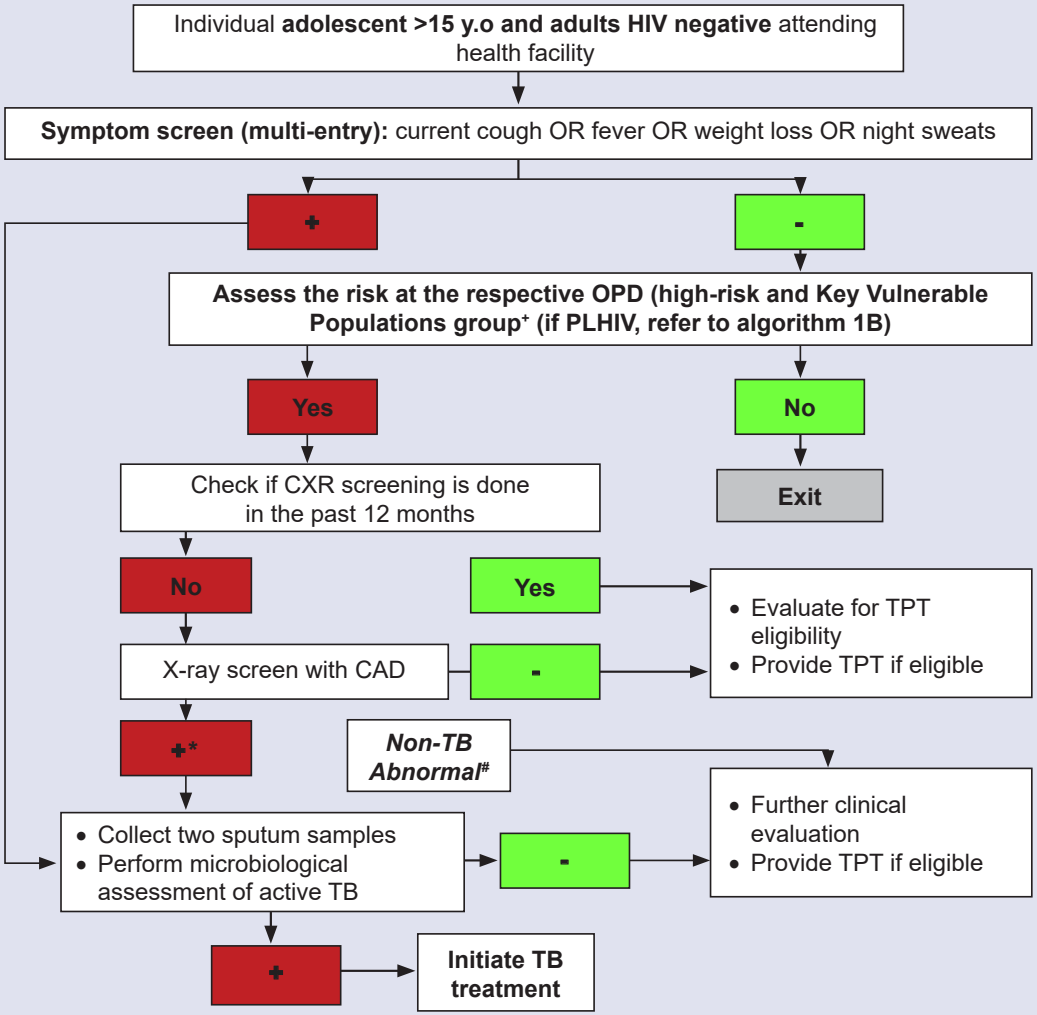
- When supervising the collection, do not stand in the windward direction from the patient
- Ensure the lid is securely closed
- Instruct the patient to wash hands after handling the sputum specimen.

3.6 Recording of TB case-finding activities

ALL presumptive TB cases detected in every model of TB case finding (either in health facilities or the community) should be recorded in the Client Management Information System (CMIS) or the paper-based presumptive register before sputum and other tests are requested. Recording the sample submission status, test results, and treatment initiation status of all confirmed TB cases should also be documented in the CMIS or a paper-based register. Health facilities should review the cascade of screening weekly and take action on any leakage/gap identified across the cascade (refer to details for the SOP on the integrated systematic TB screening with CXR and CAD/AI use)

3.7 TB screening Algorithms with CXR and CAD/AI use

Figure 10: TB screening algorithm HIV-negative individuals 15 years old and above in health facilities installed with Xray and CAD/AI

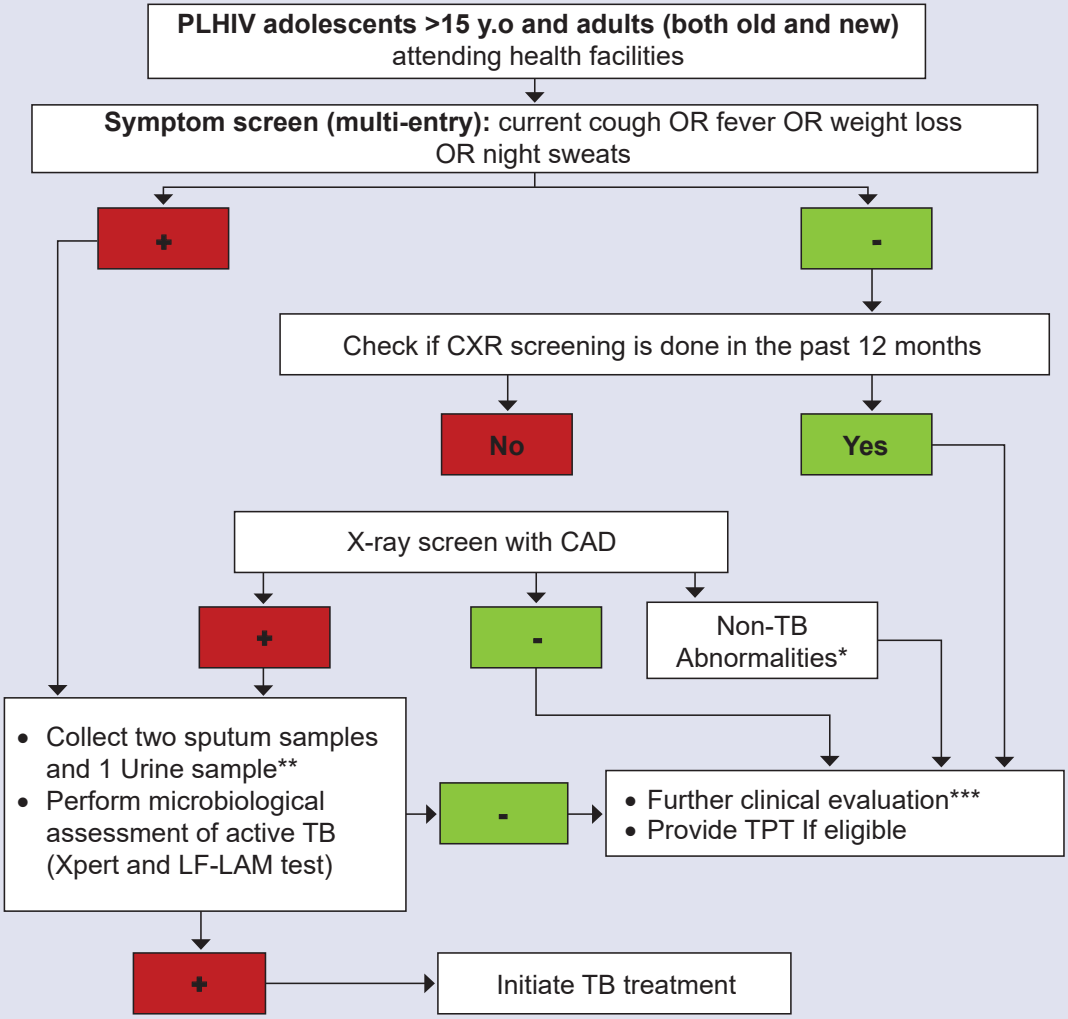


+Key Vulnerable Population groups include: TB contacts, PLHIV, miners / ex-miners*, COPD, diabetes mellitus, immunosuppressive conditions (including cancer), undernourished, inmates, smokers, alcohol/substance misuse

****If CAD reports silicosis positive refer for further assessment and treatment for sillicosis and provision of TPT if eligible***

Abnormal (not TB): e.g. cardiomegaly, possible cancer, silicosis, etc, (If smoking history is present and possibly cancer is identified in the CXR, highly suspicious of cancer).

Figure 11: TB Screening algorithm for PLHIV 15 years old and above attending health facilities with access to Xray and CAD/AI

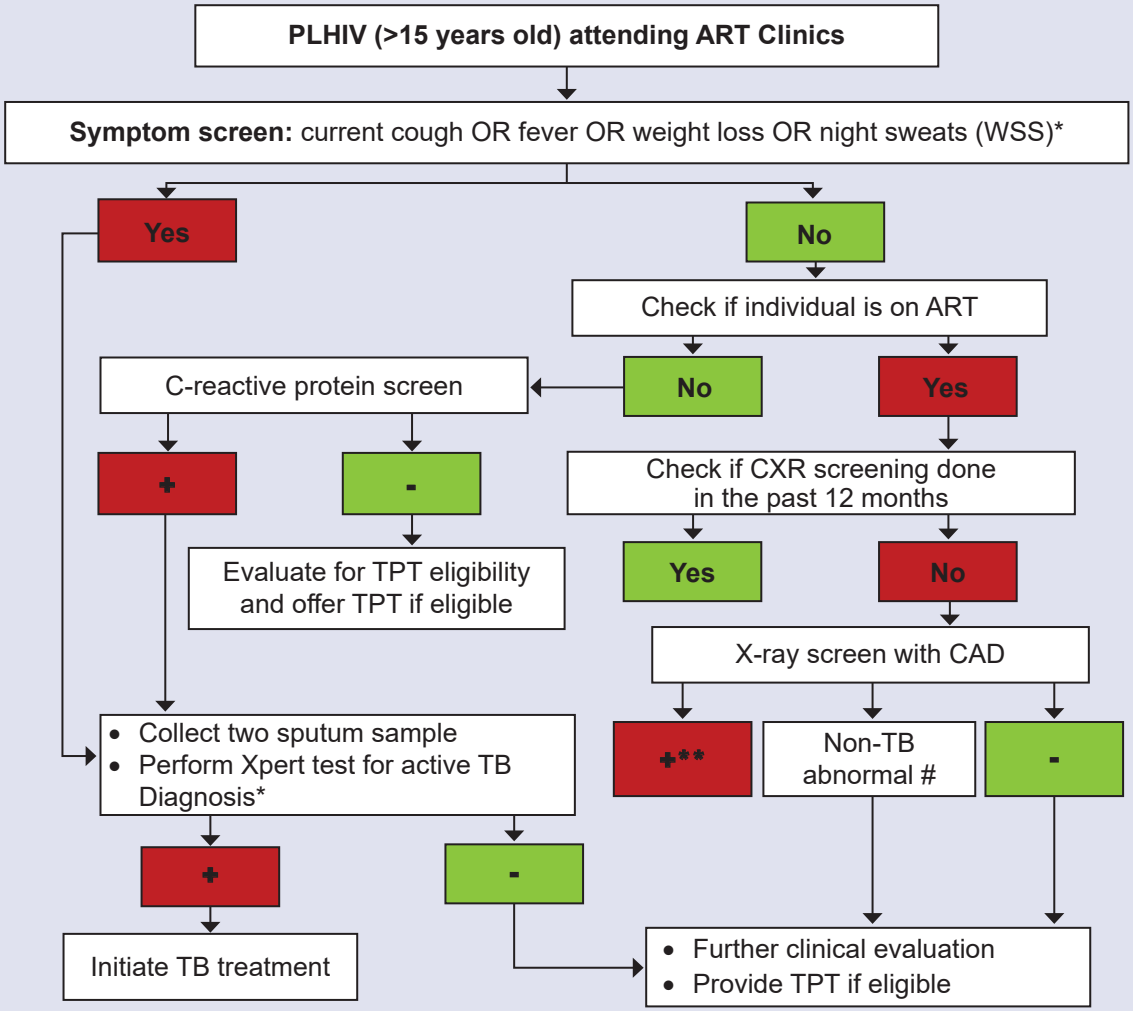


**Abnormalities e.g. cardiomegaly, possibly cancer, silicosis, etc*

***Urine sample is to be collected for any AHD client regardless of TB symptoms and /or CAD screening results for LF-LAM test.*

**** Further clinical evaluation includes clinical assessment on resolution of TB symptoms re-reading of CXR by trained clinical and further management/specialist referral as required. Upon re-read. If CXR suggestive of TB is identified among Non-TB abnormalities, evaluate for TB.*

Figure 12: TB screening algorithm for PLHIV 15 years old and above attending health facilities with access to Xray and CAD/AI and CRP

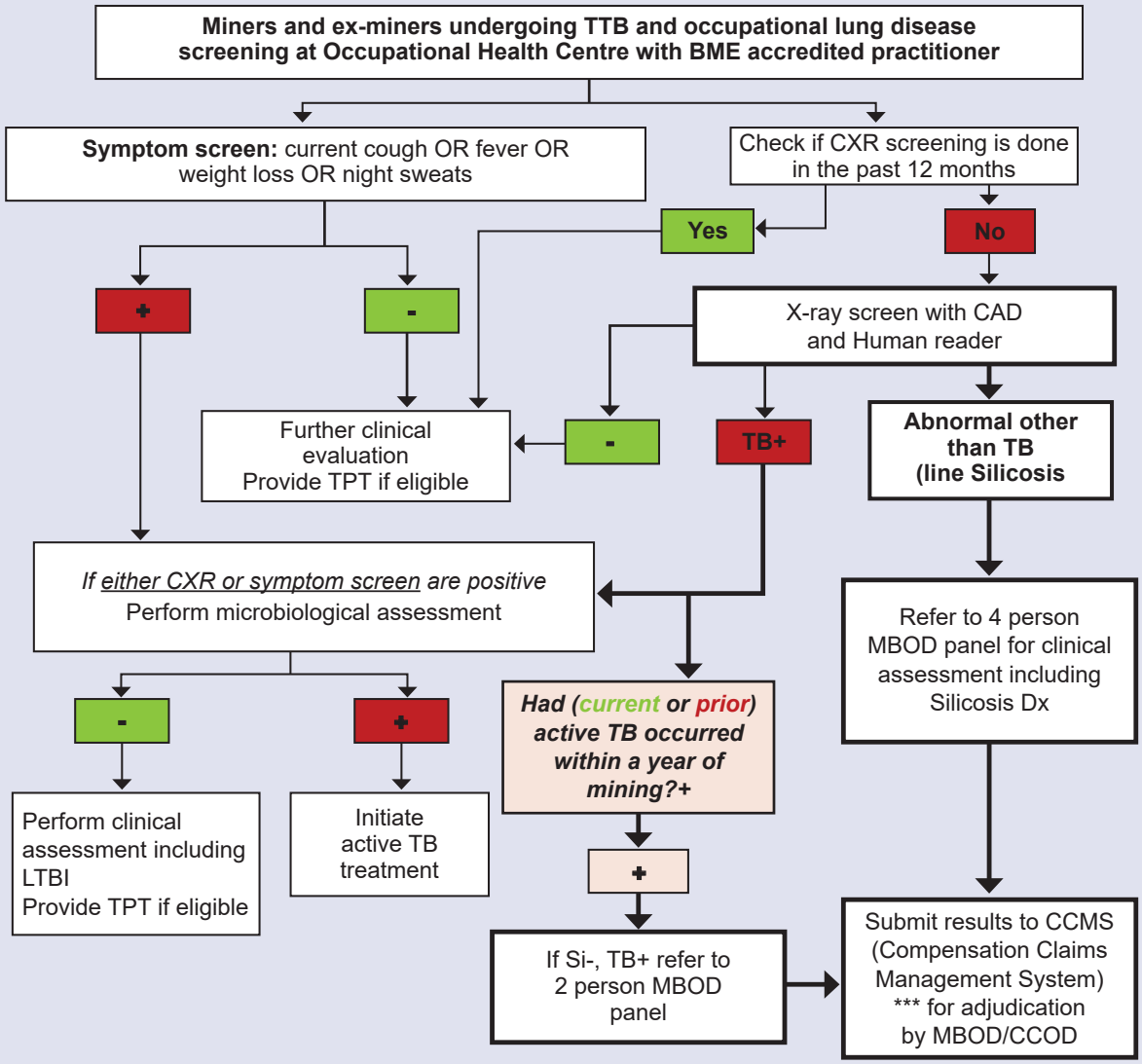


**Perform TB-LAM for all AHD (CD4<200, WHO stage 3 or 4 regardless of S/S, seriously ill regardless of CD4, all presumptive TB regardless of CD4*

***If CAD reports silicosis positive refer for further assessment and treatment for silicosis and provision of TPT if eligible*

#Abnormal (not TB): e.g. cardiomegaly, possible cancer, silicosis, etc, (If smoking history is present and possibly cancer identified in the CXR, highly suspicious of cancer).

Figure 13: TB screening algorithm for miners/ex-miners and their families using CXR and CAD/AI in the occupational health centre



Note: CAD reading for Silicosis is only preliminary reading and confirmation is by human expert reader

***Active and (inactive) 'Post-TB' both eligible for compensation if active TB had occurred as a miner or within one year of leaving the mines, OR with silicosis**

Figure 14: TB screening algorithm for health care workers using CXR and CAD/AI in the wellness centre

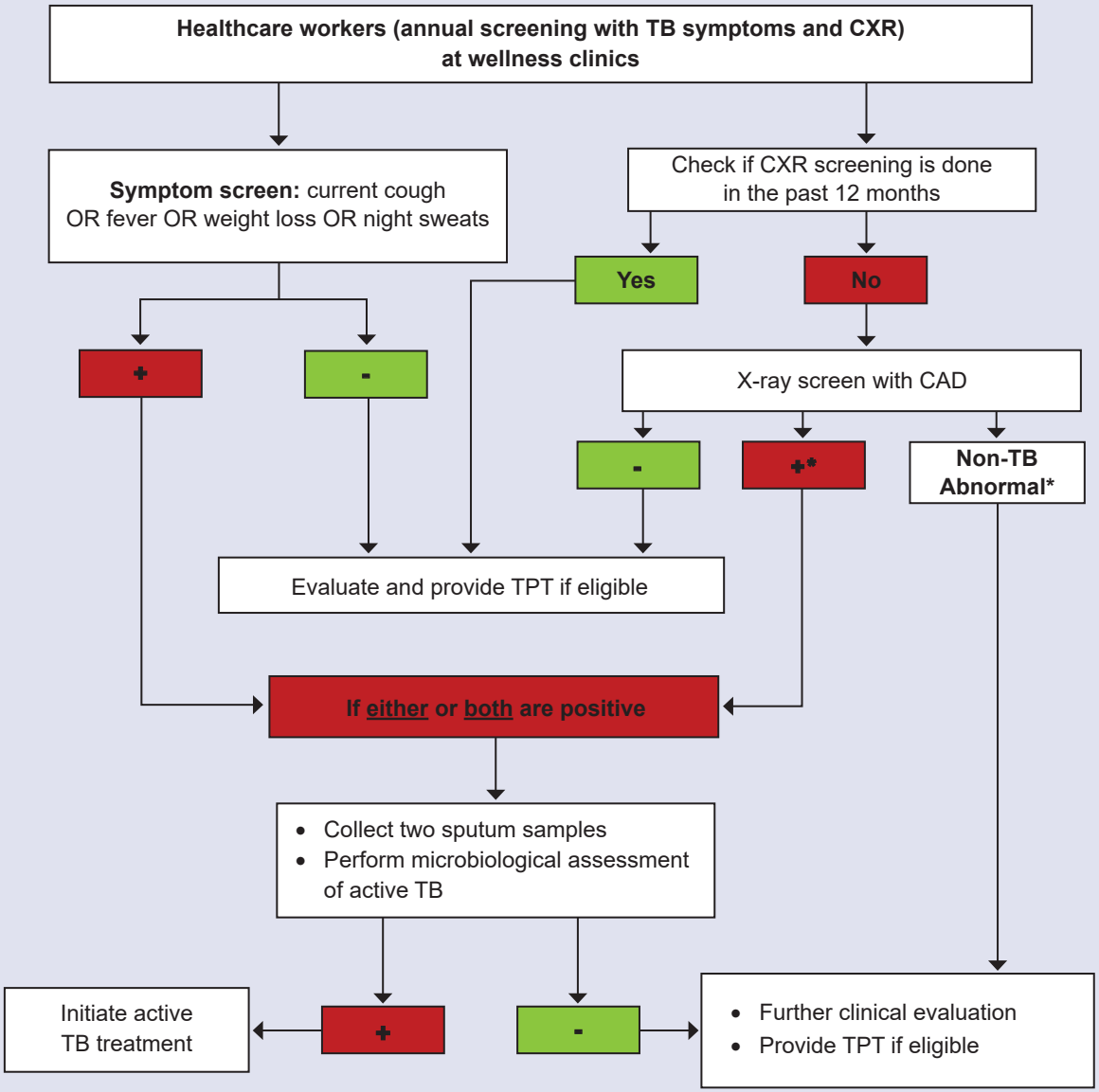
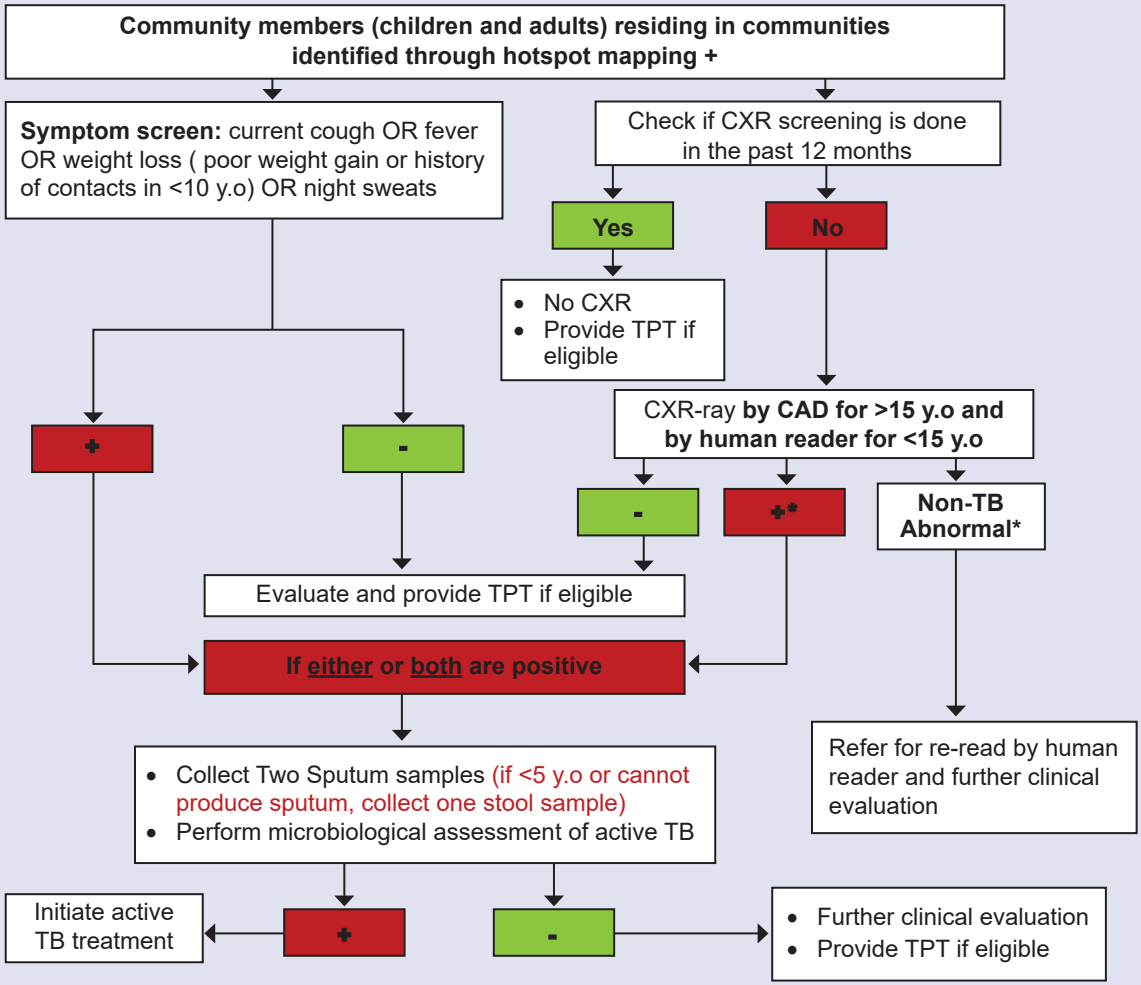


Figure 15: TB screening algorithm (3) for community member children and adults attending Integrated Mobile Clinic (IMC)



\+ *Criteria to identify in hotspot include: miners/ex-miners, factory workers and their respective communities, correctional inmates (annual screening), populations with structural risk factors for TB and limited access to healthcare, TB contacts, PLHIV, COPD, Reported Outbreaks*

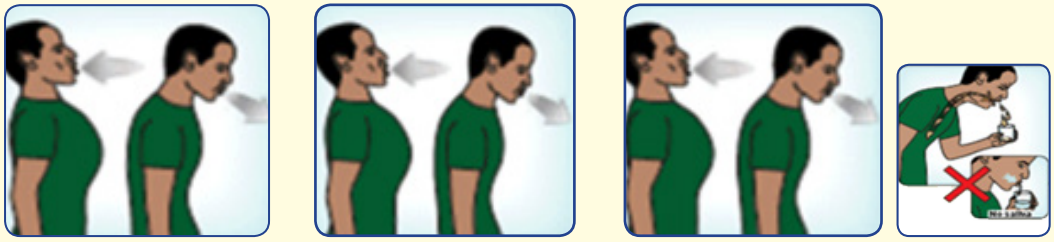
If CAD reports silicosis positive refer for further assessment and treatment for silicosis and provision of TPT if eligible.
#Abnormal (not TB): e.g. cardiomegaly, possible cancer, silicosis, etc. (If smoking history is present and possibly cancer is identified in the CXR, highly suspicious of cancer).

3.7.1 Education message for proper sputum sample collection

The screening result shows that you may probably have Tuberculosis (TB), which is caused by germs. However, it is a curable and preventable disease. Delaying diagnosis and treatment of TB can damage your lungs and can spread the disease to others. To avoid such consequences, early diagnosis and treatment are important. Getting a good quality sputum sample is important to have accurate diagnosis. Hence please follow the following guidance for the collection of sputum sample.

- Collect sputum in a well-ventilated area away from other people/or in a designated area.
- Collecting sputum from deep inside your lungs ensures accurate results. Saliva from your mouth is not suitable for this test.
- If you just have food, rinse your mouth with clean water. Presence of food particles can compromise the test result.
- Do breathing exercise; Take a very deep breath and hold the air for 5 seconds. Slowly breathe out. Repeat 3 times. Then cough out hard from the chest until some sputum comes up into your mouth. Spit the sputum into the plastic bottle.
- If it is still difficult to get sputum, drink a cup of water. After 10-15 minutes, repeat the same breathing exercises and collect sputum.
- Collect 1-2 teaspoonful or a marked line on the plastic bottle, but not more than half of the bottle.
- Screw the cap tightly on the bottle to avoid leakage. Wipe out any spill on the bottle with tissue paper.
- Submit the samples at the laboratory (or designated point).

BREATH IN AND OUT 3 TIMES



(Source: https://www.vdh.virginia.gov/content/uploads/sites/112/2019/04/Lab.pdf)

CHAPTER 4
TB AND DRUG-RESISTANT TB DIAGNOSIS

4.1 Approach to TB Diagnosis

Diagnosis of TB starts with identifying persons with presumptive TB through systematic screening using TB screening tools, by signs and symptoms and/or Chest Xray (CXR) or CRP in ART naïve clients. Medical history taking and physical examination at every service point will identify additional presumptive TB cases that are initially missed at systematic TB cases finding at the entry gate of the facility. Confirmation of active TB disease is primarily by microbiological tests. Clinical diagnosis of TB is followed only when microbiology tests cannot confirm active TB disease. Microbiological diagnosis should include assessment for drug resistance to ensure timely initiation on the most appropriate treatment regimen.

4.1.1 WHO recommended TB diagnostic test

The WHO recommended TB diagnostic (WRD) tests that employ molecular- or biomarker-based techniques. The recommended molecular tests for the initial diagnosis of TB which are low complexity nucleic acid amplification test (NAAT) include Xpert MTB/RIF Ultra and Xpert MTB/RIF, Truenat MTB, MTB Plus and MTB-RIF Dx tests and loop-mediated isothermal amplification. Other moderately complex NAAT which detect not only MTBC and RIF resistance but also INH resistance are Abbott RealTime MTB and MTB RIF/INH assays, the BD MAX MDR-TB assay, the Hain FluoroType MTBDR assay, the Roche cobas MTB and MTB-RIF/INH assays.

Follow-on tests to detect drug resistance include line probe assays (LPAs) for detection of resistance to RIF and INH, FQs and second-line injectable agents, Xpert MTB/XDR Assay which is a low complexity automated NAAT for the detection of resistance to INH, FQs, ETO and AMK, Genoscholar PZA-TB II which is high complexity reverse hybridization NAAT for the detection of resistance to PZA, targeted Next Generation Sequencing (tNGS) test to detect mutations associated with resistance to many anti-TB medicines with a single test.

4.1.1.1 The initial microbiological diagnostic tests for all persons with presumptive tuberculosis in Eswatini should include:

Xpert MTB/RIF® Ultra testing (preferred diagnostic test for all presumptive case of TB). LF- LAM for PLHIV with advanced HIV disease (i.e. CD4<200 or WHO clinical stage 3 or 4) regardless of TB signs and symptoms, presumptive TB regardless of CD4 or seriously ill regardless of CD4 count

Gene Xpert Assay

4.1.2 The follow-on test for after diagnosis of active TB disease

After active TB disease has been confirmed by the Xpert MTB/Rif (and/ or LF-LAM in PLHV), the following tests should be performed to investigate for drug-resistant TB (DR-TB).

Xpert MTB/XDR assay testing for INH, FLQs, ETO and Second line injectables (for all Xpert MTB detected cases irrespective of rifampicin resistance and all re-treatment cases of TB). Previously first-line and second-line line probe assay (LPA) was used for the rapid genotypic drug-susceptibility test for these drugs. The laboratory turn-around time of Xpert XDR is shorter and does not need sophisticated laboratory. Therefore, Xpert XDR test is recommended in the place of LPA in this guideline.

Culture (i.e. liquid media culture using mycobacteria growth indicator tube assay (MGIT) or solid media culture) and phenotypic drug susceptibility test (pDST) for all Xpert MTB detected cases irrespective of rifampicin resistance and all re-treatment cases of TB).

Targeted genomic TB sequencing (tNGS) is recommended for all INH and/or Rif resistant MTB cases at baseline and for smear/culture non-conversion or reversion or treatment failure DS and DR-TB cases including clinical failure cases.

4.2 A brief about TB laboratory diagnostic tests

4.2.1 Xpert® MTB/RIF Ultra (GeneXpert) test

This is an automated cartridge-based rapid molecular test for Mycobacterium tuberculosis as well as detection of Rifampicin resistance (RR)-conferring mutations directly from pulmonary and extrapulmonary samples (sputum, plural fluid/ aspirate, CSF, stool etc.), providing both results within 2 hours.

This Assay has about 25% sensitivity gain over light microscopy and 5% over Xpert MTB/ RIF. It gives an additional advantage in diagnosing TB in PLHIV, children less than 15 years who often have paucibacillary smear and in extra pulmonary TB samples. Xpert Ultra can be used on all Gene Xpert instrument platforms and is suitable for use at central or national reference laboratory level, regional and district levels. Gene Xpert has the potential to be used at the peripheral level, provided there is uninterrupted electricity supply and temperature conditions. A typical 4-module GeneXpert can perform about 16 tests per working day.

Practical considerations for installation of Xpert® MTB/RIF Ultra and Xpert MTB/XDR Assay

The following should be observed for any site/facility for placement of GeneXpert equipment:

1. GeneXpert should be used at the peripheral level of the laboratory network as it has similar biosafety requirements to microscopy.
2. Xpert MTB/RIF® Ultra testing should be used for testing all people with presumptive tuberculosis
3. Ensure stable uninterrupted power supply and use UPS for each unit while in operation.
4. Ensure adequate and secure storage space for Xpert Cartridges.
5. There should be dedicated staff to perform the Xpert MTB/RIF® and MTB/XDR tests.
6. Ensure calibration of the Xpert Module after every 2000 tests or once a year, whichever comes first.

The results of the Xpert MTB/Rif Ultra test are:

- MTB Detected and RIF Resistance detected
- MTB Detected and RIF Resistance NOT detected
- MTB Detected and RIF Resistance indeterminate: require repeated test
- MTB Trace detected: refer to the algorithm for Trace result
- MTB Not Detected
- Invalid, Error, no result: required repeated test

4.2.2 Microscopy

The main use of microscopy is for follow-up of TB patients receiving anti-TB therapy to monitor treatment response. For microscopy to be reliable, consistent quality-assurance (QA) is required. The number of acid-fast bacilli (AFB) seen in a smear provides an indication of the patient's infectiousness. Two sputum samples are required for microscopy.

Two types of microscopy methods are available in Eswatini, namely: the direct smear light microscopy using the conventional Ziehl Nelsen's (ZN) staining technique; and the fluorescent-LED method where the AFB are visualized as fluorescence in a dark background.

The fluorescent LED microscopy has an advantage over the light microscopy in terms of ability to detect the bacilli easier and faster, reducing time to detection.

The main use of the microscopy is the follow-up of TB patients receiving anti-TB therapy to monitor treatment response.

Results for microscopy are given quantitatively according to the number of bacilli seen on each smear:

A positive result is defined as one showing an actual number or 1+ to 3+

A positive result in one of the two samples indicates non-conversion and the patient might still be infectious.

For positive smears at 2 months, 5 months and end of treatment, follow up on the baseline DST results to rule out resistance, if not available repeat Xpert and send another sample for MTB/XDR and phenotypic DST.

All positive sputum results should be recorded in both the laboratory and TB registers in red ink for ease of identification.

The laboratory identification number and the date the examination was performed should be entered in the column next to that for the result of the examination.

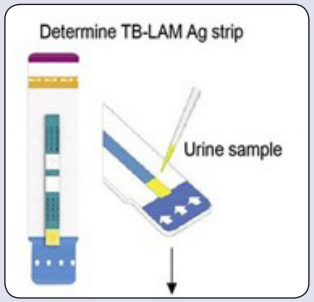
Table 10: Guide for grading results of smear microscopy

Number of Bacilli seen on a smear	Fields to examine	Results reported
Number of AFB per 100 oil immersion fields	100	Negative
1-9 AFB per 100 oil immersion fields	100	Indicate actual number (1-9)
10-99 AFB per 100 oil immersion fields	100	1+
1-10 AFB per 1 oil immersion field	50	2+
>10 AFB per 1 oil immersion field	20	3+

Source: Laboratory services in tuberculosis control. WHO/HTM/TB/98.258

4.2.3 Lateral Flow urine - Lipoarabinomannan Assay (TB-LAM/LF-LAM)

Tests based on the detection of mycobacterial lipoarabinomannan (LAM) antigen in urine have emerged as potential point-of-care tests. The TB-LAM antigen is a lipopolysaccharide present in mycobacterial cell walls, which is released from metabolically active or degenerating bacterial cells and appears to be present only in people with active TB disease. Urine based testing would have an advantage over sputum-based testing because urine is easy to collect and store and lacks the infection control risks associated with sputum collection.



The current commercially available TB-LAM assay is the Alere DetermineTM TB LAM Ag test, which is performed manually by applying 60 µl of urine to the Determine™ TB Lam Ag test strip and incubating at room temperature for 25 minutes. The strip is then inspected by eye, and the intensity of any visible band is graded against the manufacturer-supplied reference card.

Several studies and a meta-analysis of an earlier generation LAM-ELISA test have demonstrated improved sensitivity of urinary LAM in the presence of HIV-TB co-infection, which further increases with lower CD4 counts of less than 200 cells/mm^3.

4.2.4 Xpert MTB/XDR Assay

Xpert MTB/XDR assay is a low complexity automated nuclei acid amplification test (NAAT) for detection of resistance to INH and second-line anti-TB drugs. This test uses a cartridge designed for the GeneXpert instrument to detect resistance to INH, FQs, ETO and second-line injectable drugs (Amikacin). However, unlike Xpert MTB/RIF Ultra, which are performed on a GeneXpert instrument that can detect 6-colors, the new test requires a newer 10-colour GeneXpert instrument. For facilities without the 10-colour GeneXpert instrument on site, samples should be referred to the National Tuberculosis Reference Laboratory (NTRL) through the national sample transportation system.

The Xpert MTB/XDR assay is intended for use as a follow-on test in specimens determined to be *Mycobacteria TB Complex (MTBC) positive;* it offers a chance to improve access to rapid DST in intermediate and even peripheral

laboratories. The Xpert MTB/XDR test provides results in less than 90 minutes, leading to faster time to results than the current standard of care (i.e. LPAs or culture-based phenotypic DST). Laboratories should use the sample left over from Xpert Ultra Testing, to test for MTB XDR Assay without any additional request by the clinician (reflex testing).

Indications for Xpert/XDR test in Eswatini is for all MTB detected cases with or without Rif resistance, smear or culture reversion and treatment failure cases.

The result of the Xpert MTB/XDR test detected

For MTB, the result is the same as in the MTB/Rif (Ultra) test. For each drug (i.e. INH, FQ, Eto and Injectable) susceptibility test, it will be reported as "Detected", "Not Detected" and "Indeterminate". For Eto, there will not be indeterminate results. For INH and FQ, low level resistance detection will also be reported. If MTB not detected, invalid, error or indeterminate for any drugs, the test should be repeated using a fresh sample.

4.2.5 Mycobacterial Culture and Drug Susceptibility Testing (DST)

Mycobacterial culture method is considered the gold standard for the bacteriological diagnosis of TB. Culture significantly increases the number of TB new episodes found (often by 30–50%) and allows earlier detection of new episodes (often before they become infectious). Culture also provides the necessary isolates for conventional drug susceptibility testing (DST). The disadvantage of this method lies in the relatively longer turn-around-time (TAT) for obtaining the result, and need for advanced BSL3 infrastructure.

Two culture methods have been adopted in Eswatini namely:

- The conventional solid culture method (L-J techniques)
- Liquid culture uses the Mycobacteria Growth Indicator Tube (MGIT), an automated system, which has about 10% sensitivity gain over solid media culture.

The MGIT method therefore reduces the TAT for culture results from about 60 days in the case of L-J to about 15-30 days. The results can be reported as early as 10 days (if the culture is positive), or up to 42 days to report a final culture-negative result.

Mycobacterial culture should always be performed in containment laboratories with biosafety level (BSL) III due to the manipulation of large volumes of infectious material.

Positive cultures must be speciated to distinguish *M. tuberculosis* from non-tuberculosis to non-tuberculous mycobacteria/ mycobacteria other than tuberculosis (NTM/MOTT), which are more prevalent in HIV-infected patients.

In addition to the diagnosis of TB, culture is also used for treatment monitoring of a person on DR-TB treatment (refer to details in the DR-TB treatment chapter).

Thin Layer Agar (TLA) culture and DST method

Thin Layer Agar (TLA) uses solid media which is impregnated with isoniazid and rifampicin to allow bacilli to grow in their favourable environment, and a few days later to observe the specimen under direct microscopy.

The growth of MTB in media containing Rifampicin or Isoniazid is then directly visualized, thereby giving DST results for R and INH.

The advantage of this method lies in its rapidity, with culture and DST results being reported simultaneously in 7-10 days and its relatively low cost per test.

However, the TLA method is not used in Eswatini for programmatic management of TB and DR-TB except in approved research studies.

4.2.6 Genome Sequencing

Eswatini has a high prevalence of MDR TB strains with a particular rifampicin resistance mutation (rpoB I491F) not detected by molecular WHO recommended diagnostics (mWRDs) tests (GeneXpert Ultra, Line Probe Assay) or liquid phenotypic DST methods recommended by WHO, currently in use in the country since 2012. For this reason, the implementation of new sequencing technologies is crucial to support optimal TB diagnosis in Eswatini. A TB drug resistance survey (TB-DRS) conducted in 2017 showed that 58 per cent of MDR TB cases are missed by all diagnostic tests used in Eswatini thereby amplifying transmission by approximately 50%. An important indicator for strains harbouring this mutation is that most of them are resistant to isoniazid when tested using MGIT culture, MTB XDR Assay or LPA.

The Deeplex kit is used to perform targeted next-generation sequencing (NGS), which targets 18 genomic regions within the Mycobacterium tuberculosis complex and provides resistance information for at least 13 genomic regions for drugs used to manage TB patients, including first- and second-line drugs. This method can be used on both direct sputum and culture isolates. It has two advantages that allow it to minimize turnaround time of results: it can be applied immediately to sputum without the need to culture the samples, and it predicts drug resistance to both first and second line, making it easier for clinicians to manage patients.

The indications for sequencing in Eswatini are as below:

- At Baseline for Rif and/or INH-resistant MTB cases diagnosed by GeneXpert Ultra and Xpert MTB/XDR assay, phenotypic DST,
- At 4 months when DR-TB patients fail to convert culture
- Failure of first line and second-line anti-TB treatment (clinically and/or bacteriologically)
- When there is a culture reversion
- When there is a TB case during the post-treatment follow-up period

4.2.7 Use of Commercial Sero-diagnostics

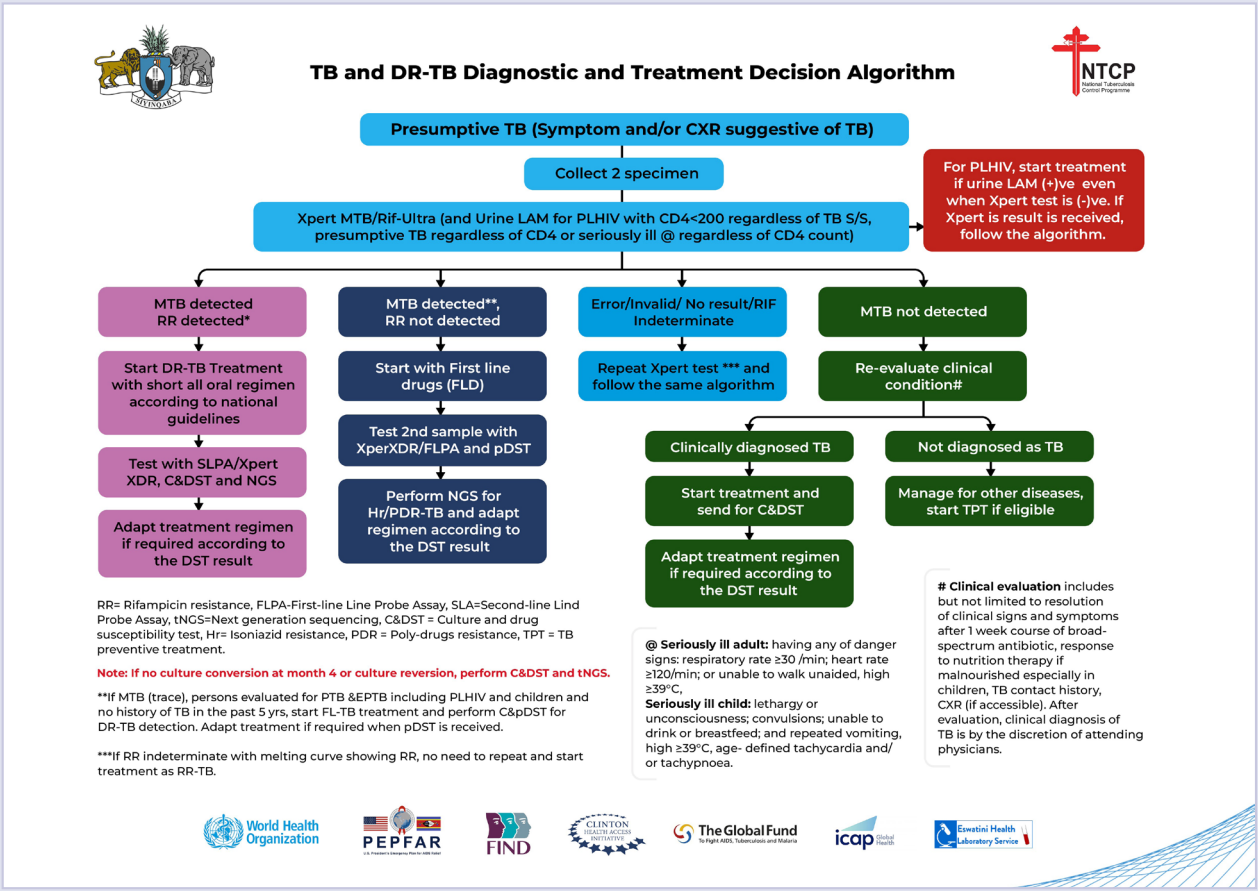
Serological tests for diagnosis of tuberculosis are tests developed based on antibody recognition of antigens of *Mycobacterium tuberculosis complex* by the humoral immune response, as opposed to antigen recognition by the cellular immune response (e.g. interferon-gamma release assays).

Sero-diagnostic tests for TB are currently not endorsed by WHO, and hence not recommended in this manual for the diagnosis of TB in adults or children.

4.3 Microbiological diagnosis of TB and DR-TB

The following algorithm illustrates the steps of TB and DR-TB diagnosis, and treatment decisions based on the test results.

Figure 16: Diagnostic and treatment decision algorithm for TB and DR-TB



Given the high HIV prevalence among incident TB episodes in Eswatini, Xpert MTB/RIF® Ultra Testing is the recommended initial diagnostic test for all persons with presumptive TB.

Upon receiving the Xpert results, treatment decisions should be made as follows:

MTB was Detected and Rifampicin resistance not detected

(All patients whose diagnosis of TB has been confirmed by Xpert® MTB/RIF Ultra but without evidence of Rifampicin resistance)

Should be registered as MTBC positive, bacteriologically confirmed TB = MTB+ve/Rif-ve

Reflex Xpert MTB/XDR Assay should be done to rule out INH and fluoroquinolone resistance.

Facilities with Xpert MTB/XDR onsite are to initiate treatment after receiving Xpert MTB/XDR assay results.

Start first-line anti-TB treatment for MTB +ve/Rif -ve while waiting for Xpert MTB/XDR and DST results if not available onsite

All Xpert positive (MTB +ve/Rif-ve) cases must have reflex MGIT culture and DST done on a second sample at the time of diagnosis

Xpert MTB-positive patients should be monitored while on treatment using smear microscopy at the recommended intervals until completion of treatment.

Note: *Xpert MTB/RIF® Ultra can detect dead bacilli so culture confirmation is needed for previously treated cases. Awaiting culture, should not delay initiation of TB treatment but treatment should be based on the clinical condition of the patient. If in doubt, it is also important to consult a Medical Officer.*

MTB was detected, and Rifampicin resistance detected

(All patients whose diagnosis of TB has been confirmed by Xpert MTB/RIF® Ultra with evidence of Rifampicin resistance)

Should be registered as *Rifampicin-resistant (RR-TB)* cases = *MTB +ve/Rif +ve*.

RR-TB diagnosis is considered a proxy for MDR-TB; and should therefore be started on a DR-TB treatment regimen according to the DR-TB management chapter.

All Xpert diagnosed RR-TB positive *(MTB +ve/Rif +ve)* cases must have reflex Xpert MTB/XDR Assay to determine INH and fluoroquinolone resistance.
Targeted genome sequencing, MGIT culture and phenotypic DST should be done on the second sample at the time of diagnosis.
Xpert-diagnosed RR-TB patients should be monitored by sputum smear microscopy and MGIT culture as per the National TB management guidelines.

4.3.1 Interpretation of "trace calls"

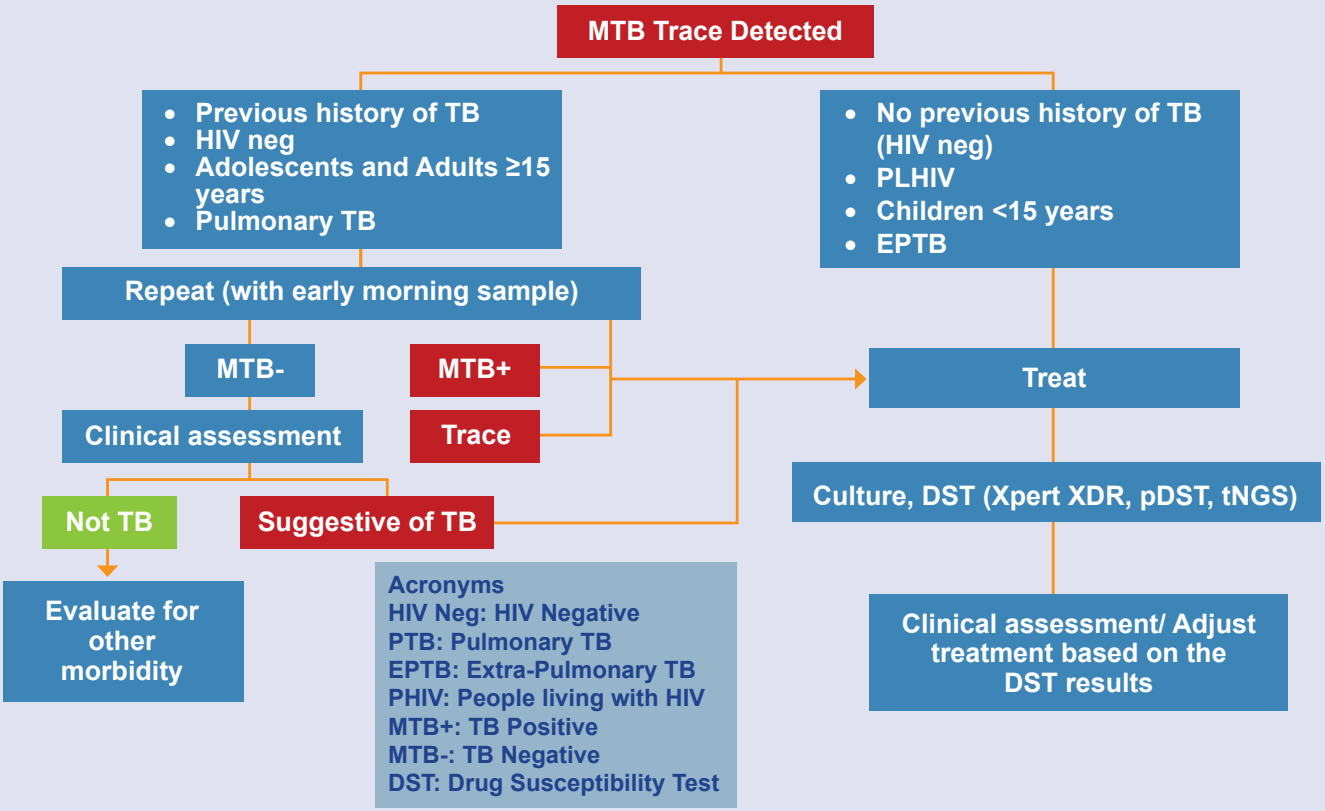
Among persons with HIV, children (≤ 15) and extra pulmonary specimens, "trace calls" should be interpreted as true positive results for use in clinical decisions and patient follow-up.

Among HIV negative persons, with an initial "trace call" positive result, a fresh specimen from the patient should undergo repeat testing and the result of the second Ultra test be used for clinical decisions and patient follow-up rifampicin resistance.

While clinical and available radiological information should always be considered in the diagnosis of tuberculosis, a second "trace call" positive is sufficient to make a diagnosis of pulmonary TB unless there is a recent history of TB.

Among all persons that test "trace call" positive additional investigations are needed to confirm or exclude resistance to rifampicin. Figure 17 below shows the interpretation of trace results.

Figure 17: Interpretation of trace result from the Xpert MTB/Rif (Ultra) Test



4.3.2 Repeat of Xpert® MTB/Rif Ultra test

A repeat of the Xpert test should be requested only in the following circumstances:

- When the test is negative, but patient's symptoms are highly suggestive of TB (e.g. Patient does not show improvement on broad spectrum antibiotics, CXR highly suggestive of TB);
- Error, Invalid, No result
- Indeterminate Rif results. (unless the rpoB rifampicin gene melting curve shows resistance)
- Trace results on Xpert Ultra in a previously treated TB case
- When the initial test result is 'trace' among people not at risk for HIV
- At month 2 or 5 for non-conversions or reversion respectively in cases where baseline culture and DST results are not available

PLHIV with TB-LAM positive, Xpert negative (treatment start with TB-LAM result and adapt regimen if required upon receipt of result)

If symptoms persist, Xpert is negative and CXR is not suggestive, with the discretion of clinicians, culture may be considered. Alternative diagnoses may also be considered

A second sputum specimen must be sent to NTRL where culture and other reflex tests (pDST, sequencing) will be performed if culture test result is positive.

4.3.3 Repeating TB diagnostic tests during treatment for people on DS-TB treatment

For individuals who are on TB treatment and fail to convert at the end of two months:

- Assess treatment adherence of patient
- Assess clinical condition
- Follow up on baseline DST results to rule out drug resistance
- Consider repeating Xpert MTB/Rif Ultra and/or Xpert MTB/XDR Assay (specify the reason for the Xpert repeat on the lab request form)
- Send a second sample for sequencing, culture and phenotypic DST if no baseline results are available
- Decision to either continue with DS-TB treatment, assign a failure outcome or change to DR-TB is dependent on the adherence status of the patient, clinical condition, and the baseline/or repeated DST results.

For individuals who are smear-positive at 5 months of treatment.

- Assess treatment adherence of patient
- Assess clinical condition
- Consider repeating Xpert ultra and/or XDR Assay (specify the reason for the Xpert repeat on the lab request form)
- Send a second sample for sequencing, culture and phenotypic DST if no baseline results are available
- Assign a treatment failure outcome and refer the patient to a DR-TB treatment site
- The result of Xpert ultra, XDR-assay, sequencing, culture and phenotypic DST will assist in regimen choice for DR-TB treatment

Note: Xpert MTB/RIF and MTB/XDR should not be used as follow-up test for monitoring response to TB treatment

4.3.4 Use of LF-LAM for TB diagnosis in PLHIV

TB-LAM may be used to assist in the diagnosis of TB in people living with HIV *(adults and children; in-patients and out-patients in the following scenarios:*

- PLHIV (both children and adults) with advanced HIV disease including those with CD4 count <200 cells/mm^3 regardless of whether there are signs and symptoms of TB or not or WHO clinical stage 3 or 4
- PLHIV who are seriously ill with danger signs regardless of CD4 count

Seriously ill is defined as:
In **adults:** having any danger signs that include respiratory rate ≥30 /min; heart rate ≥120/min; or unable to walk unaided, high temperature ≥39°C,

In **children:** lethargy or unconsciousness; convulsions; unable to drink or breastfeed; repeated vomiting, high temperature ≥39°C, age-defined tachycardia and/or tachypnea.

Children less than 5 years and HIV positive who have not yet been stable on ART for at least 12 months regardless of CD4 count and signs and symptoms suggestive of TB.

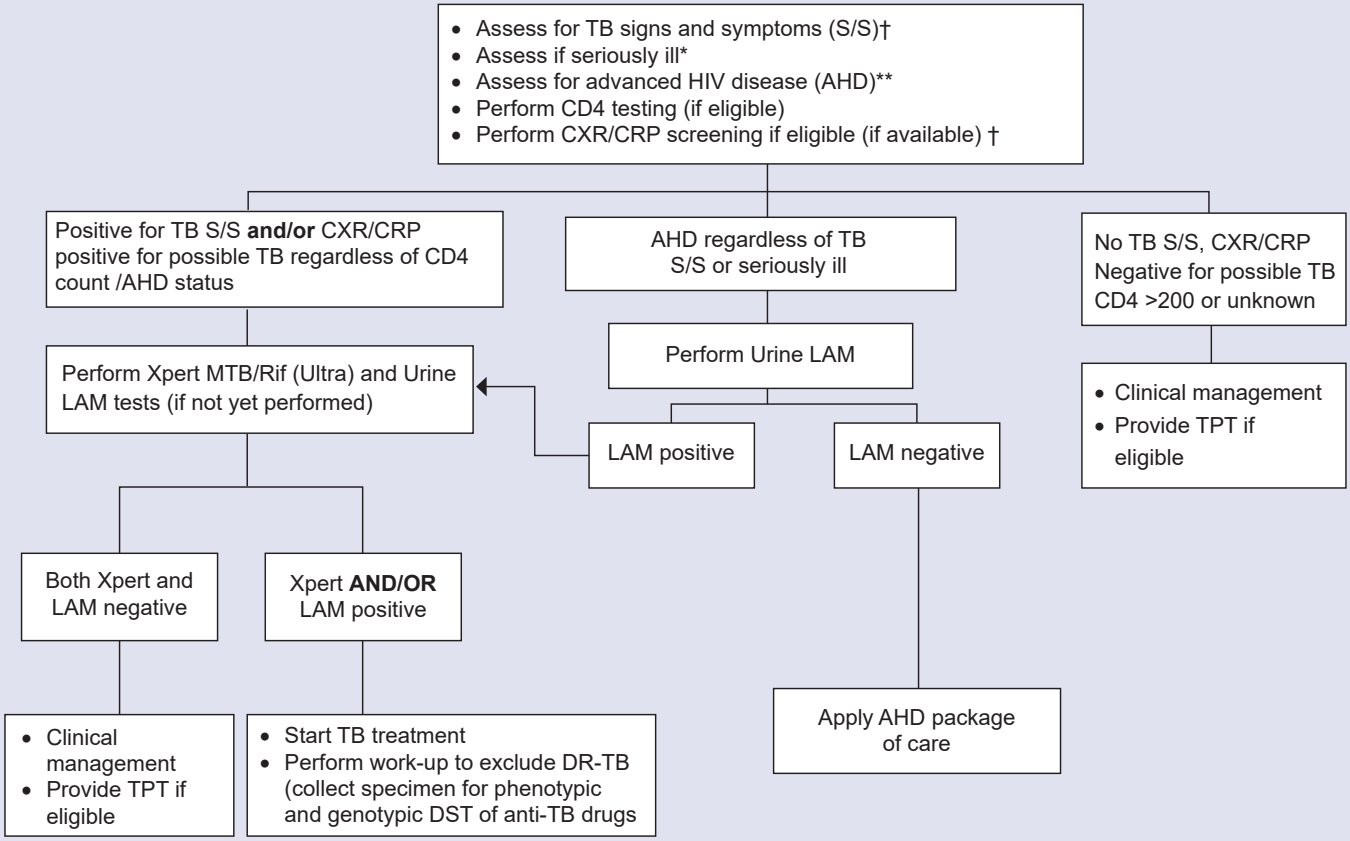
LF-LAM **should not be used** as a TB **screening** test for all PLHIV and should not be used as TB diagnosis or screening tool for non-PLHIV.

Note: The test does not tell you whether you are dealing with PTB or EPTB, hence the importance of history and examination.

Sputum and other specimens should be collected immediately for Xpert testing for bacteriological confirmation and to rule out DR TB.

Chest x-rays should be a minimum requirement for seriously ill patients with danger signs. See algorithm below

Figure 18: Algorithm to evaluate for TB among PLHIV



† Refer to National TB Management Guidelines amd SOP for TB screening
**Seriously ill is defined as presence of at least one of the following signs: respiratory rate >30/min, Heart rate >120/min, T° > 39°C, or unable to walk unaided*
***AHD is defined as CD4<200 cells or being at WHO clinical stage 3 or 4. For children <5 years and have not been on treatment for at least 12 months*
@CRP value of >5m/L is defined as possible/presumptive TB

4.4 Sputum sample collection, sample transportation and storage

The quality of the TB samples submitted for bacteriological examination of TB is critical in determining the correct outcome of the test. The Xpert MTB Assay is particularly sensitive and requires a good quality sample free of particulate matter to avoid error readings by the equipment. Educate clients on how to produce sputum to collect a good-quality sample. Two sputum samples of 3-5 ml (1-2 teaspoonful) are required for the diagnosis of TB. Ideally, one spot and one early morning specimen are required. However, if clients live far away from the health facility, two

spot specimens may be collected. One specimen will be tested with Xpert MTB/Rif ultra for TB diagnosis and the second specimen will be used for diagnosis is drug-resistant TB with Xpert MTB XDR, culture, pDST and sequencing.

Sample preparation and testing should start as soon as possible, and samples should not be stored for longer than 7 days in the refrigerator (2-8^{0}C) or 3 days at room temperature.

The National Sample Transportation System (NSTS) personnel should ensure the collection of TB samples from the requested health facility to the referral laboratories, where the following takes place:

Samples for smear microscopy and Xpert MTB/RIF® testing are processed at the referral laboratories and results are sent back to the clinics.

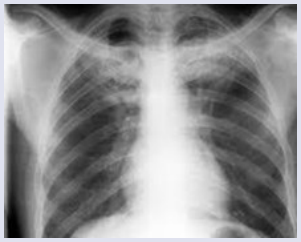
If Xpert MTB/XDR is not available onsite, samples are to be sent and processed at the NTRL

Samples for culture and Sequencing will be sent to NTRL through the NSTS.

Note: The triple packaging system should be strictly observed when transporting sputum samples

4.5 Clinical Diagnosis Pulmonary Tuberculosis

4.5.1 Role of plain chest radiography (Chest X-ray)



Although the role of chest X-ray is increasingly recognized for TB screening, its use in TB diagnosis has been limited by poor specificity for TB because there is NO typical Chest X-ray appearance for PTB in the setting of high HIV-TB co-infection. *There are also many other conditions whose radiographic features may mimic TB, including bacterial pneumonia, lung abscess, fungal infection (Aspergillosis, Histoplasmosis, etc), lung cancer, occupational lung disease (silicosis), inflammatory disorders (sarcoidosis), lymphoma, pulmonary infarct. In immunocompromised people (e.g. PLHIV with advanced HIV disease), the differential diagnosis should be considered for subacute bacterial pneumonia (e.g. Nocardiosis), Pneumocystis jiroveci pneumonis, Histoplasmosis, Non-TB mycobacteria infection, Kaposi Sarcoma, etc. When access to culture is a challenge, direct smear microscopy of sputum specimen may be helpful to identify other bacterial infections or yeast (e.g. PCP) or mould (Aspergillosis, Cryptococcal) for fungal infection or rapid test for Histoplasmosis. CT-Scan will also help aid the diagnosis of certain fungal infections or cancers.*

These conditions should also be ruled out as much as possible by referring/consulting with specialist/experienced physicians. Other management steps like a course of broad-spectrum antibiotics to treat a respiratory infection, treating malnutrition in case of severe malnutrition and clinical re-evaluation if symptoms/conditions have improved

may help the clinician judge the clinical diagnosis of pulmonary TB. It is not recommended to use Fluroquinolones (i.e. Levofloxacin, Moxifloxacin) as antibiotic trial to avoid drug-resistant development since these drugs are also important drugs for second-line anti-TB treatment, rather other broad-spectrum antibiotics like amoxicillin or erythromycin should be used. The use of Chest X-ray in the diagnosis of PTB is therefore relatively unreliable BUT can be useful in diagnosing extra-pulmonary TB e.g. pleural TB with effusion, pneumothorax, pericarditis, etc. and a diagnostic aid in children (see below for Diagnosis of childhood TB). A Chest X-ray may not be necessary in a case where bacteriological confirmation is available, and the absence of a chest X-ray should not be an obstacle to diagnosing and initiating TB treatment.

Chest X-rays are not necessary for the routine follow-up of a patient on TB treatment but can be used for exceptional cases such as EPTB and in children.

They are not required to change to continuation phase or to stop treatment in patients who are clinically responding well to TB therapy.

Chest x-rays are contra-indicated in pregnancy especially during the first trimester. **If absolutely required, it is to be taken with protective LED-shield.**

4.6 Confirming diagnosis of Extra-Pulmonary TB

Extra-pulmonary tuberculosis (EPTB) diagnosis is confirmed under the following situations:

- One specimen from an extra-pulmonary site with *'MTB Detected'* on Xpert MTB/RIF® testing, smear positive for AFB or culture-positive for *M. tuberculosis*.

OR

- Histological evidence of TB disease or with features suggestive of TB disease on biopsy

OR

- Strong clinical evidence consistent with active EPTB and Laboratory confirmation of HIV infection or strong clinical evidence of HIV infection.

AND

- A decision by a clinician to treat with a full course of anti-tuberculous chemotherapy.
- All TB cases, including those diagnosed by histological examination should be reported as extra-pulmonary TB.
- Type of EP-TB, clinical features and diagnostic procedures are briefly detailed in Table 11 below.

Table 11: A brief details of type of EP-TB, clinical features and diagnostic procedure

Type of EPTB	Clinical Features	Diagnosis
TB Lymphadenitis (most common EPTB site)	Fever, weight loss, fatigue and occasionally night sweat or no symptoms at all. Enlarged lymph nodes (>2cm). They can break down due to the formation of caseous pus. Cervical LN is the most common. Mediastinal or abdominal LNs, if large may obstruct nearby 'hollow' organs producing such symptoms as stridor, dysphagia, intestinal obstruction, etc.	• Fine needle aspiration of the LN and send the specimen for Xpert MTB/RIFUltra® and Xpert MTB/XDR testing and culture/DST, and tNGS where applicable. • If the aspirate is dry then an LN biopsy should be taken, sending the material for histological examination.
Pleural TB (Extra-pulmonary TB)	Acute or sub-acute illness varies from a few days to a few weeks. Pleuritic chest pains, non-productive cough and dyspnoea, sometimes fever. In an empyema complicated pleural TB, the patient may be acutely ill with chest pains, breathlessness, and cough with expectoration, fever and toxaemia. Occasionally it may be present as a chest wall mass or draining sinus tract.	• By therapeutic/diagnostic tap and sending the fluid for Xpert MTB/RIF Ultra® and Xpert MTB/XDR testing and culture / DST and tNGS where applicable. • If the patient has empyema, he must be admitted; the empyema drained and the material for Xpert MTB/RIF Ultra® testing, culture/DST, and tNGS where applicable.
TB Meningitis	Meningism (neck stiffness, Kerning's sign), irritability, anorexia, vomiting, fever and sometimes seizures. Complete or partial loss of vision is a major complication of TBM. Without treatment the patient may descend into a coma and death would follow in five to eight weeks. Thus, patients need immediate admission.	• Lumbar puncture for CSF examination: increased lymphocytes, increased proteins and decreased glucose. • CSF should be sent for Xpert MTB/RIF Ultra®, and Xpert MTB/XDR testing and culture/DST. • If the patient is HIV+, CSF should also be sent for CrAg and India ink staining.

Type of EPTB	Clinical Features	Diagnosis
Abdominal TB	Symptoms are non-specific and depend on the organs involved and extent of the disease. Loss of appetite, malaise, diarrhea, low grade fever, weight loss, night sweats, ascites, masses or abscess, obstructive jaundice, etc.	• Diagnostic/therapeutic tap for ascites and send for Xpert MTB/RIF Ultra® and Xpert MTB/XDR testing and culture/DST, and tNGS where applicable.
Pericardial TB	Fever, weakness, cough, vague chest pains, dyspnoea, weight loss and swollen feet. On examination there may be muffled heart sounds, pericardial rub, elevated jugular venous pressure, and signs of right-sided ventricular failure.	• Clinical diagnosis, cardiomegaly on the chest X-ray and echocardiogram. • In case pericardiocentesis is performed, the liquid should be sent for Xpert MTB/RIF Ultra and Xpert MTB/XDR® testing and culture/DST, and tNGS where applicable.
TB of the bones and joints	Spinal TB (Potts disease) is the most common, usually, constitutional symptoms (weakness, loss of appetite and weight, night sweats) will be present before any signs of spinal involvement (chronic back pain and gibbous deformity). If untreated, patients can develop neurological deficits and paraplegia. TB of the joints affects the movement of the affected joints and produces pain.	• Spinal X-ray will show paravertebral soft tissue shadowing, vertebral collapse and loss of intervertebral disc space. • These patients need to be referred to a specialist for treatment.
Miliary TB	This is disseminated TB and patients are usually very ill with signs of systemic toxaemia: fever, circulatory collapse and tachycardia. There may be cough, meningism and hepato-splenomegaly.	• Chest X-ray: diffuse miliary nodules. • Sputum samples for Xpert MTB/RIF Ultra and MTB XDR Assay® testing and culture/DST, and tNGS where applicable. • CSF, liver biopsy and bone marrow biopsy may reveal evidence of TB.

4.6.1 Tuberculous Lymphadenitis

Tuberculous lymphadenitis should be suspected in any patient with enlarged lymph nodes that are firm, asymmetrical, more than 2 cm in diameter, or where a node has become fluctuant or developed a fistula over several months. It most commonly affects the LNs in the neck (cervical region) and is difficult to distinguish clinically from other common causes of enlarged LNs, such as reactive and/or HIV-related lymphadenopathy, malignancies and other LN infections. Therefore, fine needle aspiration (FNA) using recommended techniques should be carried out at the first outpatient visit for all patients. Aspirate should be submitted for Xpert MTB/RIF Ultra®, Xpert MTB/XDR testing and culture/DST, and tNGS where applicable.

For non-caseating LNs, an LN biopsy can be obtained and the diagnosis confirmed by histological examination. Where the capacity for histology does not exist, the patient can be initiated early on anti-TB treatment based on the decision of a Medical Officer to treat as EPTB.

4.6.2 Miliary TB

Miliary TB results from widespread blood-borne dissemination of TB bacilli. This is either the consequence of a recent primary infection or the erosion of a tuberculous lesion into a blood vessel.

The patient is usually very ill and presents with constitutional symptoms of fever, night sweats and weight loss. Hepatosplenomegaly may be present, and choroidal tubercles can be seen on fundoscopy. Miliary TB is an underdiagnosed cause of end-stage wasting in HIV-positive individuals. Diagnosis should be established using Chest X-ray findings showing diffuse, uniformly distributed, small Miliary nodules (“Military” means “like small millet seeds”) which is pathognomonic of that form of the disease. Sputum samples should be collected for Xpert MTB/RIF Ultra and Xpert MTB XDR assay® testing, culture/DST and tNGS, and if possible other biological specimens from extra-pulmonary site to confirm disseminated TB (CSF, liver biopsy, blood culture, bone marrow biopsy, urine for LF -LAM). However, Miliary TB is defined as pulmonary TB.

4.6.3 Tuberculous Pleural Effusions

Inflammatory tuberculous effusions may occur in any of the serous cavities of the body, i.e. pleural, pericardial or peritoneal cavities. They are a common form of TB in HIV- positive patients.

Patients usually have systemic and local features.

Xpert MTB/RIF Ultra® testing of the aspirates from tuberculous serous effusions rarely shows MTB because the fluid forms an inflammatory reaction to TB lesions in the serous membrane.

Finding straw-coloured fluid from the pleural tap is highly indicative of TB pleural effusion and should be treated as such.

4.6.4 TB Meningitis

TB meningitis (TBM) results from the rupture of a cerebral tuberculoma into the subarachnoid space or blood-borne dissemination of TB bacilli from erosion of a pulmonary lesion into a blood vessel. It is a life-threatening condition with serious complications if not treated promptly. Diagnosis is confirmed by demonstrating relevant clinical signs backed with positive laboratory results.

Clinical diagnosis of TBM

Patients present with gradual onset of headache and depressed level of consciousness.

Examination reveals neck stiffness and a positive Kernig's sign (flex one of the patient's legs at the hip and knee with the patient lying on their back and then straighten the knee - resistance to straightening the knee and pain in the lower back and posterior thigh suggest meningeal inflammation).

Cranial nerve palsies result from exudates around the base of the brain.

Tuberculomas and vascular occlusion may cause focal neurological deficits and seizures.

Obstructive hydrocephalus may develop, resulting in headaches followed by vomiting, nausea, blurred or double vision, sun setting of the eyes and loss of motor coordination.

Spinal meningeal involvement causes paraplegia (spastic or flaccid).

Laboratory diagnosis of TBM

A lumbar puncture should be performed for patients with no evidence of severely raised intracranial pressure (no papilledema on fundoscopy) or without focal neurological deficits. CSF should be examined for the following features of probably TBM:

Clear CSF

Elevated pressure

High levels of protein (>1g/ l)

High lymphocyte count (30-300/mm^3)

Low glucose (<50% of plasma glucose)

'MTB Detected' on Xpert MTB/RIF® testing (a minority of cases).

Some of the CSF findings may be normal, especially in HIV-positive patients.

Note: Patients with presumptive TBM should be referred to the hospital without delay.

4.6.5 Tuberculosis of the spine

This is a severe form of TB when there are neurological sequelae. It is seen both in adults and in children, usually within three years following primary infection for the latter. In many cases, more than one intervertebral disc space is involved.

As the disease develops, the vertebral body adjacent to the disc space is affected. A para-vertebral abscess forms and pus can track forward towards the mediastinum or the retroperitoneal space, to the vertebral body and spinal canal resulting in compression of the spinal cord, back along the vertebral column eventually appearing as a subcutaneous “cold” abscess, or down the iliopsoas muscle into the pelvis or hip joint resulting in pelvic pain. Collapse of adjacent vertebral bodies affected by TB may lead to angulated kyphosis. The sites most involved are the lower thoracic, lumbar and lumbosacral areas.

The main differential diagnoses are malignancy and pyogenic spinal infections. Malignant deposits in the spine tend to erode the pedicles and spinal bodies, leaving the disc intact. Pyogenic infections tend to be more acute than TB, with more severe pain. Diagnosis can be confirmed through an X-ray of the spine revealing typical findings consistent with destruction of the intervertebral disc, para-vertebral soft tissue shadowing and wedge collapse of the vertebrae.

CHAPTER 5
QUALITY ASSURANCE OF LABORATORY SERVICES

5.1 Key terms used in Quality Assurance

Quality Control (QC) or Internal Quality Control, includes all the 'bench-top' procedures by which the laboratory personnel performing TB testing control the process, including checking of the instruments, new lots of reagents (cartridges for GeneXpert testing), staining solutions, smear preparation, grading (for smear microscopy) etc. It is a systematic internal monitoring of working practices, technical procedures, equipment, and materials, including the quality of stains.

External Quality Assessment (EQA) A process to assess laboratory performance. EQA includes 'on-site evaluation' (OSE) of the laboratory to review QC and evaluation of entire GeneXpert Testing and smear microscopy processes, and random blinded re-checking of routine smears for microscopy Testing. EQA also allows participant laboratories to assess their capabilities by comparing their results with those obtained in other laboratories in the network (intermediate and central laboratory) through panel testing and rechecking of patient slides, using both un-blinded and blinded procedures. EQA is also termed "Proficiency Testing" as described by IUATLD.

Quality Improvement (QI) A process by which all components of diagnostic services are carefully analyzed, periodically, to look for ways to permanently remove obstacles to success. Appropriate data collection, data analysis, correct interpretation of the results and creative problem solving, are the key components of this process. It involves continued monitoring, identifying defects, followed by remedial action including retraining when needed, to prevent recurrence of problems. QI mostly relies on effective on-site evaluation visits.

5.2 TB Laboratory Network in Eswatini

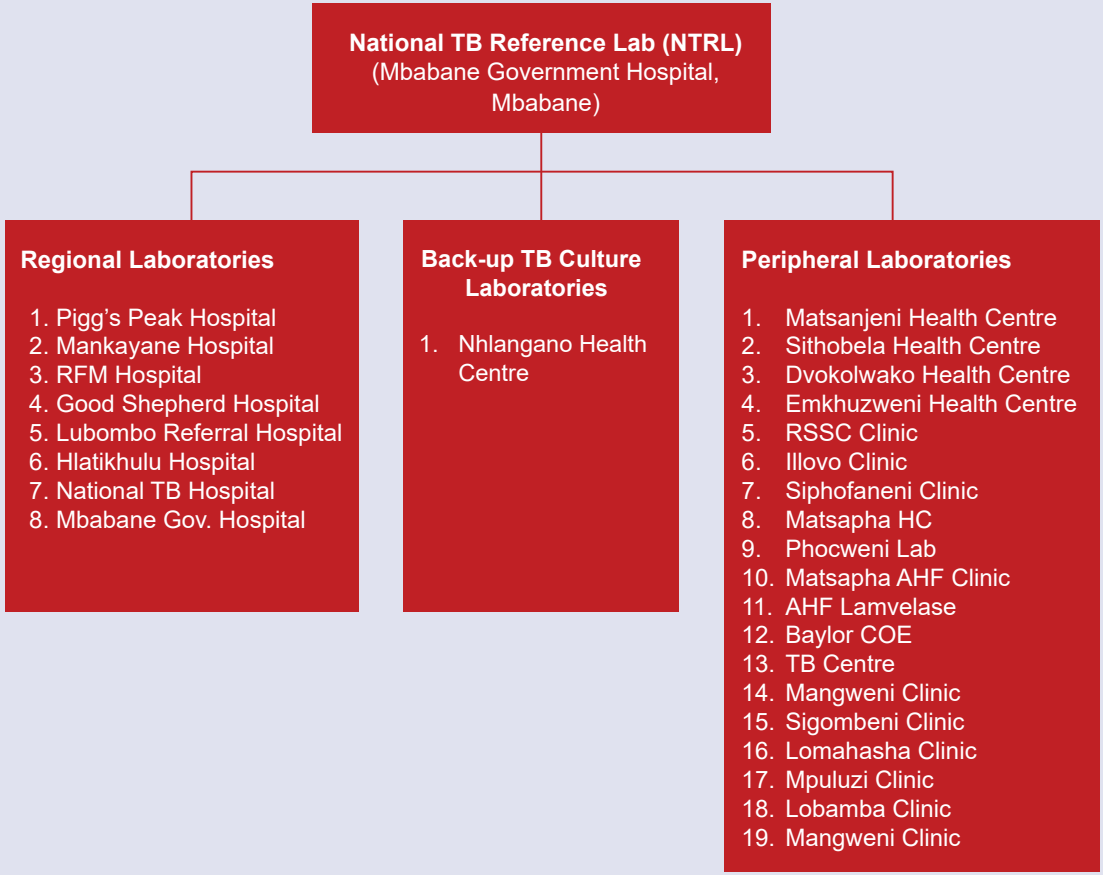
Tuberculosis laboratory services in Eswatini form part of overall health laboratory services in the country and are organized according to technical complexity.

The activities performed, and functional roles are as follows:

5.2.1 The National TB Reference Laboratory

The National TB Reference Laboratory (NTRL) is situated within the National Reference Laboratory and Blood Bank Complex in Mbabane. The NTRL performs mycobacterial species identification, using Xpert MTB Assays, MGIT culture and first & second-line drug susceptibility testing (DST) and Next-generation sequencing (Deeplex Myc MTB). Besides the core technical activities, the NTRL provides capacity building and training for laboratory staff, external quality assessment (EQA), contributes to surveillance of TB, including drug resistance surveillance, and participates in epidemiological and operational research. The establishment of TB culture facilities in the country aims to achieve at least 1 centre per 500,000 population.

Figure 19: Laboratory Data Quality Assurance



5.2.2 The Regional Laboratories

Except for the Nhlangano TB Laboratory which can perform MGIT culture and DST, the regional laboratories, which are located within hospitals, health centres and some clinics in the country primarily perform Xpert MTB/RIF® testing and direct sputum smear microscopy, using either the conventional Z-N technique or the LED microscopy. The NTCP and the Eswatini Health Laboratory Services (EHLS) aim to have at least one GeneXpert machine serving about 50,000 populations.

For EQA, the NTRL Receives Proficiency Testing (PT) panels for microscopy and DST (including FL and MTB XDR Assay) from SRL Uganda and culture PTs form NHLS in South Africa. Culture and DST panels are received once a year while microscopy panels are received twice a year.

Quality-assured results are accurate, reproducible and timely. To ensure quality-assured results, a comprehensive and standardized quality assurance system should be implemented in all clinical and testing sites providing Xpert MTB Assay testing services in Eswatini. Support for sites in implementing all the requirements for quality assurance is Given by the NTRL through the GeneXpert Focal Person and implementing partners. Quality assurance is just one part of a Laboratory Quality Management System, required to ensure the quality of all a testing site's processes. Quality assurance activities for Xpert TB Assay should not be seen in isolation rather they should be integrated with quality assurance for TB smear microscopy and/or other testing, where possible.

5.2.3 Site Supervision

The NTRL, the Regional Coordinator, and/or GeneXpert Focal Point are responsible for conducting regular supervisory visits to clinical sites where GeneXpert testing is conducted. The supervision will encompass the performance and use of all tests: microscopy, culture and DST and sequencing, LF-LAM ordering and results utilization. Supervisory visits should be documented using an up-to-date Clinical Checklist and supervisors undertaking testing site monitoring and supervision visits on behalf of the NTCP to assess Xpert MTB/RIF test implementation should use the checklist. All GeneXpert sites shall receive quarterly supervisory visits. Existing troubleshooting channels will then be utilized as per the checklist recommendation (i.e., follow-up intervention visits). A brief narrative report on supervisions conducted must be compiled and submitted to NTCP/EHLS every quarter. All testing sites will receive quarterly supervisory visits by the GeneXpert Focal Person.

5.2.4 GeneXpert Panel Testing (inter-laboratory comparisons)

When a GeneXpert instrument is installed at a new testing site, it will be registered in the EQA program. Currently, the EHLS is using an Xpert MTB/RIF Ultra proficiency test panel (EQA) provided by the CDC. To register, testing sites must supply contact details as well as postal addresses to the GeneXpert Focal Person (done at installation). Testing sites will receive samples from the start of the next EQA round after registration. Xpert MTB/RIF panels will be supplied twice a year, and all sites must submit the results form with the completed tests. The CDC returns the outcomes of proficiency panels directly to the NTRL EQA coordinator or GeneXpert Focal Person who in turn will subsequently distribute the results to the testing sites and the EHLS. The testing site staff must examine the returned results, and any discrepancies must be investigated to determine the root cause. Corrective actions should be carried out, documented and reviewed for success. The GeneXpert focal person/NTRL EQA Coordinator should follow up with the site to ensure patient testing has not been affected. If a testing site continues to experience EQA discrepancies (i.e. in the next round of testing) then the site will be contacted by the GeneXpert Focal Person and further actions taken. All sites should participate in an EQA Programme.

5.2.5 Assuring quality of smear microscopy

Results of TB laboratory investigations are critical for diagnosis and follow-up of patients on treatment according to national guidelines. The credibility, success and sustainability of the Programme depend on the capacity of the TB laboratory network to produce reliable results. Poor quality diagnostic services result in failure to identify infectious TB cases for proper case management and prevention of community transmission. Errors in the reading of follow-up smears may result in wrong outcome classification for TB cases often with negative consequences on TB control efforts.

In order to achieve the required technical quality in laboratory diagnosis, a continuous system of quality assurance (QA) needs to be established. Intermediate laboratories should supervise the peripheral network, while the central or reference laboratory should supervise the intermediate network.

An effective QA system of sputum smear microscopy network is of crucial importance for the Programme. QA is a comprehensive system consisting of internal quality control (QC), assessment of performance using external quality assessment (EQA) methods, and continuous quality improvement (CQI) of laboratory services. To optimize QA, the supervision and monitoring of the laboratory network is essential. This process requires the active support and participation of the NTRL and regional laboratories.

5.2.6 External Quality Assessment

External Quality Assessment is one of the most important components of a laboratory QA program. The NTRL should play a central role in the organization and maintenance of the network in terms of developing guidelines, ensuring high quality and standardized smear microscopy, and therefore must have the capacity to provide training and EQA, including providing panel testing and rechecking to intermediate and peripheral laboratories.

EQA should focus on the identification of laboratories where there may be serious problems resulting in poor performance, and not on the identification of individual slide errors or the validation of individual patient diagnoses. It is also a very important tool for communication with and motivation of laboratory technicians who may otherwise feel isolated in their work. Three methods should be combined to evaluate laboratory performance:

- Onsite evaluation
- Panel Testing
- Blinded Rechecking

5.2.6.1 On-site evaluation of Microscopy Centers

The on-site evaluation includes a comprehensive assessment of laboratory safety, condition of the binocular microscope, adequacy of supplies as well as the technical components of sputum smear microscopy, including preparation, staining and reading of smears. On-site evaluation should always include macroscopic as well as microscopic examination of randomly selected 5 stained positive and 5 negative smears.

Checklists should be used to assist supervisors during the field visit and to allow for the collection and analysis of standard data for subsequent remedial action. The copies of the checklist, duly completed by the Supervisors, should be handed over to the charge of the laboratory as well as the Hospital authorities. This will provide written documentation of the visit, its findings and proposed corrective actions for improvement.

The On-site Evaluation visits should be conducted to every regional and peripheral laboratory semi-annually. An updated checklist for on-site evaluation of Microscopy centres should be used- refer to laboratory quality manual.

5.2.6.2 Panel Testing

Panel testing is a method of EQA that evaluates a technician's performance in staining and reading, and not the whole laboratory activities. Utilization of panel testing for EQA is considered to be less effective than random blinded rechecking of routine slides because it does not monitor routine performance.

Panels are to be prepared and distributed to all laboratories every quarter, which should be followed by analysis of results and feedback to facilities.

The panels should consist of a set of 10-panel slides, including negatives and covering all the positive grades of test smears. These slides should be read and graded within the normal routine programme conditions. Based on the results, gaps and remedial actions including training will be determined to address technical skill deficiencies and errors to achieve a higher level of proficiency.

5.2.6.3 Random Blinded Rechecking of Routine Slides

Blinded rechecking is a process of re-reading a statistically valid sample of slides from a laboratory to assess whether that laboratory has an acceptable level of performance. This method provides reliable assurance that NTCP is supported by an efficient and reliable sputum microscopy laboratory network.

Random blinded rechecking involves the selection of a representative sample of slides from a Microscopy Center (both positives and negatives). The results of the slides are blinded before being read by a supervisor (first controller)

The discrepant results are resolved by a higher supervisor (umpire reader). Timely feedback is provided every month to the laboratory staff heads of labs for improvement in the quality of microscopy.

The Central and intermediate laboratories would also be supervising the peripheral Microscopy Laboratories on a routine basis, and reports of their visits should be handed over to in-charges at all levels. Corrective measures should be implemented based on the findings of these reports.

5.2.6.4 Operation of the blinding rechecking using the IQLS system

All regional and peripheral labs participate in blinded rechecking EQA and every quarter, each lab provides 40 slides for rechecking. A sample size of 40 slides per lab (microscopy centres) for the EQA per site was determined using the Lot Quality Sampling method based on the annual volume of slides read. A blinded rechecking team of 8 lab technologists was established to pick slides and re-read them.

Each quarter, 40 slides are randomly picked at each participating laboratory, and their results are recorded on the IQLS blinded rechecking form. The form is sent for data capture into the IQLS system and filing a Data Analyst at the NTRL while the slides are being re-read. The results of the second reading are also recorded independently including details on the quality of the stain on the slide, thickness, evenness and stain grade.

The results entered the IQLS system will generate a comparison table for the two readings for each lab. The Data Analyst prints the comparison tables which are given to the rechecking team and discordant slides are picked for

a third reading. The slides are re-read by a different technologist, and the result is recorded and captured as the tiebreaker and final. The final comparison list is now sent back to their original laboratories through rechecking teams who will also give feedback and technical assistance on the findings.

5.2.6.5 Conducting supervisory visits to microscopy centres

Microscopy Laboratories are supervised by supervisors from the national and provincial levels. The NTCP will work with the Supervisors to make sure that tuberculosis-related laboratory services are performed according to national quality guidelines. Visits to the microscopy centres must be adequately planned, and a supervisory checklist should be used.

PREPARING FOR VISITS

Supervisory visits should be planned such that all laboratories are visited at least once. Every quarter by a national laboratory supervisor. Information should be given in advance about the visit to the laboratory.

Review the recommendations made during previous visits and the actions taken.

Ensure the availability of an updated lab supervision checklist

CONDUCTING THE VISIT

Visiting the laboratory requires good time management to ensure a productive supportive visit without significantly disrupting the daily work schedule of the supervisee. The supervisor should be focused and systematic in conducting the visit. The following techniques could be employed to check the laboratory operations:

Review the Tuberculosis Laboratory Register for completeness, consistency and accuracy of recording; and verify that monthly summaries are made correctly.

Discuss with the laboratory technicians: to verify their understanding of the national guidelines concerning the correct number of sputum specimens required for diagnosis and follow-up examinations; the importance of limiting administrative errors and accurately recording the results of TB sample smear examinations on the Laboratory Form for Sputum Examination; and storing the examined. TB Simple smear slides of all patients for EQA purposes.

Examine supplies: to determine if there are adequate numbers of TB sample containers, slides, reagents, forms and other laboratory supplies for the expected patient turnover.

5.2.7 Follow-up Quality Improvement.

The findings of the supportive supervision visit should be discussed with the supervisee with the view to finding solutions to the problems identified. This should include on-the-job capacity building where required.

The supervisor should, within one week, produce a report of the supervisory visit and forward it to the next level along the line management structure. A copy of such a report should also be made available to the facility management and the laboratory visited.

Adequate follow-up should be ensured concerning the recommendations of the report.

5.2.8 Monitoring documentation related to microscopy examinations and other diagnostic methods

Every TB microscopy laboratory must have a Tuberculosis Laboratory Register, which should be filled up completely and accurately to ensure that the results are entered for the right person.

In processing TB samples for examination, the specimen. Containers and slides should be marked correctly with a Laboratory Serial Number, and the results of the TB sample. The smear examination is accurately recorded on the form.

Furthermore, all examined slides should be kept serially in the box without segregation of positive and negative slides, until the Laboratory Supervisor reviews them for QA.

During the on-site visit, the NTRL supervisor should select five smear-positive and five smear-negative slides randomly and review them as per QA protocol.

Ensure that the microscopy laboratories and health facilities collect and transport. TB samples are visited at least once every month. Other health facilities which collect specimens and transport them to an off-site laboratory should assign Specimen Identification Numbers and write them on the side of the containers.

5.2.8.1 Laboratory Request Form

The laboratory request form is the first line of communication between the specimen-submitting facility/ agency/ physician and the laboratory. These forms are available on request, from the laboratory. An alternative lab testing module has been made available on CMIS hence Requests can also be made electronically. Correctly completing this form will ensure that the patient and the specimen are properly identified and matched, the requested procedures are performed promptly, and the results are returned to the facility/agency/physician as requested. All results will be delivered to the requesting facility/agency/physician only, as hard copies [by hand or via the NSTS or electronically (by the Laboratory Information Systems (LIS) and Client Management Information System (CMIS)].

The request form includes a place to enter many identifying elements. The EHLS adopted a single laboratory request form-clinical laboratory services general request form), for all specimens including sputum testing for TB. It has a place for the requesting physician or agency, patient information, specimen information, medical necessity justification, and procedures requested.

5.2.8.2 Tuberculosis Laboratory Register

The Tuberculosis Laboratory Register is used to record the results of Xpert MTB/RIF® and TB sample Smear examinations. The register should contain the patient's data as well as the name of the treatment facility, the reason for the examination and the results of the examinations. Every week the person in charge of the laboratory should review the Tuberculosis Laboratory Register to ensure that the correct numbers of TB Samples have been submitted for diagnosis, including reflexive culture and DST requests for all Xpert ® MTB/RIF diagnosed cases.

Smear microscopy is no longer used for TB diagnosis, but all patients should have two sputum samples examined for diagnosis (by Xpert ® MTB/RIF).

All follow-up cases should have at least one sputum sample examined using smear microscopy.

Up to three-sputum specimen examination results can be recorded for each patient on one row of the Tuberculosis Laboratory Register.

Regional TB Coordinators should endeavour to compare. TB Test results are mentioned in the Tuberculosis Laboratory Register with those mentioned in the TB Treatment Cards and TB Treatment Registers. This can be done by randomly selecting cases from the facilities to cross-check their results in the laboratories.

Laboratory staff should not use the Tuberculosis Laboratory Register to record the results of any other laboratory examinations. All results of TB samples Examinations done in a Microscopy Centre should be written only in one Tuberculosis Laboratory Register, and not in any other register.

The laboratory technician should summarize the information on TB specimen Examinations were done during that month. This information should be summarized in the monthly summary form at the end of each month, and printed in the Laboratory Register itself. Patients from the following month should start from a new page.

5.3 Disposal of Laboratory Materials

TB Specimens examined in the laboratory are potentially infectious. Hence, after examination, they must be disinfected and destroyed so that the risk of infection is reduced. All disposable containers must be used only once. Sputum cups which contain sputum can be disposed of by any one of the following methods:

Disinfection	After the TB specimens have been used, all sputum cups should be kept in a bucket containing 5% hypochlorite, 10% bleach solution (freshly prepared), or 5% phenol solution. The caps of the sputum cups must be removed and the cups, caps and wooden sticks completely submerged in the solution in a secure place for at least 18 hours. After this, the solution, cups, caps and wooden sticks can be discarded with other hospital waste. This bin/bucket should have a lid which is foot operated.

Incineration	Wherever incinerators exist, the type specified under the Biomedical Waste Management & Handling Rules of the country, with a combustion efficiency of 99%, should be used. Sputum cups made of polypropylene should be used wherever available. (Note: If sputum cups are made of other varieties of plastic, they should be disinfected and destroyed as per the hospital waste management rules). Burning is NOT recommended.
Autoclaving	The sputum cups and lids, with the lids removed, along with wooden sticks can be autoclaved at the end of each day's laboratory work. The autoclave cycle should have a holding time of 15 minutes at 121°C HTAT (Holding time at temperature), 10 minutes at 126°C HTAT or 3 minutes at 134°C HTAT. The material can be discarded with other waste after proper cooling.

If none of the above is available, cotton and wooden Sticks can be disinfected and buried at a safe distance away from inhabited areas in a landfill site ensuring deep burial as specified by the infectious material disposal rules of the country.

Used slides should not be broken. They should be disposed of through the health care waste management system or in a secured pit for sharps by prevailing guidelines. Slides once used for sputum microscopy should not be reused.

5.4 Laboratory commodities and drugs supply

Robust and resilient supply ecosystems are essential to support the fight against TB. The Central Medical Stores (CMS) is the national supplier of laboratory commodities and TB drugs to facilities.

5.4.1 Inventory Management

Health facilities must keep a minimum stock of 2 months and a maximum stock of 3 months. When receiving stock from CMS, health facility staff should:

- Check the supply against the invoice, check and inspect for quality
- Store the received commodities according to good storage practices as per manufacturer's specifications to maintain quality
- Submit complaints, if any, using *product complaints from* within three working days.

The movement of stock between health facilities must always be accompanied by supporting documents (stock movement forms). Donations of medicine and medical supplies must be made through CMS.

5.4.2 Logistics Management Information System (LMIS) Reporting and Ordering

Stocktake *(physical count of commodities available in stock)* should be conducted monthly before assessing stock status (determining how long the current stock on hand will last i.e. enough, less or more than what is needed to offer services to patients) during the ordering process. Facilities should order TB drugs using the TB LMIS report and order book. Laboratory commodities are ordered using the Clinic or Hospital Laboratory LMIS report and order book.

Emergency orders can ONLY be placed on Tuesdays and Thursdays at CMS. Emergency orders are limited to 5 items. Before placing an emergency order, a call should be made to check the availability of products and the ability of CMS to process that emergency order.

Scenarios to place an emergency order:

- When CMS receives a shipment of medicines or laboratory commodities they are stocked out of stock
- When CMS misses a monthly delivery, and the facility needs an item to maintain a minimum stock
- When a facility realizes they are below minimum stock

In the event of laboratory reagents stockouts at both facility and CMS levels and re-distribution has been exhausted, facilities should utilize an established chain of communication through the NTCP Laboratory Focal person and TB Drugs stock-outs should be communicated through NTCP Regional TB coordinators for guidance.

Note: The LMIS reports should be submitted to the regional health offices (Regional Pharmacist and Regional Lab Coordinator) every month for review before submission to CMS.

5.4.3 Expired/ damaged laboratory and drug commodities

All health facilities should have a demarcated area for storage of products that have expired or have been damaged. It is recommended that this should not be in the same area where there is usable stock. Approval of disposal of pharmaceuticals and laboratory chemicals must be sought from the Government Stores department by completing and submitting TF 108/TF106 forms before destruction occurs *(see Health Facility Pharmaceutical & Laboratory Supply Chain SOPs)*.

CHAPTER 6
TREATMENT OF DRUG-SUSCEPTIBLE TUBERCULOSIS

6.1 The aims of TB treatment

The key to interrupting the spread of TB in the community is early identification and effective treatment of people who are coughing up viable TB bacilli.

The aims of TB treatment are:

- Controlling the spread of TB in the community through early identification and early- effective treatment of people who are coughing up viable TB bacilli.
- Providing timely and appropriate treatment for all forms of TB using effective treatment regimens and treatment support to ensure the cure of patients with active disease.
- Preventing the development of drug resistance.

6.2 Treatment Initiation

6.2.1 Eligibility for first-line anti-TB treatment

Eligibility for first-line anti-TB treatment is determined based on a thorough clinical evaluation, diagnostic tests, and drug susceptibility testing. The following groups are eligible for first-line TB treatment:

- Patient with a positive Gene-expert result without rifampicin resistance.
- Patients who are clinically diagnosed with TB with no history of contact with a drug-resistant TB patient.
- Patients who are MTB not detected but culture positive to MTB, with no resistance to first-line anti-TB drugs.

(a) The following procedures are to be performed for the initiation of treatment.

Identify patients and prepare to start enrolling on treatment by giving treatment education and counselling to patients and family members.

The education covers.

- TB (cause, mode of transmission, signs and symptoms, diagnosis, etc.,)
- The drugs used length of treatment, and treatment follow-up schedule
- Possible adverse events and support that will be available for the patient
- Infection prevention and control at home/community setting
- Availability of TB drugs free of charge
- Counselling covers
- Provider-initiated HIV counselling and testing
- Available treatment support intervention
- Identification of potential barriers to adherence to treatment and management accordingly.

(b) History Taking and Baseline Examination

- Take a thorough history including previous TB treatment history (when, where which regimen and outcomes).
- Perform a thorough physical examination.
- Past medical and social history include:

HIV infection	**Acute or chronic liver disease**
Diabetes mellitus	**Renal insufficiency**
Malnutrition	**Pregnancy**
Hypertension	**Alcohol and substance use**
Heart disease	**Smoking**
Cancer	**Chronic steroid use**

Random blood sugar or (HBA1C if available) is to be performed at baseline and months 2, 5 and 6 for those identified as having diabetes mellitus. Liver function tests (AST, ALT, Bilirubin) and renal function tests (urea, creatinine) are also recommended to conduct at baseline and follow-up tests if clinically indicated (e.g. those with chronic liver disease, chronic renal disease).

6.3 Essential first-line anti-TB drugs

Anti-tuberculosis drugs have three main properties namely bactericidal, sterilizing activity and the ability to prevent resistance. For anti-TB treatment to be effective, a combination of these properties is required in a treatment regimen.

- Rifampicin is the cornerstone of short-course chemotherapy for TB treatment; it has activity against all populations of *Mycobacterium Tuberculosis* and is key to a relapse-free cure.
- Isoniazid is a very potent bactericidal drug active against rapidly multiplying bacilli, and together with rifampicin are the most powerful bactericidal drugs.
- Pyrazinamide is active in an acid environment against TB bacilli inside macrophages.
- Ethambutol is bacteriostatic and has a protective effect on other FLDs, preventing the selection of resistant strains during combination therapy.

Table 12: Essential anti-TB drugs and recommended daily dosages by weight

Essential TB drugs	Recommended Daily Dose (Dose range in mg/kg)	
	Adults	Children
Isoniazid (H) (max 300mg)	4 – 6 mg/kg	10 – 15 mg/kg
Rifampicin (R) (max 600mg)	8 – 12 mg/kg	10 – 20 mg/kg
Pyrazinamide (Z) (max 2g)	20 – 30 mg/kg	30 – 40 mg/kg
Ethambutol (E) (max 1.6g)	15 – 20 mg/kg	15 – 25 mg/kg

Source: Treatment of tuberculosis guidelines. 5th Edition. WHO/HTM/TB/2017

6.4 Standard TB treatment regimens for adults

Treatment of all forms of TB in Eswatini is based on the WHO-recommended treatment regimens for the respective case registration groups.

For treatment, TB patients fall into three broad groups based on previous TB treatment history namely:

New episode: A person with TB disease who is classified as a new case, a recurrent case or a case with unknown previous treatment history (i.e. any case apart from a re-registered case).

Re-registered: A person with TB disease who has been notified previously as a TB case, who started treatment and took TB drugs for at least 1 month but who was not declared cured or treatment completed, and is now being started on a new course of TB treatment

MDR-TB Cases: All patients diagnosed with rifampicin, or both rifampicin and isoniazid resistance using rapid molecular methods or phenotypic methods.

Note:
All persons with TB (New or re-registered) should have access to culture and DST at or before initiation of TB treatment to determine the presence of resistance to any of the first-line anti-TB drugs.

There are two treatment phases for DS-TB:

- The initial (or intensive) phase: which consists of 4-5 drugs given to ensure rapid reduction in bacillary load
- The continuation phase: which usually consists of fewer drugs (2), given for a longer period to sterilize lesions and prevent relapse

TB treatment regimens have a standard code and are abbreviated as shown below:
2(RHZE) / 4(RH)

The code indicates the following:

- Both treatment phases (intensive and continuation) are separated by a slash
- The treatment duration in each phase in months is denoted by the number preceding the bracket
- Anti-TB medications are represented by the letters within the brackets
- Brackets denote that all drugs within it are in a fixed dose combination form
- The code includes both treatment phases, which are separated by a slash. A number is placed before a phase to indicate the duration of that phase in months. Letters enclosed in brackets indicate fixed-dose combinations.

Table 13: Summary of DS-TB treatment regimens for adult TB cases

TB Registration	TB Patients	Treatment Regimens	
		Intensive Phase (daily)	Continuation Phase (daily)
New Episode	All new cases of TB, regardless of site (except severe EP-TB*), type or severity of disease.	2RHZE	4RH
Re-registered	Previously treated cases with the outcome of cure, completed or LTFU (in the previous treatment episode).	2RHZE	4RH
	Previously treated case with the outcome of 'failure' (in the previous treatment episode)	Repeat GeneXpert and first-line DST then refer for DR-TB treatment.	
	All patients should receive pyridoxine with isoniazid to prevent peripheral neuropathy.		

6.4.1 Fixed-Dose Combinations

The use of fixed-dose combination tablets is recommended over separate drug formulations in the treatment of patients with drug-susceptible TB.

6.4.1.1 Advantages of FDCs compared to single formulation drugs

Prescription errors are less likely or less frequent because dosage recommendations are more straightforward and adjustment of dosages according to patient weight is easier.

The pill burden on the patient is reduced and may thus encourage patient adherence.

The patient cannot be selective in the choice of drugs to ingest.

6.4.1.2 Disadvantages of FDCs compared to a single formulation

The obvious disadvantage to combination products is that they are "fixed" doses and are not available in every possible dosing combination of their component drugs. Therefore, clinicians do lose some level of flexibility when a combination product is desired, but a patient requires an unavailable dosage.

In cases of adverse drug events, combinations make it more difficult to determine the offending agent.

Table 14: Recommended treatment regimen and dosages for adult cases of new and re-registered cases

Phase of treatment	Drugs	Weight in Kg			
		25-34.9	35-54.9	55-70	>70
The intensive phase of 2 months	(RHZE) 150mg/75mg/400mg/275mg)	2 tabs	3 tabs	4 tabs	5 tabs
Continuation phase of 4 months	(RH) (150mg/75mg)	2 tabs	3 tabs	4 tabs	5 tabs
For severe extrapulmonary TB cases (TB meningitis and Bone & Joint TB: total treatment duration is from 9-12 months with 2 months of RHZE and 7-10 months of RH depending on the response to treatment. For TB meningitis, refer to section 6.7 for further details.					
Vitamin B6 for peripheral neuropathy prophylaxis: 25-50 mg (25 mg tablets)					

Patients whose treatment has failed or grouped under the 'Other' group may have a high likelihood of drug-resistant TB. As such, all efforts should be made to trace phenotypic DST results so that the patient receives an effective treatment regimen.

6.5 Pyridoxine Supplementation

Isoniazid may cause symptomatic pyridoxine deficiency resulting in neuropathy, especially in severely malnourished children and children living with HIV on ART. Pyridoxine supplementation is given as standard therapy for all children at 2.5 mg/kg body weight, though certain situations may permit a higher dose of pyridoxine at 5-10mg/kg. These are.

- Pregnant adolescent
- Malnourished children
- Breastfeeding infants
- HIV-infected children

6.6 Treatment of Extra-Pulmonary Tuberculosis (EPTB)

The drugs used for the treatment of extra-pulmonary disease are the same as those for pulmonary TB (PTB).

6.6.1 Treatment of less severe forms of extra-pulmonary TB

These guidelines recommend six months' treatment duration for less severe forms of extra-pulmonary TB such as the following:

- TB lymphadenitis
- Pleural TB
- Abdominal TB
- Genital TB
- Skin TB

Note: The treatment duration may be extended if clinical (or bacteriological response where possible) is not sufficient.

6.6.2 Treatment of more severe forms of extra-pulmonary TB

These guidelines recommend a treatment duration of 9 months to 12 months, depending on clinical response, for more severe forms of EPTB that are either life-threatening or cause debilitating conditions causing disability such as the following:

- TB Meningitis
- TB Pericarditis
- Bone and Joint Tuberculosis (e.g. TB spine)

Unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for TB meningitis and pericarditis.

Surgical intervention may be required in the diagnosis of some EPTB but is mainly indicated in the management of late complications of the disease such as hydrocephalus, obstructive uropathy, constrictive pericarditis and neurological involvement from Pott's disease (spinal TB).

For large, fluctuant lymph nodes that appear to be about to drain spontaneously, aspiration or incision and drainage are beneficial.

HIV testing is especially important in people with presumptive EPTB because of the increased frequency of extrapulmonary involvement in people with immunosuppression.

EPTB is a WHO clinical Stage 4 HIV disease.

The presentation of extrapulmonary TB varies with age and is common in younger children.

6.6.3 Treatment of TB Meningitis (TBM)

Despite success in the treatment of PTB with standard regimens, mortality remains high (>50%) in TBM. The following drugs penetrate the CSF with a rate of >80%.

- Isoniazid
- Pyrazinamide
- Levofloxacin
- Ethionamide
- Linezolid
- Cycloserine

Despite low CSF penetration of 20%, rifampicin achieves a CSF concentration above the MIC (Minimum Inhibitory Concentration) and hence plays an integral role in TBM management. Recent studies have demonstrated added benefits with increasing the dosage of rifampicin (15mg/kg vs the usual 10mg/kg). Thus, this guideline recommends increasing the dosage of rifampicin in TBM patients.

The addition of linezolid to the standard TB treatment in comatose patients with TBM had a beneficial effect on rapid Glasgow Coma Scale recovery in one study.

Linezolid has a very good CSF penetration rate (80%-100%), but some of the side effects which include optic neuritis might be difficult to distinguish from the focal neurological signs due to TBM.

For ease of managing neurotoxicity in drug-susceptible cases of TBM, this guideline recommends the addition of levofloxacin in the intensive phase of severe forms (stage 2 or 3 TBM management for adults and children).

Levofloxacin is bactericidal, orally effective, has good CSF penetration, effective in MDR tuberculosis with no focal neurological side effects.

6.6.3.1 Recommended regimen for adults based on British Medical Research Council (BMRC) staging

- BMRC Stage I (No definite neurological symptoms on admission or in the history before admission, with or without meningism): 2RHZE/10RH; (increase the dose of Rifampicin to 15 mg/kg).
- BMRC Stage II (Signs of meningeal irritations with or without slight clouding of consciousness with focal neurological signs such as cranial nerve palsies or hemiparesis) 2RHZE+Lfx/10RH+Lfx; (increase the dose of Rifampicin to 15 mg/kg).
- BMRC Stage III (Severe clouding of consciousness or delirium, convulsions and serious neurological signs such as hemiplegia, paraplegia, involuntary movements) – 2RHZE+Lfx/10RH+Lfx (increase the dose of Rifampicin to 15 mg/kg).

Table 15: Indications for adjuvant corticosteroids in adults

Increased Intracranial Pressure
Spinal Block
Altered Consciousness
Tuberculous Encephalopathy
Focal Neurological Findings

The use of adjuvant corticosteroids in patients with a normal mental status and no neurological findings remains controversial, but when a decision to treat is made, patients should receive intravenous dexamethasone for 2 weeks (0.2 mg/kg per day in week 1, then 0.1 mg/kg per day in week 2), followed by the same oral taper as described earlier.

It is recommended that the steroid treatment should start as soon as possible after initiation of appropriate first-line anti-tuberculosis drugs.

TB Treatment regimens in special circumstances

Where a TB clinician is not sure about the management of patients that fall under the category of “special circumstances”, considerations should be made to refer for management by a TB specialist.

6.6.4 Treatment for pregnant women

The benefit of treating active TB disease in a pregnant woman far outweighs the risks that the drugs may pose to both the mother and the foetus.

- Every woman of childbearing age diagnosed with TB should be screened and tested for pregnancy before starting TB treatment.
- Although most first-line anti-TB drugs are safe for use in pregnant women, for TB diagnosed during pregnancy, the objective of treatment is to ensure that the woman is culture-negative at the time of delivery.
- **On delivery, rule out TB on the newborn, those without disease should be initiated on latent TB infection (LTBI)/TB preventive therapy (TPT) and BCG vaccination should be withheld until 2 weeks after completion of LTBI/TPT.**

6.6.5 Management of a newborn from a mother with TB

- A baby born from a mother who has been on anti-TB treatment for at least 8 weeks before delivery is less likely to be infected as the woman is usually non-infectious at the time of delivery, but they should still be evaluated for TB symptoms.
- A newborn delivered within 8 weeks of the mother starting TB treatment, diagnosed with TB at delivery or soon thereafter is at a high risk of infection or disease with TB.
- The newborn should be immediately screened for TB.
- The presentation of TB symptoms may be nonspecific but signs of fever, feed intolerance, poor weight gain, and hepatosplenomegaly may be realized.
- Mothers diagnosed with TB should immediately after birth have the placenta and the baby carefully investigated for possible indication of congenital TB.
- Symptomatic neonates should be treated for TB and those who are without TB disease should be put on preventive treatment for 3 or 6 months and withhold BCG vaccination until two weeks after completion of TPT.
- If the BCG vaccine was given immediately before TPT was initiated, the BCG should be repeated following completion of treatment if there are no contraindications.

If the baby has been exposed to a mother with MDR-TB, consult an expert. The benefits of breastfeeding still outweigh the risks during this period. However, the mother should be carefully educated on infection prevention and control she can implement while at home to prevent TB transmission. These will include:

- Limiting contact with the neonate
- Covering her mouth and nose with a mask while breastfeeding and breastfeeding outside if possible
- Keep all windows wide open when indoors
- Spend a greater part of the day outdoors

6.6.6 Treatment for Breastfeeding Women

A woman who is breastfeeding and has TB disease should receive a full course of anti-TB treatment. Timely and properly applied treatment is the best way to prevent transmission of tubercle bacilli to the baby.

- All first-line TB drugs are compatible with breastfeeding and a woman taking them can safely continue to breastfeed her baby.

- The mother should be educated on the following IPC measures:
  - ✓ Practice respiratory hygiene, including wearing surgical masks and cough etiquette
  - ✓ Good ventilation
  - ✓ There should be limited interaction between the mother and baby.
  - ✓ The baby should continue to breastfeed in the normal way but be given TB preventive treatment such as 3RH and pyridoxine or Isoniazid 10mg/ kg and pyridoxine for six months after screening negative for TB.

Note: Pyridoxine supplementation is recommended for all pregnant or breastfeeding women taking a treatment regimen with isoniazid.

6.6.7 Treatment for women taking contraceptive pills

Rifampicin interacts with contraceptive pills with a risk of decreased protective efficacy against pregnancy.

- A woman who is receiving contraception while receiving treatment with rifampicin should be encouraged to use dual contraception with a barrier method for the duration of treatment.
- Alternatively, a physician may prescribe an oral contraceptive pill containing a higher dose of estrogen (50 µg).

6.6.8 Treatment for patients with liver disorders

Isoniazid, rifampicin and pyrazinamide are all associated with hepatitis. Of the three, pyrazinamide is the most hepatotoxic, and rifampicin is the least likely to cause hepatocellular damage. The risk of isoniazid-induced hepatocellular damage is increased with underlying hepatopathy, such as alcohol-induced hepatitis. Rifampicin is also associated with cholestatic jaundice. The patients with the following conditions can receive the usual short-course chemotherapy (SCC) regimen if there is no clinical evidence of chronic liver disease:

- Hepatitis virus carriage
- History of acute hepatitis
- Excessive alcohol consumption

However, hepatotoxic reactions to TB drugs may be more common in these patients and should be anticipated

- All patients with pre-existing liver disease should be closely monitored clinically, including liver function tests during treatment.
- *Expert consultation (from specialist physicians, pediatricians, hepatologists, TB doctors, and clinical advisors) is advisable in treating patients with advanced or unstable liver disease.*

Management is as follows:

- Stop ALL drugs if AST, ALT or serum bilirubin > 3x ULN and symptomatic or > 5x ULN even if asymptomatic.
- Monitor liver function (LFTs, clinical), do an abdominal ultrasound scan and provide supportive management.
- Rule out other causes of hepatitis e.g. alcohol, hepatitis B, hepatitis C etc.
- Re-introduce TB drugs gradually when LFTs < 3x ULN.
- Do not re-challenge with RHZ if the hepatitis resulted in hepatic failure (coagulopathy, encephalopathy).
- Ethambutol is not hepatotoxic
- Rifampicin least likely cause: associated with cholestatic jaundice: start with R&E
- Repeat liver enzymes (twice weekly) until the medication has been taken for 3-7 days and enzymes are stable.

- ✓ H can then be added: if the patient does well, do not re-introduce Z. Design a new regimen i.e. 9RHE.
- ✓ If H is the offending drug, use RZE for 6-9 months depending on the treatment response.
- ✓ If R is the offending drug or >1 offending drug, 3 months of isoniazid, ethambutol + Clofazimine and a fluoroquinolone, followed by 15 months of isoniazid, ethambutol and a fluoroquinolone*. If both R and H are offending drugs treat with a standardized MDR-TB regimen as in the DR-TB treatment chapter.

In situations where possible, products of Milk Thistle (Silymarin or Silybinin) may be used as adjuvant therapy in patients with severe hepatotoxicity. Animal studies in rats have demonstrated a clear 'hepato-protectant' effect of these agents.

The mechanism of hepatoprotection is three-fold.

- Increased hepatocellular regeneration through enhanced synthesis of DNA and RNA.
- Free-radical scavenging thereby enhancing integrity of the hepatocellular membrane against xenobiotics.
- Modifying transporters and receptors of cell membranes.

This manual recommends the following treatment approaches for patients with severe hepatotoxicity. Silymarin 140mg capsule/tablets three times per day for two weeks or Silybinin 240mg twice a day for two weeks to one month.

There are suggestions in the literature of possible interactions with non-nucleoside reverse transcriptase inhibitors (NNRTIs) (especially Efavirenz (EFV)) through partial inhibition of CYP34. The potential effect would be delayed excretion of EFV metabolites from the body. However, this is considered not to be clinically relevant in patients who are taking Rifampicin as the CYP450 induction effects of Rifampicin will counter the effects of Silymarin on EFV.

The medication is widely tolerated but common side effects may be included.

- Headaches, gastro-enteritis and dermatological symptoms in the form of a mild rash.
  There is no evidence regarding safety in children and pregnant and lactating women. Caution should be exercised in patients with breast cancer, ovarian cancer, uterine cancer, endometriosis and uterine fibroids.
  - ✓ Monitor LFTs every 2 weeks for a month then monthly until 3 months or as guided by an expert clinician.
  - ✓ ART stopped can be re-introduced or re-initiated after at least 2 weeks on the full TB drug regimen to prevent IRIS.

Since some of the drugs recommended in the options above may not be available in all TB BMUs, this guideline recommends that patients with severe hepatopathy be referred for management by a doctor at a health center or hospital where these medications are available. It is encouraged that the management of these cases be discussed by the managing clinician with a team of peers and TB specialists.

These patients should still be reported as DSTB patients since the change in regimen is informed by toxicity rather than resistance to the FLDs.

Note: Without rifampicin in a treatment regimen, treatment cannot be short course i.e. patients should be treated for at least 18 months.

6.6.9 Treatment for patients with renal failure

Isoniazid, rifampicin and pyrazinamide are either eliminated almost entirely by biliary excretion or metabolized into nontoxic compounds by the liver. These drugs can, therefore, be given in normal dosages to patients with renal failure.

There is significant renal excretion of ethambutol and metabolites of pyrazinamide, and doses should therefore be adjusted when CrCl is <30ml/min.

Three times per week administration of these two drugs at the following doses is recommended: pyrazinamide (25 mg/kg), and ethambutol (15 mg/kg).

Where facilities are available to monitor renal function closely, it may be possible to give ethambutol in reduced doses. The safest regimen to be administered in patients with renal failure is 2RHZ/4RH.

Creatinine clearance can be calculated by the following formula.

$$eGFR\ for\ males = \frac{(140 - Age\ in\ years)(body\ weight\ in\ kg)}{(72)(serum\ creatinine, mg\ per\ dL)}$$

OR

$$\frac{(140 - Age\ in\ years)\ (body\ weight\ in\ kg)\ (1.23)}{(serum\ creatinine\ in\ \mu mol/l}$$

$$eGFR\ for\ females = \frac{(140 - Age\ in\ years)(body\ weight\ in\ kg)(0.85)}{(72)(serum\ creatinine, mg\ per\ dL)}$$

$$OR$$

$$\frac{(140 - Age\ in\ years)\ (body\ weight\ in\ kg)\ (1.04)}{(serum\ creatinine\ in\ \mu mol/l}$$

Note: The first formula need to be used if serum creatinine results are in mg/dl. Most of the time they are received in micromol/l. Please use the formula below to convert the results to mg/dl OR use second formula.

$$eGFR = \frac{(140 - Age\ in\ years)(body\ weight\ in\ kg)(0.85\ for\ women)}{(72)(serum\ creatinine\ in\ \mu mol/l \div 88.4)}$$

Normal values for the CrCl/eGFR are:

- Men: 97 to 137 ml/min
- Women: 88 to 128 ml/min

6.7 The Role of Adjuvant Steroid Treatment

Adjuvant steroid treatment is the addition of a steroid to anti-TB drug treatment. Studies have confirmed the benefit of steroids for TB meningitis and pleural and pericardial TB. Steroids are also of benefit in HIV-positive patients with pericardial TB.

Adjuvant steroid therapy is recommended in the following conditions:

- TB meningitis (decreased consciousness, neurological defects, or spinal block).
- TB pericarditis (with effusion or constriction).

For the other conditions listed below, steroid use is beneficial, from expert opinions and experience in clinical practice.

- TB pleural effusion (when large with severe symptoms)
- Hypoadrenalism (TB of adrenal glands)
- TB laryngitis (with life-threatening airway obstruction)
- Severe hypersensitivity reactions to anti-TB drugs
- Renal tract TB (to prevent ureteric scarring)
- Massive lymph node enlargement with pressure effects.

Steroids are not benign; they can also result in harmful effects but the benefits in these conditions outweigh the harm.

Rifampicin is a potent inducer of hepatic enzymes that metabolize steroids; therefore, rifampicin reduces the effectiveness and bioavailability of prednisolone (McAllister et al., 1983). The suggested treatment doses of prednisolone depend on the condition as indicated in Table 16.

Table 16: Steroid indication and recommended doses in TB management

Indication	Prednisolone treatment (dose for children in brackets)	Dexamethasone treatment
TB Meningitis	60 mg (1–2 mg/kg) daily for weeks 1–4, then decrease over several weeks	Intravenous dexamethasone for 4 weeks (0.4 mg/kg per day in week 1, 0.3 mg/kg per day in week 2, 0.2 mg/kg per day in week 3, and 0.1 mg/kg per day in week 4), followed by a taper of oral dexamethasone (4 mg/day, 3 mg/day, 2 mg/day and 1 mg/day, each for 1 week).
TB Pericarditis	60 mg (1–2 mg/kg) daily for weeks 1–4 30 mg (0.5–1 mg/kg) daily for weeks 5–8, then decrease over several weeks	
TB Pleural Effusion	30 mg (0.5–1 mg/kg) daily for 1–2 weeks	

Source: TB/HIV. A Clinical Manual WHO/HTM/TB/2006.420

Steroids are immunosuppressive and may worsen pre-existing immune-paresis and increase the risk of opportunistic infections in PLHIV. However, on balance, TB/HIV co-infected patients are still likely to benefit from the use of steroids in the presence of the above conditions.

6.8 Monitoring Tuberculosis Treatment

6.8.1 Basis for monitoring TB treatment

Monitoring patients' clinical as well as bacteriological responses to anti-TB therapy is an essential element of TB treatment and care. Regular monitoring of patients also facilitates treatment completion and allows the identification and management of adverse drug reactions.

All patients on anti-tuberculosis treatment should be monitored systematically throughout treatment. Patients, their treatment supporters and health workers should be instructed to report

- Persistence or reappearance of symptoms of TB (including weight loss),
- Symptoms of adverse drug reactions, or treatment interruptions.

6.8.2 Clinical Monitoring

Monitoring the improvement in the patient's clinical state provides a guide to treatment response. During regular follow-up visits, clinical assessment in the form of a focused history and physical examination should be conducted and the results documented in the patient's treatment card.

Evidence of clinical improvement includes

- A reduction or disappearance of symptoms including cough, fever, tiredness and weight gain.
- A sudden unexplained drop in the patient's weight should be investigated by the clinician.

6.8.3 Monitoring extra-pulmonary TB

- Response to treatment is usually monitored clinically and depending on the organ affected,
- Radiology may play an important role.
- As in clinically diagnosed (X-pert MTB/RIF test negative) pulmonary disease, the weight of the patient is also a useful indicator in monitoring clinical response in extra-pulmonary disease.

6.8.4 Monitoring clinically diagnosed pulmonary TB patients

Clinically diagnosed PTB patients should be monitored clinically,

- CXR (at month 6 before treatment completion);
- Body weight is a useful progress indicator.
- Sputum smear testing (at month 2,5 and 6)
- Sputum smears should be checked at the end of the second month in case of the following possibilities:
  - ✓ Disease progression due to non-adherence to treatment.
  - ✓ A laboratory error at the time of initial diagnosis (i.e. a true bacteriologically positive patient misdiagnosed); or
  - ✓ Drug-resistant TB disease.

- ✓ A patient initially diagnosed clinically and becoming positive in the second month should be investigated for MDR-TB using the rapid DST methods e.g. LPA. A full conventional DST should also be requested.

- In case of any DST result showing DRTB, the treatment outcome should be "failure" and the patient should be referred to a DRTB unit.
- In case of any positive smear result during the treatment, follow the steps described in the box above.

All PTB patients regardless of whether they were bacteriologically confirmed or clinically diagnosed should also have sputum samples collected at months 2, 5 and 6 of TB treatment (except for young children diagnosed clinically in whom repeat testing requires an invasive procedure)

6.8.5 Bacteriological Monitoring

Patients with bacteriologically confirmed PTB should be monitored by a sputum smear examination. These are usually adults and sometimes older children.

- Xpert MTB/RIF® testing should NOT be used to monitor treatment response.
- Routine monitoring of treatment response by CXR is also not recommended.
- Serial sputum smear examinations should be performed at the recommended intervals (see Table 17) to verify the effectiveness of the treatment in killing the bacilli.
- Two sputum samples should be obtained from the patient for examination at the end of the second and fifth month and the end of treatment for all bacteriologically confirmed PTB patients.
- The samples should be collected as "spot, spot" or "spot, early morning samples".
- Sputum specimens should be collected without interrupting treatment and transported to the laboratory as soon as possible thereafter.
- In the event of an unavoidable delay, specimens should be refrigerated or kept in as cool a place as possible.

Table 17: Recommended Schedule for follow-up sputum examinations for PTB patients

When to monitor	Regimen for New TB cases 6-month treatment regimen	Regimen for Previously treated Cases (6-month Regimen)
At the time of diagnosis	Xpert MTB/RIF® ULTRA test Culture & DST	Xpert MTB/RIF® ULTRA test Culture & DST
At the end of the initial phase	Sputum smear (end month 2)	Sputum smear (end month 2)
In continuation phase	Sputum smear (end month 5)	Sputum smear (end month 5)
During the last month of treatment	Sputum smear (end month 6)	Sputum smear (end month 6)

Source: Treatment of tuberculosis guidelines. WHO (2018)

6.8.6 Treatment monitoring of all bacteriologically confirmed pulmonary TB patients

Follow-up sputum smears for people on new episodes and registered treatment who have bacteriologically confirmed pulmonary TB, should be performed at the end of the second and fifth month and in the last month of treatment.

- If the sputum smear result is positive at the end of the second (2nd) month:
  - ✓ A repeat X-pert MTB/RIF test should be performed immediately (in addition to the baseline culture & DST performed reflexively for all bacteriologically confirmed TB cases). A rapid DST method, e.g. the LPA should also be used.
  - ✓ If the 2nd month culture is positive, this constitutes treatment failure and a thorough adherence assessment should be made and considerations for empirical treatment for MDR-TB made, if DST results are not available.
  - ✓ If DST results are available, treatment should be modified based on the results as per Chapter 7 treatment of DR-TB).
- If the sputum smear result is still positive at the end of the fifth (5th) month, this constitutes treatment failure:
  - ✓ A repeat culture & DST should be performed immediately (in addition to the baseline culture & DST performed reflexively for all bacteriologically confirmed TB cases). A rapid DST method e.g. the LPA should be used.
  - ✓ The treatment should be discontinued, and the patient should be initiated on empirical MDR-TB treatment while awaiting DST results.

Clinicians are advised to review or follow up baseline DST results at month two before changing patient to continuation phase.

6.8.7 Management of treatment interruption

When a patient misses an arranged appointment to receive treatment, such a patient should be contacted immediately to ensure that the treatment can be continued.

- The Adherence Officer should ensure that the patient is contacted within a day after missing a scheduled appointment during the initial phase, and within a week during the continuation phase.
- The patient can be traced using the locating information previously obtained.
- It is important to identify the reasons for the patient's failure to attend a scheduled appointment so that appropriate action can be taken, and treatment can continue.

The management of patients who have interrupted treatment takes into consideration several factors, such as the time at which the treatment was interrupted, the length of treatment interruption, the smear and Xpert MTB/RIF® result after return, as shown in Table 18.

- A sample for Culture and FL-DST should be sent to the laboratory upon return of patients who interrupt treatment after at least 1 month of anti-TB treatment or any patient who interrupted treatment for more than 2 consecutive weeks regardless of how long they have received ant-TB treatment.

Table 18: Management of TB treatment interruption

Length of treatment	Length of interruption	Sputum status upon return	Actions to be taken		
			Treatment outcome	DST	Registration and further treatment
< 1 Month	< 2 weeks				Continue treatment from the point it was stopped
	2-7 weeks	(-)		Rapid DST (Xpert MTB/RIF®)# MGIT Culture & DST	Restart treatment without new registration if there is no RIF resistance on rapid DST, otherwise register as DRTB case if there is RIF resistance
		(+)			
	> 7 weeks	(-)	Lost to follow up	Rapid DST (Xpert MTB/RIF®)# MGIT Culture & DST	If no resistance, give outcome of LTFU and register again as re-registered and restart treatment regimen. If there is resistance, register as DR TB case
		(+)	Lost to follow up		
> 1 Month	< 2 weeks			Rapid DST (X-pert MTB/RIF®) MGIT Culture & DST	Continue treatment from the point it was stopped if there is no RIF resistance on rapid DST. If there is RIF resistance register as DR-TB case
	2-7 weeks	(-)		Rapid DST (Xpert MTB/RIF®)# MGIT Culture & DST	Continue treatment from the point it was stopped if there is no RIF resistance on rapid DS, if there is RIF resistance register as DR-TB
		(+)			
	> 7 weeks	(-)	Lost to follow up	Rapid DST (Xpert MTB/RIF®)# MGIT Culture & DST	Give outcome of LTFU on previous registration status; Restart treatment with new registration as a re-registered for treatment if there is no RIF resistance on rapid DST. If there is RIF resistance, register as a DR-TB case
		(+)			

Source: Adapted from Treatment of Tuberculosis guidelines. 4thEdition. WHO/HTM/TB/2009.420

6.9 Care and support people with TB

It is important to provide continuous care and support to people with TB to achieve optimal treatment adherence and cure of TB. The following care and support will be provided to them throughout treatment.

- Educate clients and family members/caregivers about TB disease and treatment including treatment duration, follow-up schedule, adverse events, the importance of adherence to daily medication as well as TB infection prevention and control at home, particularly cough hygiene and sputum disposal, at the time of diagnosis and treatment initiation and during follow-up as needed.
- Provision of counselling support to clients who have potential barriers to adherence to treatment or interrupted treatment

- Promptly tracing clients who interrupted treatment within 2 days by telephone if available initially or home visit within 5 days of treatment interruption by treatment adherence officers or community cadres
- Provision of supplemental food package monthly if resources are available. TB clients with severe malnutrition (Marasmus, Kwashiorkor) are priority group including children younger than 5 years old with MUAC less than 11.5 cm or weight for height/age Z score <3 or having Kwashiorkor (bilateral pitting oedema), children more than 5 years old, adolescents and adults with BMI<16.5. In addition to nutrition status, if resources are available, other vulnerable factors like household member vulnerability, and socio-economic vulnerability may be considered for determining the provision of a nutrition support package to DS-TB patients if the support cannot be provided systematically to every DS-TB patient.
- Offer treatment adherence support intervention including digital adherence technology (e.g. smart pillbox, video-observed therapy) to clients (caregiver in case of children or who need assistance e.g. elderly) if available.

6.10 Treatment outcomes

The treatment outcomes of TB patients are defined as in Table 19 below

Table 19: Definition of TB treatment outcomes

Outcome	Definition
Cured	A bacteriologically confirmed case, who is smear or culture-negative in the last month of treatment and on at least one previous occasion (at least 7 days apart)[a]
Treatment completed	A patient who completed treatment but who does not have a negative sputum smear or culture result in the last month of treatment and in at least one previous occasion[b]
Treatment Failure	• A patient whose sputum culture is positive at 2 months, or smear is positive at 5 months or later during treatment. • Clinically diagnosed PTB or extra-pulmonary TB patients with clinical condition not improving or worsening (clinically judged) • Patients found to harbour a DR strain at any time during the treatment (excluding baseline sample)
Died	A patient who dies for any reason during the course of treatment
Loss to follow-up	A patient whose treatment was interrupted for 2 or more consecutive months
Not evaluated	Patient for whom no treatment outcome is assigned; Include former “transfer-out” in this category
Treatment success[c]	The sum of cured and completed treatment
(a) These definitions apply to bacteriologically confirmed and clinically diagnosed pulmonary TB patients, and patients with extra-pulmonary disease. (b) The sputum examination may not have been done, or the results may not be available (c) For all patients, bacteriologically confirmed and clinically diagnosed pulmonary TB patients, and extra-pulmonary TB patients.	

6.11 COVID-19 Vaccination in TB patients

Both COVID-19 and TB affects primarily the lungs. People who are at risk of TB such as diabetes, the elderly and COPD are at risk of severe forms of COVID. People with both TB and COVID-19 may have poor TB treatment outcomes. Therefore, people with TB and those at risk of TB should be vaccinated against COVID-19 if they are free of fever and other symptoms of COVID-19.

6.12 Post-TB Lung Disease

People with TB experience chronic sequelae even after successful completion of TB treatment and more common in low-income countries. These sequelae include fibrosis, cavities, pleural thickening, bronchiectasis, pulmonary hypertension, and secondary bacterial and fungal infections. These sequelae can be evaluated through medical history and clinical examination, CXR, pulmonary function testing (PFT) using spirometry, blood oxygen level by pulse oximeter and quality of life questionnaires (see Table 22 questionnaires) during TB treatment starting from month 2 and end of treatment. Anyone identified with chronic lung disease or requires pulmonary resuscitation (PR) should be linked to care at the relevant care department (e.g. physiotherapy department, chest clinic, etc.). Patients who need chronic care or PR should be educated, counselled and followed up on the effectiveness of management including PR (see Table 20). Some management strategies for PR are briefly outlined in Table 21.

Table 20: Assessment of post-TB lungs disease and indication for pulmonary resuscitation

Assessment Parameter	Examination	Indication for Pulmonary Rehabilitation
Clinical Assessment	Respiratory focused history taking: • Pulmonary disease: asthma including childhood asthma, bronchiectasis, COPD and previous TB treatment history, frequent respiratory tract infection during childhood, COVID-19 • Vaccination history: COVID-19, Influenza, Pneumococcal • Comorbidity: HIV, Diabetes • Health hazardous exposure: smoking, biomass fuel, silica dust • History of hospitalization for chronic repository disease	• Presence of comorbid conditions such as chronic obstructive pulmonary disease, asthma, bronchiectasis, pulmonary fibrosis, pulmonary hypertension, and/or a need for surgery. At least one hospitalization or two exacerbations in the past 12 months.
	• Clinical examination: Weight, height, BMI, Vital signs (Temperature, Heart rate, Respiratory rate) • Sings of repository distress	• Reported/presence of respiratory symptoms (dyspnoea, cough, sputum, wheeze, chest pain, fatigue) • Ineffective cough and/or difficult to clear bronchial secretions

	• Clubbing, coarse crepitation, raised jugular venous pressure, oedema, anaemia • Oxygen saturation by pulse oximeter • Blood and urine as clinically indicated (e.g. CBC if anemia is present, urea & creatinine and electrolyte if oedema is present)	• Abnormal blood gas PaO2, 80 mmHg/ 10.6 kPa and/or PaCO2.45 mmHg/6.0 kPa and/ or nocturnal and exercise-induced desaturation
Imaging CXR		
Functional Assessment	• Spirometry test • Minute walking test (6MWT) – can apply for 4-year-old and above	• Impaired pulmonary function showing airflow obstruction or restriction or mixed abnormalities and bronchodilator response and/or impaired diffusing capacity for carbon monoxide • Impaired exercise test
Subjective Evaluation	Quality of life (QOL) questionnaire (TB specific QOL questionnaires: EUROHIS-QOL (see Table 22)	Impaired quality of life ≥16

(Source: Adapted from the Clinical standards for the assessment, management and rehabilitation of post-TB lung disease, INT J TUBERC LUNG DIS 25 (10):797–813 Q, 2021 The Union)

The core components of pulmonary resuscitation and suggested management strategies are briefly outlined in the table below.

Table 21: Management strategies for pulmonary resuscitation

• **Impaired exercise capacity, limited by dyspnoea and or other respiratory symptoms** • **Restriction in daily life activities**	• **Free walking on a treadmill** • **30 min 2–5 times/week for 4–8 week**
• **Reduced muscle mass and strength of peripheral muscles. Lower muscle weakness with risk for falls.** • **Impaired activities of daily living involving the upper extremities (including dressing, bathing, and household tasks)**	• Free weights (dumbbells and ankle-brace) • 20–30 min 2–5 times/week for 4–8 week
• **Difficult to remove secretions or mucous plugs** • **Frequent bronchial exacerbations (>2/year)** • **Concomitant diagnosis of bronchiectasis**	• Airway clearance

• **Resting hypoxaemia despite stable condition and optimal medical therapy (partial pressure of oxygen <7.3 kPa (<55 mmHg) or 8 kPa** • **(≦60 mmHg) with evidence of peripheral oedema, polycythaemia (haematocrit > 55%) or pulmonary**	• Titrate oxygen flow that maintain oxygen saturation >92–93% • Long term oxygen therapy should be initiated on a flow rate of 1 L/min and titrated up in 1 L/min increments until oxygen saturation > 90% at rest has been achieved • Non-hypercapnic patients initiated on long term oxygen therapy should increase their flow rate by 1 L/min during sleep in the absence of any contraindications • Ambulatory oximetry may be performed to allow more accurate flow rates to be ordered for exercise • Provide formal education to patients referred to home • Schedule periodic re-assessment every 3 month
• **Malnutrition (body mass index ,16 kg/m2 or body mass index ,17 kg/m2 in patients with TB-HIV, MDR-TB, or pregnant and lactating mothers**	• Nutritional assessment • Treatment of malnutrition and medical supplements
• **Social isolation, depression and anxiety. Impaired health status and/or quality of life despite optimal pharmacological treatment.** • **Low adherence to medical treatment**	• Psychological assessment • Psychological support • Consider self-help group

The questionnaire has 8 parameters, and each question was answered using a five-point Likert response scale numerically scored with “0” being very dissatisfied and “4” being very satisfied. A score ≤16 is defined as” ill-being” or “impaired quality of life” and indicates pulmonary rehabilitation.

Table 22: TB Specific QOL Assessment: EUROHIS-QOL8

QOL Assessment Parameter	Score
1. How would you rate your quality of life?	a. Very poor (0) b. Poor (1) c. Neither poor nor good (2) d. Good (3) e. Very good (4)
2. How satisfied are you with your health?	a. Very dissatisfied (0) b. Dissatisfied (1) c. Neither satisfied nor dissatisfied (2) d. Satisfied (3) e. Very satisfied (4)

3. Do you have enough energy for everyday life?	a. Not at all (0) b. A little (1) c. Moderately (2) d. Mostly (3) e. Completely (4)
4. How satisfied are you with your ability to perform your daily activities?	a. Very dissatisfied (0) b. Dissatisfied (1) c. Neither satisfied nor dissatisfied (2) d. Satisfied (3) e. Very satisfied (4)
5. How satisfied are you with yourself?	a. Very dissatisfied (0) b. Dissatisfied (1) c. Neither satisfied nor dissatisfied (2) d. Satisfied (3) e. Very satisfied (4)
6. How satisfied are you with your personal relationships?	a. Very dissatisfied (0) b. Dissatisfied (1) c. Neither satisfied nor dissatisfied (2) d. Satisfied (3) e. Very satisfied (4)
7. Have you enough money to meet your needs?	a. Not at all (0) b. A little (1) c. Moderately (2) d. Mostly (3) e. Completely (4)
8. How satisfied are you with the conditions of your living place?	a. Very dissatisfied (0) b. Dissatisfied (1) c. Neither satisfied nor dissatisfied (2) d. Satisfied (3) e. Very satisfied (4)

CHAPTER 7
DRUG- RESISTANT TUBERCULOSIS MANAGEMENT

7.1 Introduction

The evolution of Drug-resistant TB (DR-TB) management has been very rapid in the past five years with the development of new drugs. WHO recommended the use of all oral regimens in 2019 replacing injectable with Bedaquiline and the treatment duration was shorter to 9-12 months instead of 18-24 months. Just within 3 years, based on the evidence from NIX, ZeNIX and PRACTECAL clinical trials, the WHO released an updated recommendation on the preferrable use of shorter, 6-month long novel MDR/RR-TB treatment regimens (BPaLM and BPaL) through rapid communications in May 2022, followed by the consolidated guidelines and operational handbook in December 2022. Eswatini adopted these recommendations and introduced the new regimens in 2023. In August 2024, WHO released a rapid communication that recommended 6-9 months regimen of (Bdq-Dlm-Lfx-Lzd-CFz) and three more 9-month regimens including a) Bdq-Lzd-Mfx-Z, b) Bdq-Lfx-Lzd-Cfz-Z, c) Bdq-Dlm-Lzd-Lfx-Z) based on the evidence emerged from the BEAT-TB and end-TB trials respectively. These new recommendations are also adopted in these guidelines.

7.2 Anti-TB drugs used in DR-TB treatment

Anti-TB drugs used in DR-TB treatment (also called as secondline drugs) are categorized in order of priority use by the WHO. Table 23 below shows the grouping of anti-TB drugs for DR-TB treatment.

Table 23: Medicines Grouping in order of priority (source: WHO)

Group	Medication	Abbreviation
Group A* (Include all three medicines unless they cannot be used)	Levofloxacin **or** Moxifloxacin Bedaquiline Linezolid	Lfx **or** Mfx Bdq Lzd
Group B (Add both medicines unless they cannot be used)	Clofazimine Cycloserine OR 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 **or** Meropenem Amikacin (or Streptomycin) Ethionamide OR Prothionamide p-aminosalicylic acid	E Dlm Z Ipm-cln **or** Mpm Am (s) Eto Pto PAS

**Pretomanid does not yet appear in the revised medicine classification*

7.3 Treatment of DR-TB

7.3.1 DR-TB Treatment Considerations

The country has adopted the use of short all-oral (non-injectable based) regimens for DR-TB, a move to patient-friendly and more effective regimens to optimize treatment adherence and favourable outcomes and preventing morbidity and mortality due to severe adverse events (SAEs).

(a) Use BPaLM or BPaL as the primary treatment regimens for patients with MDR/RR-TB, PDR-TB, Hr-TB treatment failure and pre-XDR-TB if eligible.
(b) Screen thoroughly for eligibility to BPaL(M) regimen for patients after initial diagnosis of MDR/RR TB, PDR-TB or failed on Isoniazid (INH) resistant TB treatment. If eligible for BPaLM, start treatment. Ensure if the client has submitted sputum samples for baseline culture second line drug susceptibility testing (SL-DST) through checking the CMIS or checking with laboratory onsite or mother site for the peripheral clinic. If not, collect one quality specimen and send it to NTRL. Tests that will be used for SL-DST include:
    i. Xpert MTB-XDR or Line Probe Assay (LPA),
    ii. Next generation sequencing (NSG) and,
    iii. Culture and phenotypic DST.

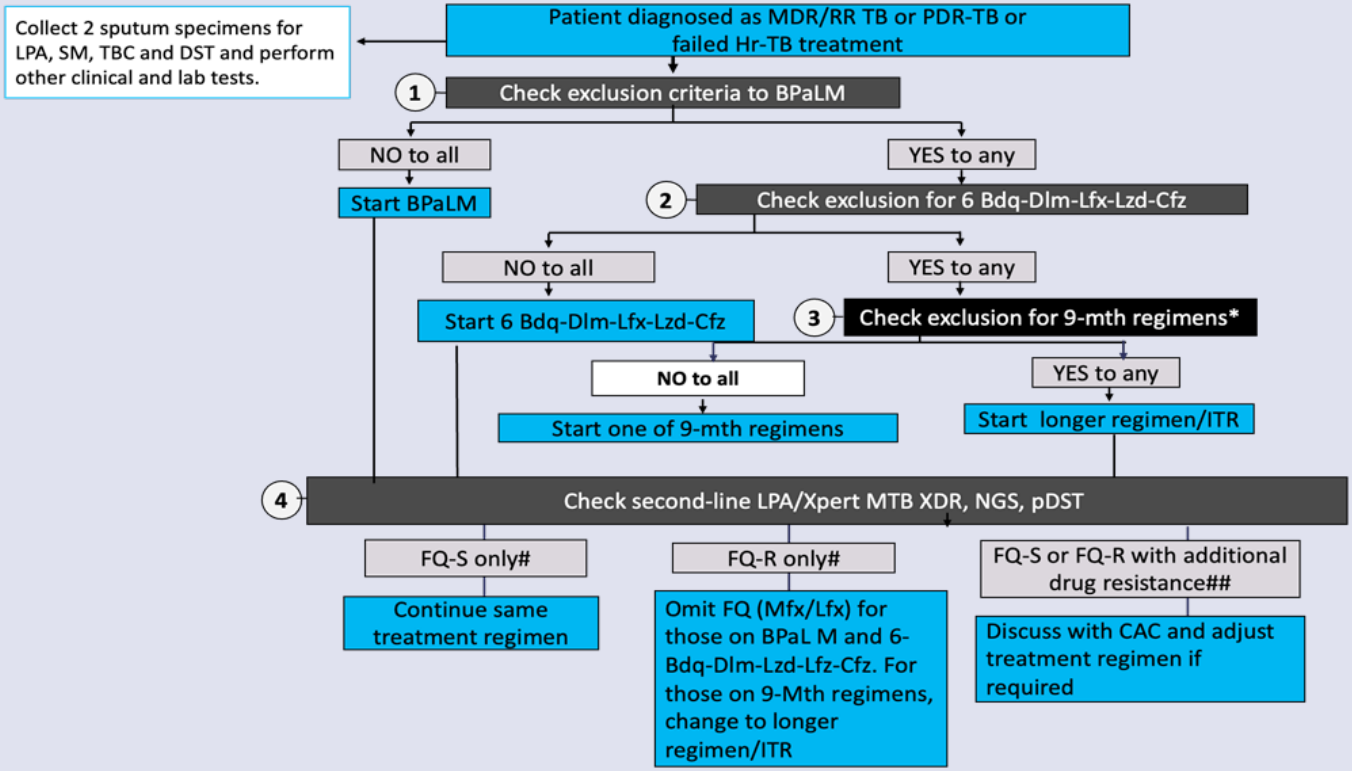
(For details of DR-TB diagnosis, refer to TB and DR-TB diagnosis chapter.)

Before initiation of treatment:

1. Educate client and family members about DR-TB treatment including side effects and infection prevention and control practices, especially cough etiquette.
2. Perform thorough medical history taking, clinical examination and baseline tests (see table 18; baseline and follow-up treatment monitoring)
3. Assess eligibility to the RR/MDR-TB regimens and initiate treatment (see box 1, 2 and 3)
4. For FQ-susceptible RR/MDR-TB patients, BPaLM regimen is preferrable.
5. 6-months Bdq-Dlm-Lfx-Lzd-Cfz regimen is alternative regimen to BPaLM. Usually children, pregnant and lactating women who are not eligible for BPaLM regimen can be treated with this regimen.
6. For patients with RR/MDR and FQ resistant TB (Pre-XDR TB), 6 mth Bdq-Dlm-Lzd-Cfz regimen is preferable than BPaL.
7. It is not required to wait for FQ drug susceptibility result to start treatment for RR/MDR-TB patients with BPaLM or 6 Bdq-Dlm-Lzd-Lfx-Cfz regimens but follow-up of result should be donewithin 1 month.
8. For those ineligible to BPaLM or 6 Bdq-Dlm-Lfx-Lzd-Cfz regimens, use 9-month Bdq-based treatment regimens (a. 9 Bdq-Lzd-Mfx-Z, b. 9 Bdq-Lzd-Lfx-Cfz-Z, c. 9 Bdq-Dlm-Lzd-CfzZ) after checking eligibility. Among the three 9-months regimens, Bdq-Mfx-Cfz-Z containing regimen is preferred over other regimens.
9. Longer treatment regimen (LTR), which is 18-20 months duration, is the last option for MDR/RR-TB and pre-XDR-TB patients who are not eligible for BPaLM, BPaL or 6–9-month Bdq-Dlm-Lfx-Lzd-Cfz or 9-month regimens. This is usually an option for XDR-TB patients.
10. Follow-up the results of second-line DST results vigilantly and adjust the initial treatment regimen according to the DST pattern if required.
11. Regularly monitor treatment progress and adverse events.

12. Immediately and adequately manage any adverse events (AEs).
13. Give each medication dose through treatment support interventions by trained health workers, community health worker/volunteer (CHW/CHV) or video observed treatment (VOT) throughout therapy.
14. Mark each supported dose on the Treatment Card

Figure 20: Algorithm for treatment selection and modification



= no other second line drug resistance (e.g. Bdq, Cfz, Lzd, Cs), ## = other second line drug resistance (i.e. Bdq, Cfz, Lzd, Cs)

7.3.2 Eligibility to BPaLM/BPaL or mSTR regimen

Box 1: Eligibility criteria for the BPaLM regimen

- Rif resistance, PDR or MDR detected by genotypic or phenotypic DST
- Clinically diagnosed TB case who had close household contact with an index case meeting the eligibility criteria for BPaLM
- Non-pregnant & lactating women, 15 years of age and above.
- Less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid.
  - ✓ When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.
- Have no severe extrapulmonary TB. e.g., TB meningitis, Osteoarticular, disseminated TB or miliary TB.
- Potential of drug intolerance/AEs:
  - ✓ QTcF>500 ms
  - ✓ Hb <8.0 g/dl
  - ✓ Neutrophil <0.75/109
  - ✓ PLT <150/109
  - ✓ Existing peripheral neuropathy, etc.,)

Box 3: Eligibility criteria for 6 Bdq-Dlm-Lfx-Lzd-Cfz

- PTB or EPTB except severe EPTB (e.g. CNS & osteoarticular, disseminated or miliary, pericardial TB)
- Children and adults with clinically diagnosed DR-TB when bacteriological confirmation or DST is not available.
- No previous exposure to Bdq, FQ, Cfz, Lzd and Dlm (for FQ-R regimen) >1 month or no resistance to the specific medicines with such exposure has definitively been ruled out
- No XDR-TB (WHO 2021 definition)
- Regardless of HIV status
- Regardless of pregnancy status
- Potential of drug intolerance/AEs[#] (QTCF <500 ms, AST/ALT <3 time of ULN, Hb >8g /dl, etc..)

Box 4: Eligibility criteria for 9-Mth regimens

- PTB or EPTB except severe EPTB (e.g. CNS & osteoarticular, disseminated or miliary, pericardial TB)
- No previous exposure to Bdq, FQ, Cfz, Lzd and Dlm > 1 mth or no resistance to the specific medicines with such exposure has definitively been ruled out
- No Pre-XDR/XDR-TB (WHO 2021 def)
- Regardless of HIV status
- Regardless of pregnancy status
- Potential of drug intolerance/AEs# (QTCF <500 ms, AST/ALT <3 time of ULN, Hb >8g /dl, etc..)

7.3.3 Summary of Types of DR-TB treatment regimens and their eligibility

Table 24: Type of DR-TB treatment regimens, the duration and composition of the regimens and eligible client groups

Oral MDR TB regimens	Regimen composition	Eligible group and a brief guide for regimen use
BPaL	6-9 Bdq-Pa-Lzd	An alternative treatment regimen for Pre-XDR-TB patients ≥15 years old. (Note: pregnant and lactating women are not eligible.)
BPaLM	6 Bdq-Pa-Lzd-Mfx	The primary treatment regimen for MDR-TB/RR-TB/PDR-TB ≥15 years old. (Note: pregnant and lactating women are not eligible.)
6 Bdq-Dlm-Lfx-Lzd-Cfz	**6 Bdq-Dlm-Lzd-Lfx-Cfz** **Can change as below when the FQ DST result is available.** **If the DST result shows.** **FQ susceptible, omit Cfz and continue with Bdq-Dlm-Lzd-Lfx.** **FQ resistant, omit Lfx and continue with Bdq-Dlm-Lzd-Cfz.**	Alternative regimen to BPaLM for RR/MDR with/without FQ resistance. Children and pregnant and lactating women are eligible for this regimen. **For clients with known FQ resistance, this regimen by omitting Lfx is preferable (ie. Bdq-Dlm-Lzd-Cfz) to BPaL.**
9-month regimens	**a. 9 Bdq-Lzd-Mfx-Z#** **b. 9 Bdq-Lzd-Lfx-Cfz-Z** **c. 9 Bdq-Dlm-Lzd-Lfx-Z** **(# priority regimen among the three 9 mth regimens)**	MDR/RR-TB without FQ resistance who are not eligible to BPaLM or 6 Bdq-Dlm-Lfx-Lzd-Cfz regimens
LTR (standardized - STDTR or individualized-ITR)	**STDTR** **18-20 Bdq/Lzd/DLM/Cfz/Trd(Cs)** **ITR: composed of 4-5 likely effective drugs containing Group A&B drugs as a priority**	For those who are not eligible for the BPaL or mSTR, XDR, Severe EP TB (meningitis, Osteoarticular, pericardial), disseminated or military TB
Hr-TB Regimen	**6 RHZE**	If the absence of Rifampicin resistance cannot be confirmed (i.e., lack of rifampicin-resistant report by sequencing which is missed to detect by pDST and Xpert test) 6RHZE is preferable to avoid drug resistance amplification, especially for Lfx which is an important core drug in second-line treatment), If Hr-TB without any confirmed additional resistance to other drugs with the availability of full DST results, a 6 (H)RZE+Lfx regimen may be used.

7.3.4 RR/MDR-TB treatment regimens

(a) BPaL / BPaLM Regimen

The BPaL/BPaLM regimens are 6-month regimens including Bedaquiline, Pretomanid, and Linezolid with additional Moxifloxacin (BPaLM) or without the additional Moxifloxacin (BPaL). The BPaLM and BPaL regimens are abbreviated:

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

BPaL: 6-9 (Bdq-Pa-Lzd)

BPaLM is the preferred treatment regimen for patients diagnosed with MDR-TB/RR-TB/PDR-TB and INH treatment failure, non-pregnant & lactating women, 14 years and above. The total treatment duration is 26 weeks (6 months). The medicines are to be given 7 days per week (except for Bdq) and administered with food for better absorption of Bdq and Pa.

Note: Avoid dairy products, Ca+ supplements or Ca+-containing antacids at least 2 hours before a dose and within 4 hours after the dose to ensure optimum absorption of Mfx.

BPaL is an alternative treatment regimen for patients diagnosed of Pre-XD-TB (i.e., those with MDR-TB and additional fluoroquinolone-resistance) who are non-pregnant & lactating women,14 years and above. The recommended treatment duration is 6 months with a possibility of extension to 9 months if there is no culture conversion at month 4 of treatment.

(b) Modification of BPaLM and BPaL treatment regimen

No regimen modification is allowed except for Lzd dose reduction to 300 mg if a 9-week consecutive treatment is completed. If culture remains positive or reversion occurs from month 4 to the end of the BPaLM regimen and month 6 to the end of the BPaL regimen, assign the treatment outcome “failure”.

(c) Switch to ITR shall be considered earlier in patients with a clear lack of response (clinically, smear grading, culture).

(i) 6-month Bdq-Dlm-Lzd-Lfx-Cfz treatment regimen

- This regimen is composed of Bedaquiline (Bdq), Delamanid (Dlm), Linezolid (Lzd), Levofloxacin (Lfx) and Clofazimine Cfz). Treatment duration is 6 months (24 weeks) and extendable to 9 months (36 weeks) if there is no culture conversion at 4 months of treatment. Patients with RR/MDR-TB with severe pulmonary TB and non-severe EP-TB are eligible for this regimen. However, patients with severe EP-TB or disseminated TB are not eligible for this regimen. Patients who have a previous exposure history of Bdq, Dlm, Lzd, Lfx and Cfz for more than one (1) month or DST confirmed resistance to any of these drugs are not eligible for this regimen.
- This regimen can be used for children, adolescents, pregnant and breastfeeding women since the study that provided the efficacy and safety of this regimen included these population groups. Hence for these population groups, it is a preferred regimen.

- This regimen may be used with or without Lfx or Cfz depending on the fluoroquinolone (FQ) drug susceptibility test (DST) result, BDLLfx is continued for FQ-sensitive RR/MDR-TB TB; BDLC for FQ-resistant RR/MDR-TB. This regimen can be initiated without delay in case of unknown FQ resistance at the time of diagnosis of RR-TB and may be continued with both levofloxacin and clofazimine if FQ-DST results cannot be obtained.
- Drug dosing is by body weight band (see Table 31). If there are any missed doses, the missed doses need to be made up at the end of treatment and added to the treatment duration. Linezolid is administered at 600 mg once daily throughout the treatment. Medication is to be given daily.

(ii) 9-month Bdq-based short-term treatment regimens

There are 3 different 9-month Bdq-based treatment regimens. These regimens are.

- 9 months of Bdq-Lzd-Mfx-Z
- 9 months of Bdq-Lzd-Lfx-Cfz-Z
- 9 months of Bdq-Dlm-Lzd-Lfx-Z

These regimens are alternative regimens when the two 6-month regimens (BPaLM and BDLLC) cannot be used for RR/MDR-TB patients and are preferable over longer (18-20 months) regimens. These regimens are to be used after confirmation that FQ is susceptible (needed exclusion of FQ resistance before treatment initiation) and patients who have no previous exposure to Bdq, Lzd,Lfx.Mfx, Cfz for > 1 month or no confirmed resistance to these drugs by DSTB Treatment duration is 9 months and medication is to be given daily. Patients with RR/MDR-TB with severe pulmonary TB and non-severe EP-TB are eligible for this regimen. However, patients with severe EP-TB or disseminated TB are not eligible for this regimen. Drug dosing is by body weight band. Among these regimens, the Bdq-Lzd-Mfx-Z containing regimen is preferred over the others due to less pill burden. Linezolid is initially administered at 600 mg once daily for 16 weeks. It is then reduced to either 300 mg once daily or 600 mg three times a week until the end of treatment.

(iii) Dosing of second-line drugs

For the prescribed treatment regimen to be effective, it is important to give appropriate dosing of anti-TB drugs as recommended. For BPaLM and BPaL, the dosing is fixed regardless of body weight. For 6 mth Bdq-Dlm-Lfx-Lzd-Cfz regimen, Bdq-based 9- on months regimens and LTR according to, dosing is based on the body weight of the individual patient (see drug dosing, Table 31).

(iv) Approach to Isoniazid-resistant TB while waiting for full DST results (sequencing, phenotypic DST results)

There is DR-TB strains that are not detected by GeneXpert (Xpert MTB/Rif Ultra, Xpert XDR) and Phenotypic DST, but will be detected only by sequencing. The most common scenario is clients are initially diagnosed as isoniazid-resistant (Hr) and sequencing tests only diagnose as MDR-TB with additional second-line drug resistance, especially Bdq and Cfz.

For clients with isoniazid resistance results from Xpert XDR or pDST, the treatment strategy approach is;

- In the presence of full SLD DST results including tNGS:
  - ✓ If INH-R only is confirmed: continue 6HRZE
  - ✓ If RR/MDR and with or without additional second-line drug resistance: Switch to standardized RR/MDR-TB regimens including BPaLM/6-Bdq-Dlm-Lfx-Lzd-Cfz/9-mth regimens or longer individualized regimens according to the DST pattern.
- In the absence of full SLD result and failing (clinically or no smear conversion at month 2) on HRZE regimen: switch to 9-12 months long Dlm,Lfx, Lzd,Cs, Z. Adjsut regimen when full DST result is received in discussion with the national TB/HIV clinical advisory team and clinical advisory committee (CAC). Completion of the clinical advisory form is required upon the receipt of tNGS results.
- Clinicians are advised to consult with the national TB/DR-TB clinical expert committee for difficult cases including cases who need to switch treatment regimens due to clinical or bacteriological treatment failure or severe adverse events, extra-pulmonary DR-TB cases, etc.

7.3.5 DRTB Treatment in Comorbidities and Special Situations

7.3.5.1 HIV co-infected patients

In patients with DR-TB/HIV co-infection, there is a need to assess them for regimen eligibility and start them on the most appropriate DRTB treatment regimen immediately.

Patients who are not on ART but are HIV positive at the time of DR-TB diagnosis should start DR-TB treatment before ART initiation. ART should be initiated for all DR-TB/HIV co-infected patients regardless of CD4 count. ART should be started within two weeks after DR-TB treatment initiation, or as soon as the patient tolerates DR-TB treatment, after a minimum period of two weeks.

The preferred ART regimen for DRTB patients is a DTG-based regimen as there are no interactions between BDQ and Dolutegravir (DTG). Bedaquiline cannot be used with EFV because of significant interactions (EFV reduces BDQ steady-state concentrations by 52%). Delamanid has no interactions with most ARVs currently being used and again there is no evidence on its interaction with DTG. In patients who cannot be initiated on either DTG or Raltegravir, a protease inhibitor (PI)-based regimen is considered. For patients who are already on a protease inhibitor (PI)-based regimen they should continue on the same regimen.

Note *that the ritonavir-boosted PIs (Atazanavir/ritonavir Lopinavir/ritonavir and Darunavir/ritonavir) increase BDQ steady state concentrations by 2-3 folds, carrying the risk of BDQ toxicity when co-administered. Therefore, close monitoring with ECG is important.* Active drug safety monitoring is recommended for all patients, but special attention is to be given to patients with overlapping toxicities. Co-administration of BDQ and Efavirenz (EFV) should be avoided.

HIV treatment must be taken daily without exception to prevent the evolution of drug resistance. Since DOT is an important component of DR-TB therapy, the provision of TB medications and ARVs in co-infected patients should be

through concomitant DOT. This is particularly important in the setting of second-line anti-tuberculosis therapy since it can result in a large pill burden and numerous adverse effects that make taking ARVs more difficult.

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

7.3.5.2 People with CNS or Osteoarticular Disease

Persons with either CNS or osteoarticular disease need to be treated for a minimum of 12 months. Those with osteoarticular disease can receive the 9- monthly oral regimen but it must be given for a full 12 months. People with CNS disease should be given medicines that can penetrate the CNS, conforming to the principles of designing an individualised DRTB treatment regimen.

Table 25: Central Nervous System Penetration of Second-Line anti-TB Medication

TB Drugs	CSF Penetration
Fluoroquinolones	Moderate to good: 60-80%
Injectables	Poor (<20%)
Ethionamide	Good
Cycloserine	Good
Linezolid	Good
Clofazamine	Good
Pyrazinamide	Good
Ethambutol	Poor
Rifampicin	Poor, (20%), High-dose-has good penetration
Isoniazid	Good
High-dose INH	Good
Bedaquiline	Likely poor
Delamanid	Likely poor
PAS	Poor

All other forms of EP-RR/MDR-TB can be treated with the 9-month all-oral regimen.

7.3.5.3 People with hepatic disease

People with underlying liver disease - including those with chronic active hepatitis B or C or cirrhosis of the liver, or other underlying medical conditions that affect the liver - can be treated with BPaLM or a modified 9-month all oral regimen in which highly hepatotoxic drugs are excluded (INH and PZA).

7.3.5.4 People with renal disease

Renal disease is not an absolute contraindication to BPaLM. There is need to use clinical judgement before treatment initiation with BPaLM and provide routine monitoring of renal function in this group of patients. If a regimen other than BPaLM is used, the doses of the medications should be adjusted for their degree of renal failure. Table 26 provides dosing recommendations for the TB drugs in renal disease in whom creatinine clearance is <30 ml/min.

Table 26: Recommended Dosing of TB Drugs for Patients with Renal Failure

Drug	Recommended dose and frequency for patients with CrCl < 30 ml/min or receiving hemodialysis
Pyrazinamide	25 – 35 mg/kg per dose three times per week (not daily)
Ethambutol	15 – 25 mg/kg per dose three times per week (not daily)
Amikacin	12 – 15 mg/kg per dose two or three times per week (not daily)
Levofloxacin	750 – 1000 mg per dose three times per week (not daily)
Cycloserine	250 mg once daily, or 500 mg/dose three times per week.
Amoxicillin/ Clavulanate	For CrCl 10 – 30 ml/min dose 1000 mg as amoxicillin component BID; For CrCl < 10 ml/min dose 1000 mg as amoxicillin component OD
Imipenem / Cilastin	For CrCl 20 – 40 ml/min dose 500 mg every 8 hours; For CrCl < 20 ml/min dose 500 mg every 12 hours
Meropenem	For CrCl 20 – 40 ml/min dose 750 mg every 12 hours; For CrCl <20 ml/min dose 500 mg every 12 hours

7.3.5.5 Pregnant Women and Children

There is inadequate information on the use of BPaLM in pregnant women and children. The 6- and 9-month regimens (Bdq-Dlm-Lzd-Lfx-Cfz; Bdq-Lzd-Mfx-Z; Bdq-Lzd-Lfx-Cfz-Z; Bdq-Dlm-Lzd-Lfx-Z) are recommended by WHO in these populations if there are no contraindications. To inform future policy it is important to closely monitor the treatment response among pregnant women and report birth outcomes.

7.3.5.6 People return to care after being lost to follow-up.

There may be individuals who are treated for DR-TB but are lost to follow-up (LTFU) defined as two or more months out of care. When these individuals return to care, their management will need to be considered on a case-by-case basis, considering their current clinical status, the length of time they were absent from treatment, any co-morbid conditions, and the severity of the disease at the time of initial diagnosis. All such individuals should have sputum samples sent for culture, genotypic and phenotypic DST, including BDQ, LZD, Pa and CFZ. In general, all such individuals should be started on an individualized regimen with at least 5 core medicines, adhering to the DRTB treatment regimen designed principles. Patients returning to care after LTFU should be re-registered and enrolled for individualized clinical management. Any person returning to care after LTFU should be offered counselling to understand the implications of absences on treatment and reduce future episodes of LTFU.

7.3.5.7 Monitoring treatment progress

Monitoring of both treatment efficacy (is the patient getting better?) and adverse events of the medications, i.e, active drug safety monitoring and management (aDSM) is essential through regular:

- History taking
- Physical examination
- Laboratory monitoring tests
- Psychological assessment and adherence support

Follow up regularly and perform the treatment monitoring procedures as in Table 27 for DR-TB patients while on treatment and 12 months post-treatment.

Upon identification of any adverse events, promptly and effectively manage including education and counselling about overcoming the adverse event to patient and family.

Table 27: Schedule of baseline and routine treatment monitoring during treatment and post-treatment follow-up

Investigation	Baseline	Follow up
Screening for adverse events (AEs)	Counsel on possible adverse events	At every clinical visit
Clinical evaluation and weight	√	Monthly until treatment completion
Smear microscopy	√	Monthly until treatment completion
Culture	√	Monthly until treatment completion
DST	√	Repeat phenotypic and genotypic DST, including second-line DST if: • Smear /culture remains positive after 3 months of treatment (or 2 months for H-r TB) • There is a positive culture after initial conversion.
Chest Radiograph	√	Baseline, then every 6 months or earlier as decided by the DR-TB physician
FBC	√	Monthly or as clinically required For HIV co-infected patients on AZT-containing ART regimen, monitor monthly for the first 6 months, and then as needed based on symptoms
Serum creatinine	√	Every two weeks for the first two months when initiating an injectable drug, then monthly while receiving the injectable. Patients with baseline renal insufficiency should be monitored frequently.

Investigation	Baseline	Follow up
Electrolytes	√	Every two weeks for the first two months when initiating an injectable drug, then monthly while receiving the injectable.
TSH	√	Every 2 months for the first 6 months if receiving PAS and ETO/ PTO *(It is not necessary to measure hormone thyroid levels, TSH is sufficient for screening for hypothyroidism)*
Liver serum enzymes (ALT and AST)	√	To be monitored regularly in patients who are receiving pyrazinamide, are HIV co-infected or have a history of active hepatitis; can be monitored every two months during the continuation phase
HIV testing	√	Repeat as clinically indicated (risk assessment as per Eswatini HIV Testing Guidelines)
CD4⁺ cell count	√	Every 6 months for newly initiated ART clients, in combination with viral load monitoring (follow Swaziland Integrated HIV Management Guidelines) Repeat whenever ART failure is suspected.
HIV Viral load	No	Pre-treatment viral load for ART-naive patients. At 3-6- and 12-months post-ART initiation, and then annually if the client is virally suppressed. Repeat VL whenever ART failure is suspected
Pregnancy tests	√	Repeat as clinically indicated. All women of childbearing age should be provided with long-term family planning methods while on DR-TB treatment.
ECG	√	Every two weeks for a month when initiating a BDQ or Dlm, then monthly while receiving these drugs. Patients with baseline prolonged QTC interval or receiving concomitant treatment with QTC-prolonging agents (Mfx and Cfz) should be monitored frequently as per clinician discretion.
Audiometry	√ **(if on injectable)**	Repeat at 72 hours post initiation, 2 times a month for high-risk patients for the first 60 days of therapy, but otherwise monthly during the intensive phase/on injectable. Repeat at 3 and 6 months after completion of injectable.
Visual test (Snellen chart and Ishihara)	√	At baseline and Monthly if on E or Lzd, otherwise use visual testing charts monthly, and refer to an ophthalmologist when indicated

Table 28: The distribution of duties among doctors, nurses and counsellors in the provision of care is delineated

Medical Doctor	Clinical assessment and consultation, physical examination. Laboratory investigation as per guideline Interpretation of ECG and all other tests Interpretation of lab results from current and previous visits (biochemistry, DST, ECG, etc.) Assessment of side effects · Prescription of medication for DR-TB and co-morbidities.
DR-TB Nurse	Clinical support Performing ECG, visual tests, ill count Adherence support by leading support group Discussing VOT and WhatsApp with patients enrolled on the digital health component Initiating patient tracing (for patients not presenting to appointments)
Counsellor/ Psychologist/ DR-TB Nurse	Psychological assessment (using PHQ-9) Adherence support Psychologist from ENAP Social workers from the DPM office

7.4 Adverse Event Management

Clinical and laboratory monitoring should be conducted to detect, manage, and report suspected or confirmed adverse drug events, as outlined in the treatment monitoring schedule. Serious adverse events (SAEs) should be monitored in a systematic and timely manner. At every encounter with the patient, health workers should ask the patient about clinical symptoms of common adverse events and record them on the patient's DRTB treatment card. Additionally, all adverse events should be reported using the appropriate reporting tools, whether paper-based or electronic. Refer to the pharmaco-vigilance chapter for the details of adverse event management and reporting.

Consider additive or potentiating side effects with concomitant therapy, as well as potential drug-drug interactions. There should be clinical follow-up for all patients at 2 weeks after DR-TB treatment initiation and then monthly until treatment completion.

The general management of adverse events is based on severity grading:

- **Grade 1 (mild) or Grade 2 (moderate)** – the drug may be continued with close monitoring except in cases of optic neuropathy where linezolid and ethambutol should be stopped.
- **Grade 3 (severe) or Grade 4 (life-threatening)** – the patient should be closely monitored and managed by a doctor. The drug may be discontinued if, in the opinion of the doctor, the AE or laboratory results indicate a significant risk in continuing treatment.

For specific management of adverse events, **refer to details in the aDSM chapter for pharmaco-vigilance**.

7.5 Treatment Care and Support

Tuberculosis including the drug-resistant forms is completely curable with early detection and complete treatment. Early detection of drug resistance through rapid diagnostics facilitates early initiation of treatment and favours good prognosis. Adverse drug reactions, comorbidities, social neglect and treatment-related costs are the major deterrents to successful treatment completion and relapse-free cure. A patient-centric approach ensuring adequate medical, social, psychological, and nutritional support is essential for a good quality of life.

Treatment support refers to the services provided to the patient enabling them to complete the treatment. These services include therapeutic, emotional, social and financial support. As part of supporting the patient, it is always important to involve the patient in any treatment decisions.

Pre-treatment counselling sessions should be provided in two sessions to **assess patient readiness** (see Table 29 for treatment readiness assessment parameters). These sessions will be conducted with the aid of educational material and invitation of the treatment supporter if already available is recommended.

Principles of treatment support:

- Minimize patient travel
- Minimize delay in treatment initiation and follow up
- Minimize Catastrophic expenditure
- Minimize infection in transit
- Maximize patient satisfaction
- Maximize adherence to treatment
- Maximize transparency in operations

The need for support should be assessed and the process of providing support should be initiated by the health system as patients may not request it. However, the health system may not be equipped to provide all forms of support with its resources. In such situations, health system personnel should be able to link the patient to appropriate sources of support. All staff in the DR-TB service delivery institutions and field should be considerate and behave humanely to patients suffering from DR-TB.

Table 29: Treatment readiness checklist parameters

Readiness Checklist Parameters
Patients are informed about their diagnosis Patient understands their diagnosis, TB disease, adherence, treatment duration, side effects, IPC measures *Health care providers will ensure this through patient education and use of educational material and necessary documentation i.e. Lab results, x-ray etc. The health care provider will provide health education on T3 and ask questions to verify patients understanding*
Ability to identify potential barriers and has solutions to them Patient understands the importance of adherence; taking medication at right dose, time and frequency; provision of DOT and treatment supporter, healthy preventative habits, actions implemented; Attending all reviews in facilities The psychosocial assessment is conducted to assist client in identifying the barriers and ensure they can come up with solutions
Patient has been offered appropriate HIV Counselling Patient has been tested for HIV; If positive, patient understands their diagnosis and the need for ARV's; If already on ART, patient understands that drugs may be changed to ensure minimal interaction with TB drugs; understands the importance of adhering to TB/HIV treatment; if Negative; HIV Prevention services have been offered *Health care provider provides health education on HIV/TB, conducts HIV test where applicable (HIV status unknown)*
Patient understands side effects and steps to take when encountering them
Patient is self-motivated Can identify individual resources or coping mechanisms to adhere to TB treatment apart from health benefits
Patient understands the importance of starting TB treatment Patient consents to TB treatment

7.6 Domiciliary, ambulatory and inpatient care

The patients in ambulatory care and patients stabilized after in-patient care will be referred to the concerned decentralized DR-TB unit through a filled Referral form. The patient will carry a copy of the Treatment card. The DR-TB counsellor/Clinician should counsel the patient on the various drugs that he/she has been initiated on and their adverse events. Patients and treatment supporters should be provided with a list of Adverse Drug Reactions and necessary actions to be taken. The counsellor should train the patient and treatment supporter on the use of an adverse event monitoring tool. The DR-TB counsellor should initiate the referral and relevant details of treatment in advance to the treating clinician to arrange drugs and necessary support.

7.7 Follow-up of treatment

At no point during diagnosis, pre-treatment, treatment and follow-up, should the patient incur any direct cost to avail of any service. Patients may incur some indirect costs such as travel expenses and loss of wages while accessing services. These are expected to be supported through the adherence enablers provided to the patient at various stages post-notification. These **adherence enablers** are expected to be provided to the patient at every monthly consultation.

7.8 Patient support for Co-morbidities

Many of the patients undergoing treatment for DR-TB might also be diagnosed with additional ailments, such as HIV, Hypertension, Diabetes, and COPD. The DR-TB unit should ensure that treatment services for these co-morbidities are made available to the patient without interruption.

7.9 Social protection at the community level

During ambulatory care, the MO / treating physician and staff of the TB unit should identify the need for various forms of social support such as travel, nutrition, substance detoxification, and social security schemes and link the patient to sources that provide this support, including support available through the programme and partners. Social interventions with the stewardship of the community have been found to be effective in promoting treatment adherence. Every DR-TB unit should have a community team which coordinates with Community-Based Organisations (CBOs) to ensure that TB patients benefit from existing social protection programs within their communities.

7.10 Treatment support for the detection and management of ADRs

Adverse drug reaction (ADR) is a major cause of fatality and loss of follow-up. Patients should be carefully monitored to detect and manage ADRs at their onset. DR-TB Clinicians and counsellors should educate the patients on potential adverse reactions, their signs and symptoms, necessity of timely reporting. The ADR should be recorded in the section provided in the treatment supporter book.

The community treatment supporters responsible for the supervision of the patient at home should actively search for signs and symptoms of ADR on every visit. Additionally, they need to keep in touch with the patient over the phone to actively enquire about ADRs. Patients should be encouraged to report even the mildest symptoms and record them in the ADR diary. On self-reporting by the patient or on elicitation by a health worker, the treating physician should clinically examine and investigate for the cause. Some of the ADRs like a drug induced gastritis or itching might be mild and managed at the decentralized DR-TB unit level.

Moderate or severe forms of ADRs such as toxicities to the liver, kidneys or nervous system, and psychiatric abnormalities may warrant stopping of drugs and referral to DR-TB facilities with admission capacity immediately. The clinician should fill out a referral form with a detailed history of the ADR and refer the patient with advance intimation to the clinician at the receiving facility. Based on the ADR management guidelines, modifications in the present regimen may be made at the admitting DR-TB unit. Once the patient is referred, the clinician should ensure that the patient has understood the modifications and educate the treatment supporter about the same.

7.11 Management of irregular and non-compliant patients

The use of directly observed therapy (DOT) in the treatment of DR TB is the standard. Even with DOT, however, there are still patients who may be irregular or non-compliant. Such patients present a challenge to the DOT worker, nurse, and physician.

The following approach should be observed:

- At the first sign that a patient is not complying with the treatment regimen, the medical team should elicit the barriers to treatment adherence.
- Arrange a Medical officer's visit with the patient, DOT worker, and nurse to discuss in detail these barriers to treatment adherence. If the missed doses are due to a scheduling problem, often accommodations can be made (e.g., delivering a dose at work with the patient's consent).
- Careful attention must be paid to the development of psychiatric symptoms.
- Psychological support is often helpful, either in the form of an appointment with a trained psychology nurse, psychologist/psychiatrist or counsellor or through participation in group therapy.
- If patients have severe symptoms of depression or psychosis and a psychiatrist/ a trained medical officer is not available, the clinician taking care of the patient may need to start anti-depressant or anti-psychotic therapy until a psychiatrist/a trained medical officer is available.
- Missed doses may be due to side effects which are not being adequately addressed. If this is the case, more progressive side effect control is indicated.
- Patients should be assessed for alcohol and drug abuse. Although such behaviours are difficult to modify, education and counselling on addiction may be helpful. In addition, support groups and twelve-step programs, such as Alcoholics Anonymous, have a proven record of helping such patients and should be used in smear-negative patients when available.
- Optimization of enablers and incentives may be used to improve adherence.
- The difference between an enabler and an incentive is that an enabler allows the patient to comply with treatment (for example, money for a bus to come to the clinic) while an incentive rewards the patient for being compliant e.g. a food basket at the end of a week of regular treatment, and clothing.
- When all means of facilitating adherence have been exhausted with no result, the patient may be asked to sign a contract with rules regarding adherence (e.g., no more than two missed doses in one month).

7.12 Interrupting DR-TB treatment

When a patient shows tendencies to interrupt therapy early, every effort should be made to explain the importance of completing the full therapeutic regimen. The reasons behind the patient's stopping treatment should be adequately discussed with the patient, and, if possible, try to improve any difficult situations that may be contributing to the patient's desire to stop therapy. Timely and effective management of side effects or changes in scheduling time of doses can help improve the situation.

Change of the treatment regimen should be avoided as much as possible, as this can undermine the importance of taking all the medicines, may cause other patients to request similar changes and compromise new medicines being added to a regimen if pertinent considerations are not followed.

As with the irregular patient, an evaluation should be done that includes an assessment of the patient for depression and/or substance abuse. Enablers and new incentives can be considered.

7.13 Post-treatment follow-up of DR-TB cases

All DR-TB cases successfully treated should be followed up after discharge to ensure continuity of care and support including psychological support and HIV prevention (if HIV-negative). Patients should also be counselled on possible signs of recurrence for good care-seeking attitudes in the event of recurrence.

In the first year of discharge, patients should be followed up.

For BPaLM/BPaL

- Monthly for the first 3 months (monthly cultures and clinical assessment), then month 6 and month 12.

For Modified shorter regimens (mSTR) / Longer treatment regimens (LTR)

- Cultures and clinical assessment, every after 3 months for the next 24 months (month 3, month 6, month 12 and month 24).

The follow-up will include an assessment of clinical condition, and management of any detected problems. For any client identified as having TB signs and symptoms during post-treatment follow-up, evaluation for TB should be performed (i.e. sputum test as described in the TB/DR-TB diagnosis Chapter). Table 30 Dosing of second-line anti-TB drugs.

Table 30: Drug dosing for BPaLM and BPaL regimen

Drugs	Suggested	Remarks
Bdq (100 mg tablets) 400 mg	400mg daily for 2 weeks Then 200mg three times per week	Minimum of 48 hours between doses after the first 2 weeks
Pa (200mg tablets)	200mg daily	7 days per week
Lzd (600mg)	600mg daily for the duration of treatment	7 days per week Alternative dosing regimens for patients with severe adverse effects: 600 mg thrice weekly (M, W, F), or 300 mg daily provided that 9 consecutive weeks of treatment is completed.
Mfx (400 mg tablets)	400 mg daily for the duration of treatment	7 days per week

Table 31: Weight-based dosing of medicines used in multidrug-resistant TB regimens, adults and children[a]

Group A Medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	3-4 kg	5-6 kg	7-9 kg	10-15 kg	16-24 kg	25-29 kg	30-35 kg	36-45 kg	46-56 kg	56-69 kg	≥70 kg	Comments
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			
	750 mg tab	–						1		1.5			
Moxifloxacin (Mfx)	**100 mg dt (10 mg/mL)**	1 mL	8 mL	1.5	2	3	4	4		–			
	400 mg tab (40 mg/mL) Standard dose	1 mL[b]	2 mL[b]	3 mL[b]	5 mL (0.5 tab)[b]	7.5 mL	1	1					
	400 mg tab high doses	–		–	–	–		1 or 1.5	1.5	1.5 or 2	2		
Bedaquiline (Bdq)	**20 mg dt**	0 to <3 months: 1.5 od (2 weeks); then 0.5 od M/W/F (22 weeks) ≥ 3 months: 3 od for 2 weeks. then 1 od M/W/F for 22 weeks		0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F 3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F ≥6 months: 4 od for 2 weeks; then 2 od M/W/F	3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F ≥ 6 months: 6 od for 2 weeks; then 3 od M/W/F	10 od for 2 weeks. then 5 od M/W/F		20 od for 2 weeks; then 10 od M/W/F		–			
Bedaquiline (Bdq)	**100 mg tab** (10 mg/mL)[d]	0 to <3 months: 3 mL od for 2 weeks. then 1 mL od M/W/F[b] ≥ 3 months: 6 mL od for 2 weeks. then 2 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] ≥ 6 months: 8 mL od for 2 weeks; then 4 mL od M/W/F[b]	3 to <6 months: 6 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	4 od for 2 weeks then 2 od M/W/F					
	100 mg tab (Alternative dosing strategy for BPaLM/BPaL and BDLLfxCfz regimens)							2 od for 8 weeks followed by 1 od					Dosing scheme is for BPaLM/BPaL regimen (>14 years) and for BDLLfxCfz in adults

Group A Medicines	Formulation (tablets, diluted in 10 mL of water, as applicable)	3-4 kg	5-6 kg	7-9 kg	10-15 kg	16-24 kg	25-29 kg	30-35 kg	36-45 kg	46-56 kg	56-69 kg	≥70 kg	Comments
Linezolid (Lzd)	**20 mg /mL susp**	2 mL	4 mL	6 mL	8 mL	11 mL	14 mL	15 mL	20 mL	–			
	150 mg dt (15 mg/mL)	2.5 mL	5 mL (0.5 dt)	1		2[e]	2	3		–			
	600 mg tab (60 mg/mL)	–	1.25 mL[b]	2.5 mL[b]		5 mL (0.5 tab)[b, e]		5 mL (0.5 tab)[b]	7.5 mL (0.75 tab)[b]	1	1	1	
LZD	**600 mg tab (alternative dosing strategy for modified 9 months regimens)**						**0.5**	1 od for 16 weeks followed by 0.5 od or 1 M/W/F until the end of treatment					**This applies to modified 9-month regimens (BLMZ, BLLCZ, BLLfxCZ)**

Group B Medicines	Formulation	3-5 kg	5-7 kg	7-9 kg	10-15 kg	16-23 kg	24-29 kg	30-35 kg	36-45 kg	46-55 kg	56-69 kg	≥70 kg	Comments
Clofazimine (Cfz)	**50 mg cap or tab**	1 M/F	1 M/W/F		1		2	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	1					
Cycloserine or terizidone (Cs/Tz)	**125 mg mini cap (Cs) (12.5 mg/mL)**	2 mL[b, g]	4 mL[b]	1	2	3	4	4		–			Pyridoxine is usually given to limit Cs toxicity
	250 mg cap (25 mg/mL)	1 mL[b, g]	2 mL[b]	5 mL[b]	1	2	2	2		3			

Group C medicines	Formulation	3-4 kg[a]	5-6 kg[a]	7-9 kg	10-15 kg	16-23 kg	24-29 kg	30-35 kg	36-45 kg	46-55 kg	56-69 kg	≥70 kg	Comments
Ethambutol (E or EMB)	**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 (Dlm)	**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) 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	2.5	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	
Imipenem–cilastatin (Ipm/Cln)	500 mg + 500 mg powder for injection, vial (10 mL)							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 vials (1 g + 1 g) bd					Only to be used with clavulanic acid

Group C Medicines	Formulation	3-4 kg[a]	5-6 kg[a]	7-9 kg	10-15 kg	16-23 kg	24-29 kg	30-35 kg	36-45 kg	46-55 kg	56-69 kg	≥70 kg	Comments
Amikacin (Am)	500 mg/2 mL solution for injection, ampoule	_i								3–4 mL	4 mL	4 mL	Recommended only in adults aged >18 years
Streptomycin (Sm)	1 g powder for injection, vial	_i								Calculate according to the dilution used			Recommended only in adults aged >18 years
Ethionamide or Prothionamide (Eto/Pto)	125 mg dt (Eto) (12.5 mg/mL)	3 mL[b]	7 mL[b]	1	2	3	4	4		–			Although once daily dose advised, two divided doses can be also given to improve tolerance
	250 mg tab (25 mg/mL)	–	3 mL[b]	5 mL (0.5 tab)[b]	1	2		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
Other Medicines	**Formulation**	**3-5 kg**	**5-6 kg**	**7-9 kg**	**10-15 kg**	**16-23 kg**	**24-29 kg**	**30-35 kg**	**36-45 kg**	**46-55 kg**	**56-69 kg**	**≥70 kg**	**Comments**
Isoniazid[j] (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	4.5	–			
	300 mg tab	–				1	1.5	1.5		2			
Clavulanic acid[j] **(as amoxicillin/ clavulanate)** (Amx/clav)	62.5 mg clavulanic acid as amoxicillin/ clavulanate (250/62.5 mg), powder for oral solution, 5 mL	1.5 mL tid	2 mL tid	3 mL tid	5 mL tid	8 mL tid	10 mL tid	10 mL bd or tid		–			Only available in combination with amoxicillin. To be given with each dose of imipenem/ cilastatin (bd) or meropenem (tid).
	125 mg clavulanic acid as amoxicillin/ clavulanate (500/125 mg) tab	–					1 tid	1 bd or tid					
Pretomanid (Pa)	200 mg tab	–						1					Currently only used as part of the BPaLM/BPaL regimens.

Notes

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.

Dosing guidance is based on currently available data and may be revised once additional data is 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 like 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 the 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 a 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 are bioequivalent to tablets swallowed whole. Vigorous stirring/shaking is needed before 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 relatively high exposures associated with the 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 are 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 premature and low birth weight infants weighing <3kg, advice should be sought from a paediatric DR-TB expert.
- For dosing 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.

CHAPTER 8
CHILDHOOD TB SCREENING, DIAGNOSIS AND TREATMENT

8.1 Introduction

TB in children has conventionally been classified the same as for adults as Pulmonary TB (PTB) and Extra pulmonary TB (EPTB) including disseminated TB (TB meningitis and miliary TB).

There is no existing approach that comprehensively characterizes the spectrum and severity of pediatric TB. Most cases of TB in children occur within 2 years after exposure/ infection with the majority occurring within 1 year. Most of the children will have PTB, however, EPTB is also common with the type depending on age. A child may have both PTB and EP-TB forms at the same time. *Severe form Pulmonary TB and EP-TB may leave behind TB-associated disability (e.g. post-TB chronic lung disease, cognitive disability due to TB meningitis, movement disability due to TB bones and joints, etc.)*. Therefore, early diagnosis through systematic screening and treatment is crucial to ensure the lives of children with TB are not hampered by the consequences of the disease.

TB symptoms in children are subtle and mimic other common childhood illnesses, diagnosing childhood TB is challenging. The clinical picture and diagnostic approach are not as straightforward as in adult TB. Diagnosis of TB in children largely depends on a high index of suspicion based on a careful history of exposure, physical examination for symptom analysis as well as investigations which include laboratory tests and chest X-ray. It is quite difficult to obtain sputum for examination in young children.

While bacteriologic testing should always be attempted, the challenges with specimen collection in children (especially in peripheral health facilities) and the suboptimal yield from the present tools used in the diagnosis of childhood TB persist due to the paucibacillary nature of TB disease in children.

8.2 Systematic Screening of TB in children

Screening tools recommended for children are the same as for adults though there is a slight difference.

The recommended screening tools are:

- Symptom-based screening using four classic key signs and symptoms of TB
- Chest Xray (with human reader for children <15 years old)
- C-Reactive protein (for Children with HIV >10 years old)

8.2.1 TB Symptom Screening Tool

The four key classical signs and symptoms of TB are included in the systematic screening of TB in children.

These symptoms are:

- Cough of any duration
- Fever

- Poor weight gain/failure to thrive
- History of contact with a TB case

The presence of at least 1 sign/symptom is defined as presumptive TB. In children younger than 10 years old, having a TB contact history alone regardless of signs and symptoms is defined as presumptive TB

Other symptoms of TB in children are:
- Reduced playfulness

8.2.2 Chest Pain
- Hemoptysis (coughing blood)
- Swollen glands
- Breathlessness
- Bone/joint deformity (gibbus) or swollen joint

Systematic screening with TB symptom screening tools should be performed at every service delivery point for children (e.g. PHU, Paediatric clinic, Immunization and Nutrition clinics, Mother and Children Care Unit, etc.).

8.2.3 Chest X-Ray
The use of CXR for TB screening in children is recommended wherever available. CXR screening can help identify asymptomatic TB cases. However, CAD software used for reading CXR for children less than 15 years old is not yet recommended by WHO (see Figure 23, for the algorithm for TB screening in children). The targeted risk groups are child TB contacts, CLHIV, undernourished children (MUAC <12.5 cm or weight for height/age Z score <-2), and vulnerable children (e.g. orphans, sexual violence survivors, etc.).

The common CXR features that are highly suggestive of TB in children are:
- Hilar/media stirnal lymphadenopathy with or without airway compression
- Consolidation
- Pleural effusion and
- Miliary TB

8.2.4 C-Reactive Protein (CRP)
CRP is recommended only for ARV naive children living with HIV (CLHIV) who are older than 10 years. The cut-off value of CRP in CLHIV >10 years old is the same as for adults (i.e. 5 mg/L). CRP is also helpful for identifying asymptomatic TB cases.

8.2.5 Defining Presumptive TB
The definition of presumptive TB in children is the same as for adults which includes
Presence of at least 1 sign/symptom (in children <10 years old, history of TB contact alone is defined as presumptive TB) and/or CXR suggestive of TB and/or CRP >5mg/L.

Note: Any children identified as presumptive TB should have a microbiological diagnosis to confirm TB by putting every effort into collecting specimens.

8.3 Diagnosis of Childhood TB

It is difficult to bacteriologically confirm the diagnosis of TB in children, however, the diagnosis can still be made with confidence in most children using careful clinical assessment.

8.3.1 Clinical assessment

Recommended approaches to diagnosis of TB in children include.

- Thorough history-taking
- Clinical examination
- Bacteriological confirmation whenever possible
- HIV testing
- Investigations relevant to suspected EPTB

(a) Thorough History Taking

In most cases, children with TB develop chronic unremitting symptoms that don't improve or resolve without appropriate TB treatment (see Figure 21 TB screening tool for children). TB should be considered earlier in high-risk children such as those living with HIV or those in close contact with people with TB.

Some screening questions that may prompt additional history-taking surrounding the risk for TB or additional testing are as follows:

- Current cough
- Poor weight gain or failure to gain weight (failure to thrive)
- Persistent fever for more than two weeks
- History of contact with index cases, especially for those under ten years of age
- Soaking night sweats
- Reduced playfulness or less active than usual for more than 2 weeks
- Loss of appetite
- Enlarged lymph nodes

(b) Physical Examination

During physical examination, the following may be found:
Suspect TB if the response to one week of broad-spectrum antibiotic trial is poor or not responding to two weeks of nutrition therapy in malnourished children (MUAC <115 cm or weight for height/age Z score <-2 or <-3). If HIV is infected, also consider another HIV-related lung disease e.g. *Pneumocystis' jiroveci pneumonia (PJP)*.

(c) Growth Assessment

Clinical advances in the management of childhood TB have emphasized the critical need to monitor weight about height or age in children. This is identified as assisting in arriving at a diagnosis for children who have TB.

Vital signs: Respiratory symptoms

(d) Respiratory System

- Increased respiratory rate
- Signs of respiratory distress (intercostal recession, use of the accessory
- Muscles for respiration, grunting)
- If pleural effusion is present, the side of the chest that is affected may have a stony dull percussion note and reduced breath sounds
- On auscultation there may be normal chest sounds, or abnormal chest sounds that may be heard (crackles, wheezing or bronchial sounds)
- Normal respiratory examination does not rule out TB, especially in non-severe disease

Clinical features suggestive of other causes of chronic lung disease:

- Generalized lymphadenopathy, oral thrush, and parotid enlargement may all suggest HIV infection
- Finger clubbing may be due to Lymphoid Interstitial Pneumonitis (LIP) or bronchiectasis in children living with HIV, but can also present with TB

Note: There may be atypical presentations in the child in the form of acute pneumonia, especially in infants and HIV-infected children. Persistent wheezing that tends to be asymmetrical and does not respond to bronchodilators can uncommonly occur and is caused by airway compression due to enlarged tuberculous hilar lymph nodes.

(e) A typical clinical presentation of TB

Acute pneumonia would be presented with:

- Fast breathing and chest in drawing is a more common presentation of TB in infants and HIV-infected children
- Suspect TB if poor response to antibiotic therapy-particularly if HIV infected or very young
- Also suspect other HIV-related lung disease e.g. Pneumocystis Jirovaci Pneumonia (PJP)
- Wheeze: Suspect TB when the wheeze is asymmetrical, persistent and not responsive to bronchodilator therapy and associated with other typical features of TB

8.3.2 Laboratory Diagnosis of Childhood TB

In children with signs and symptoms of PTB, Xpert MTB/RIF Ultra should be used as the initial diagnostic test for TB and detection of RIF resistance using sputum, gastric aspirate, nasopharyngeal aspirate or stool specimens, rather than smear microscopy. The leftover from the Xpert Ultra testing should be used for follow-on MTB XDR assay testing. Two samples are collected, one for the Xpert MTB Rif ultra and Xpert MTB/XDR assay and the second specimen is sent for culture, phenotypic DST and tNGS where applicable, *however, stool samples are not used for culture and phenotypic* DST.

Bacteriological confirmation of TB diagnosis among children is challenging due to:

- TB of a pauci-bacillary nature
- Inability to produce sputum on their own, especially younger children (<5 years old)
- Invasive procedures to obtain sputum are available only in hospitals/health centres

Because of these challenges, WHO has recommended the concurrent use of respiratory and stool sample testing in children, especially considering that stool samples is easy to collect and that small children swallow their sputum, making MTB easily detectable from stool.

The NTCP recommends concurrent samples (respiratory sample obtained by sputum induction/nasogastric aspiration, and stool sample) testing in children, especially for children less than 5 years old whenever available.

(a) Eligibility Criteria for Xpert Stool Sample Testing:

- Children <5 years old including CLHIV with presumptive TB as a first-line diagnostic test. *(It can be followed by gastric aspiration or induced sputum if the child has persistent symptoms)*.
- Older children and adolescents (6-15 years old) with presumptive TB, when sputum sample cannot be obtained.
- In children initiating TB treatment after a positive stool test, a gastric aspirate or induced sputum is needed to send for culture (e.g. RR TB is detected, contacts of DR-TB cases) since culture and DST cannot yet be performed with a stool sample.

Note: The diagnostic accuracy of stool sample tests for ADULTS is not yet endorsed by WHO. Hence do not send stool samples of adult presumptive TB cases.

Table 32: Procedures of respiratory sample and stool sample collection

Method	Techniques
Sputum Induction	• Can be performed at any age • Collection of sputa after the child inhales 3-5% hypertonic saline (induction improves the yield of sputa collection for all ages) • The child should not have eaten for 2 hours before the procedure and pretreated with salbutamol • Nasopharyngeal suctioning can be performed following the procedure if the child is unable to expectorate • Can be performed at any time but morning is preferred • 5 ml is recommended for Gene Xpert and Culture • Do not perform in children with respiratory distress or wheeze • A nebulizer and mask must be sterilized after each use

Method	Techniques
Gastric Aspirate	• Consider in children < 7 years • Nasogastric aspiration of gastric secretions using a nasogastric tube • 2-3 specimens are recommended to increase yield • Volume: 5-10 ml should be collected, if less confirm tube placement and re-attempt. If still < 5-10 ml instill up to 20 ml of sterile water and re-aspirate. • It should be performed in the early morning and fast for 4 hours (outpatient collection is fine provided these parameters are met). • Nasogastric tube should be used • If possible, neutralize the aspirate with sodium bicarbonate if the specimen is not processed that day based on pH testing
Nasopharyngeal Aspirate	• Can be performed in children under 6 years • Suctioning of the nasopharynx via a nasopharyngeal tube at 15 -20 kPa of pressure • 2 ml of aspirate is recommended • Can be performed at any time but morning is preferred, generally follows sputum induction • A suction machine is recommended for the procedure
Stool for TB	• Performed only for children under the age of 15 years. • For infants and toddlers, stools can be directly collected from the diaper as soon as possible after defecation. *(Avoiding prolonged contact with the surface of the diaper.)* • Older children are directed to defecate on a clean sheet of paper, avoiding contamination from the soil and urine. • Using a designated spatula or wooden stick, the sample is transferred into a stool container or a sputum container and sealed tightly before submitting it to the laboratory for processing. The sample container should NOT be filled to the brim. • A volume of 1g (a pea size) for a formed stool or 5 ml for a watery stool is sufficient to perform the Xpert test. • The simple one-step method (SOS) is used in the laboratory to analyse the sample. • A subsequently induced sputum or gastric aspirate will have to be collected and sent for culture and DST to the reference lab should the Xpert MTB results turn out positive.
Methods of specimen collection for Extra-Pulmonary Disease	• Specimen collection should be attempted from the presumed site of disease through fine needle aspiration of lymph nodes, collection of CSFS, pleural, ascetic fluid etc.

8.3.3 Diagnosis of EPTB in Children

In children with signs and symptoms of EPTB, Xpert MTB/RIF may be used as an initial diagnostic test for TB on lymph node aspirate, lymph node biopsy, urine, CSF, pleural, peritoneal, pericardial and synovial fluids for the corresponding form of EPTB rather than smear microscopy or culture. Imaging technology (X-ray, ultrasonography, CT-Scan, etc.,) are helpful diagnosis of EP-TB.

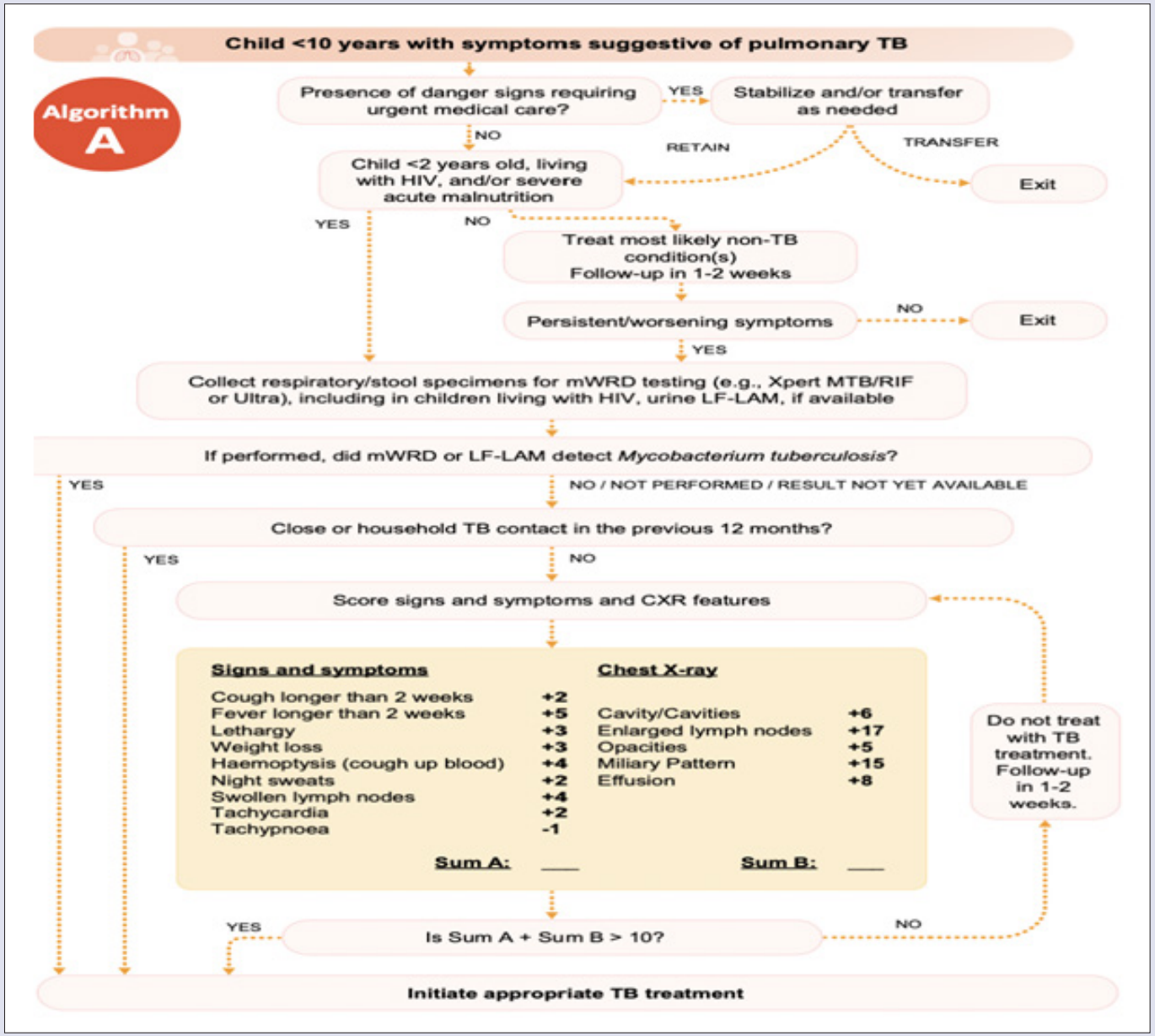
8.3.4 Clinical diagnosis of pulmonary TB and decision for treatment in children (0-10) years old

- When bacteriological confirmation of pulmonary TB cannot be made to clinically diagnose TB in children, healthcare workers should follow the algorithms Figure 21 and Figure 22 and scoring systems for the decision-making of TB treatment in children <10 years old.
- It is important to check the presence of danger signs (see Table 33) and to stabilize or transfer as needed if danger signs are present. If there are no danger signs, check risk factors for TB including if age <2 years old, living with HIV, severe acute malnutrition
- If the child has a risk factor and is considered as presumptive TB, and laboratory diagnosis cannot confirm TB or is not available, check the contact history of TB in the past 12 months.
- If TB contact history is present, it may be considered as TB disease at the discretion of the treating clinician.
- If TB contact history is not present, check the total score of possible TB diseases by applying Figure 21 (children with CXR result) and Figure 22 (without CXR).
- If the total score is >10, it may be considered as TB disease and initiation of treatment by the discretion of the treating clinician.

Table 33: Danger and Priority Signs in Children <10 Years Old

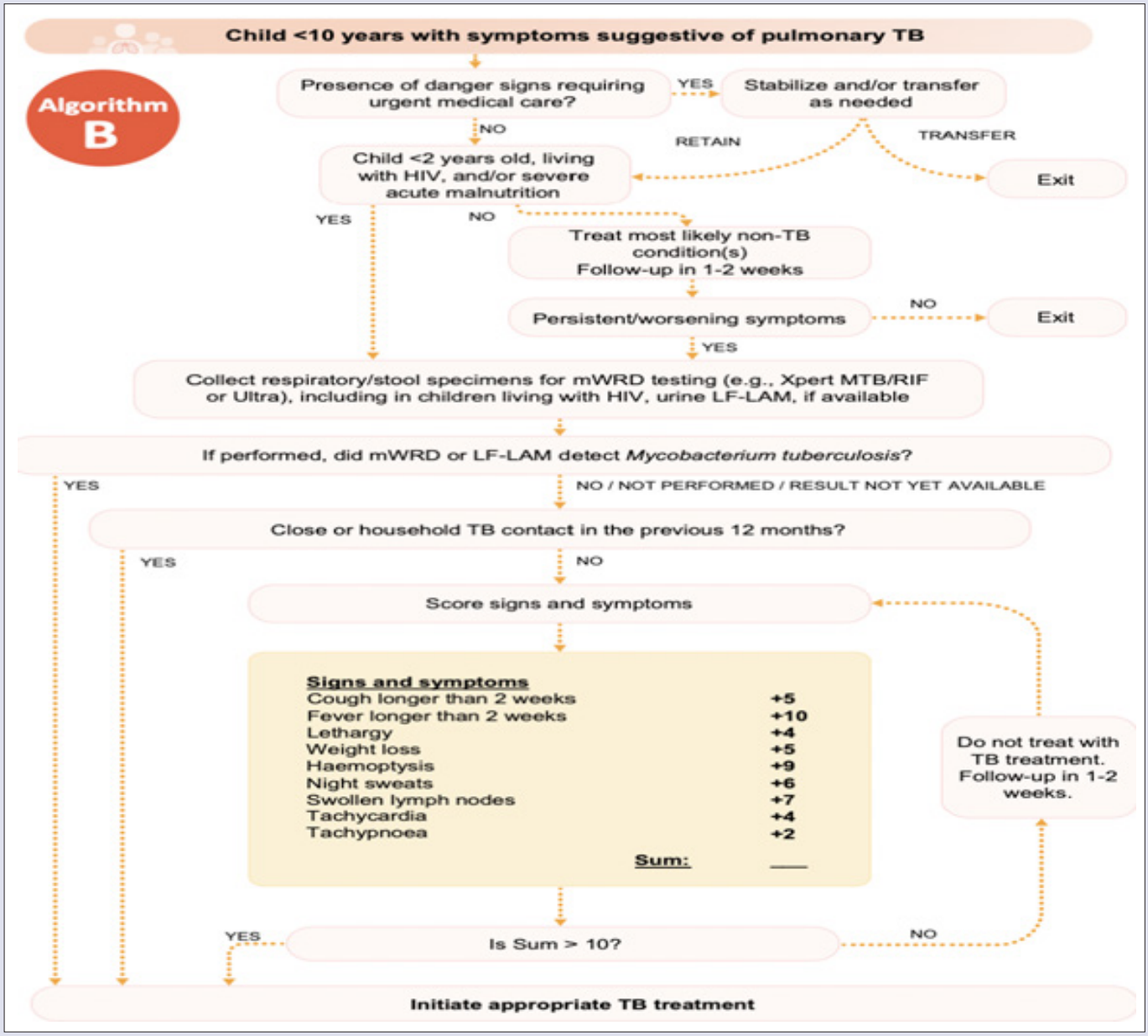
Age <5 yrs	Age <5-9 yrs	Age <10 yrs
Danger Signs (IMCI)	**Danger Signs (ETAT)**	**Priority Signs**
Gastrointestinal/circulatory: • Unable to eat or drink • Vomiting up everything • Signs of severe dehydration (sunken eyes, skin pinch returns very slowly) • Severe palmar pallor	Gastrointestinal/circulatory: • Diarrhea with any two signs of severe dehydration (lethargy, unconsciousness, sunken eyes, very slow return of skin after pinching) • Signs of shock (cold extremities with capillary refill time>3 seconds, weak and fast pulse)	Any sick child aged <2 months • High fever (>39° C) • Severe pallor • Respiratory distress • Restless, continuously irritable, lethargic • Severe acute malnutrition (SAM)
Respiratory: • Stridor • Oxygen saturation <90%	Respiratory: • Obstructed or absent • Breathing • Severe respiratory distress • Central cyanosis	
Neurological: • Seizures • Profoundly lethargic, unconscious • Neck stiffness or bulging fontanelle	Neurological: • Coma (or seriously reduced level of consciousness) • Seizures	

Figure 21: Decision tree for TB treatment in children <10 years old (for settings where CXR is available)



(Source: WHO Operational Handbook on Tuberculosis, Module 5: Management of Tuberculosis in Children and Adolescents, 2022)

Figure 22: Decision tree for TB treatment in children <10 years old (for settings where CXR is not available)



(Source: WHO Operational Handbook on Tuberculosis, Module 5: Management of Tuberculosis in Children and Adolescents, 2022)

8.4 Treatment of TB disease in children

8.4.1 Treatment of drug-susceptible TB in children

Treatment of TB in children has become much easier for physicians and care providers with the availability of dispersible child-friendly fixed-dose formulations. Child-friendly formulations are ideal for use to ensure adequate therapeutic blood levels and compliance with the treatment regimen.

Children differ from adults in their response to treatment in that:

- Treatment outcomes in children are often good if treatment is started promptly and is of good quality.
- Children tolerate the anti-TB treatment better than adults with minimal side effects.

8.4.1.1 Recommended anti-TB Treatment Regimens for Children

- All children with a severe form of TB should receive a 6-month treatment course of TB treatment; four-drug regimens (RHZE) in the initial phase for 2 months followed by two (HR) drug regimens for the continuation phase for 4 months (2RHZE/4RH). Children with malnutrition (i.e. MUAC <11.5 cm or weight for height Z score -3 are to be treated with a 6-month regimen.
- Children (3 months- less than 16 years) with a non-severe form of TB should receive a 4-month TB treatment course: 2 months of (RHZE) followed by 2 months of RH drug regimen (2RHZ(E)/2RH) if they have no TB treatment history in the past two years.
- For severe forms of extrapulmonary TB such as TB meningitis and osteo-articular TB treatment duration is 9-12 months. See Table 26 for the summary of the TB treatment regimen for children and adolescents.
- The treatment duration and dosing for new episodes and re-registered TB treatment are the same.
- Treatment of TB in CALHIV is the same as for non-CALHIV.
- For DR-TB treatment, refer to the DR-TB treatment Chapter 7.

Table 34: DS-TB treatment algorithm in Children and Adolescents (0-19 years old)

<table>
<tr><td colspan="8">Assess the Site of TB Disease*</td></tr>
<tr><td colspan="4">2Pulmonary TB (PTB): Both new and re-registered</td><td colspan="4">Extra-pulmonary TB (EP-TB): Both new and re-registered</td></tr>
<tr><td colspan="8">What is the child's age?</td></tr>
<tr><td><3 mth</td><td colspan="3">3 mth-<16 yrs</td><td>16 yrs-19 yrs</td><td><3 mth</td><td colspan="3">3 mth -19 yrs</td></tr>
<tr><td rowspan="3">2HRZE/4HR</td><td colspan="3">Assess severity</td><td rowspan="3">2HRZE/4HR</td><td rowspan="3">2HRZE/4HR</td><td colspan="3">Assess severity</td></tr>
<tr><td colspan="2">Non-severe</td><td>Severe</td><td>Non-Severe (Isolated peripheral lymphadenopathy)</td><td colspan="3">Severe</td></tr>
<tr><td colspan="2">2HRZE/4HR</td><td>2HRZE/2HR</td><td>2HRZE/2HR</td><td>Bone & Joint TB (incl spine)</td><td>TB Meningitis</td><td>All other forms of EP-TB</td></tr>
<tr><td colspan="2">2HRZE/4HR</td><td>2HRZE/2HR</td><td>2HRZE/10HR</td><td>6HRZ+Eto or 2HRZE/ 10HR</td><td>2HRZE/ 4HR</td></tr>
</table>

**If a child has both PTB and EP-TB severe form, treat with the regimen for the EP-TB severe form. Adjuvant steroid therapy: administer steroids for TB Meningitis, also for pericardial, spinal (sometimes), airway obstruction and TB-IRIS.*

8.4.1.2 Assessing the severity of TB disease in children and adolescents (3 months-<16 years old)

- If CXR and microbiological test results are available, meeting all the following criteria is defined as a non-severe form of TB.
  - CXR findings are consistent with non-severe TB (CXR should ideally be done at baseline, but it can be performed at any point during the treatment course):
    - ✓ Intrathoracic lymph node TB without significant airway obstruction; or
    - ✓ PTB confined to one lobe with no cavities and no military pattern: or
    - ✓ Uncomplicated pleural effusion (without pneumothorax or empyema)
  - Negative TB, trace, very low or low using Xpert MTB/RIF Ultra, or sputum smear-negative
  - The child or adolescent has mild TB symptoms that do not require hospitalization.

- If only a microbiological test result is available and no CXR result, meeting all 3 criteria below is defined as a non-severe form of TB.
  - ✓ Negative TB, trace, very low or low using Xpert MTB/RIF Ultra, or sputum smear-negative
  - ✓ Mild TB symptoms that do not require hospitalization
  - ✓ Complete resolution of TB signs and symptoms within 1 month of treatment initiation, completely well and normal nutrition status at 4 months of treatment

- ✓ If both microbiological test and CXR results are not available, meeting one of the following two criteria is defined as a non-severe form of TB.
- Isolated extra-pulmonary (i.e. peripheral) lymph node without involvement of extra-pulmonary site
- Mild TB symptoms that do not require hospitalization OR
- The child has a clinical diagnosis of pulmonary TB AND the child has mild symptoms that do not require hospitalization

Mild TB symptoms that do not require hospitalization are:
- None of the danger or high-priority signs listed in Table 35
- No asymmetrical and persistent wheezing
- No signs of EPTB other than peripheral lymph node TB
- None of the following: SAM, respiratory distress, high fever (over 39°C), severe pallor, restlessness, irritability or lethargy

Children and adolescents who are starting on the 4-month regimen without chest radiography need to be followed up monthly:
- TB symptoms are expected to have been resolved within one month of treatment initiation
- The child or adolescent is expected to be completely well, including a normal nutritional status (like before they developed symptoms of TB) after 4 months of treatment
- Treatment should be continued for a total of 6 months in children and adolescents who have not responded clinically (demonstrating weight gain and/or resolution of TB symptoms) after 4 months of treatment. These people should be evaluated carefully for DR-TB, non-TB-related disease (e.g. malignancy or HIV-related lung disease) and poor treatment adherence

Table 35: Danger/High Priority Signs for children <10 years old

Age <5 yrs	Age <5-9 yrs	Age <10 yrs
Danger Signs (IMCI)	**Danger Signs (ETAT)**	**Priority Signs**
Gastrointestinal/circulatory: • Unable to eat or drink • Vomiting up everything • Signs of severe dehydration (sunken eyes, skin pinch returns very slowly) • Severe palmar pallor	Gastrointestinal/circulatory: • Diarrhea with any two signs of severe dehydration (lethargy, unconsciousness, sunken eyes, very slow return of skin after pinching) • Signs of shock (cold extremities with capillary refill time>3 seconds, weak and fast pulse)	Any sick child aged <2 months • High fever (>39° C) • Severe pallor • Respiratory distress • Restless, continuously irritable, lethargic • Severe acute malnutrition (SAM)
Respiratory: • Stridor • Oxygen saturation <90%	Respiratory: • Obstructed or absent Breathing • Severe respiratory distress • Central cyanosis	

Neurological: • Seizures • Profoundly lethargic, unconscious • Neck stiffness or bulging Fontanelle	Neurological: • Coma (or seriously reduced level of consciousness) • Seizures	

8.5 Recommended dosing of anti-TB drugs in children less than 25 kg

The following table describes the daily dosing of anti-TB drugs by age group and weight band in children and adolescents.

Table 36. Recommended treatment regimen and anti-TB drug dosages for paediatrics

Child friendly dispersible TB medicine for a baby <4 kg					
Number of Tablets					
WT Bands (Kg)	Intensive Phase			Continuation Phase	
	RHZ (75/50/150) Mg	E (100 mg)	How to prepare the medicine	RH (75/50 mg)	How to prepare the medicine
2 kg	¼	¼	Dissolve one (1) tablet of RHZ in 20 ml of safe drinking water. Once fully dissolved, add the completely crushed one (1) tablet of Ethambutol and give 5 ml (1/4) of this solution measured with a syringe.	¼	Dissolve one (1) tablet of RHZ in 20 ml of safe drinking water. Once fully dissolved, give 5 ml (1/4) of this solution measured with a syringe.
2.9 kg	½	½	Dissolve one (1) tablet of RHZ in 20 ml of safe drinking water. Once fully dissolved, add the completely crushed one (1) tablet of Ethambutol and give 5 ml (1/2) of this solution measured with a syringe.	¼	Dissolve one (1) tablet of RHZ in 20 ml of safe drinking water. Once fully dissolved, give 10 ml (1/2) of this solution measured with a syringe.
3-3.9 kg	¾	¾	Dissolve one (1) tablet of RHZ in 20 ml of safe drinking water. Once fully dissolved, add the completely crushed one (1) tablet of Ethambutol and give 15ml (3/4) of this solution measured with a syringe	¾	Dissolve one (1) tablet of RH in 20 ml of safe drinking water. Once fully dissolved, give 15ml (3/4) of this solution measured with a syringe.
Vit B6	Give 1-2 mg/kg/day of vitamin B6 (25 mg tablets)				
Ethambutol is not dissolvable: crush before adding to the liquid After giving the child their dose for that day, discard the rest of the solution. Prepare a fresh solution every day. If volumes are too high the tablet may also be dissolved in 10 ml maintaining the same fraction of medication delivered					

Table 37:Child-friendly dispersible medicine for Children 4 - 24.

Number of Tablets					
WT Bands (Kg)	Intensive Phase			Continuation Phase	
	RHZ (75/50/150) Mg	E (100 mg)	How to prepare the medicine	RH (75/50 mg)	How to prepare the medicine
4-7.9	1	1	Dissolve the tablet(s) of RHZ in 10-20 ml of safe drinking water. Once fully dissolved, mix in completely crushed tablet(s) of Ethambutol and give ALL of this solution to the child. Rinse the cup and give any residual liquid.	1	Dissolve the tablet(s) of RH in 10-20 ml of safe drinking water. Once fully dissolved give ALL of this solution to the child. Rinse the cup and give any residual liquid.
8-11.9	2	2		2	
12-15.9	3	3		3	
16-24.9	4	4		4	
>25 kg	Same as in the above dosing table for adults				
VIT B6	Give 1-2 mg/kg/day vitamin B6 (25 mg tablets)				
Ethambutol is not dissolvable: crush before adding it to the liquid					

8.6 Recommended TB meningitis regimen dosing for children

The new WHO guideline for childhood TB treatment (2022) recommended a 6-month regimen for TB meningitis (TBM) including Rifampicin, Isoniazid, Pyrazinamide and Ethionamide for children and adolescents (0-19 years old) as an alternative to 2HRZE/10HR regimen.

Due to limited data for children and adolescents living with HIV, the short intensive regimen is not recommended, and the standard 12-month regimen should be used in children and adolescents living with HIV with TBM.

Adjunctive corticosteroid therapy should be given to reduce the harmful effects of inflammation while anti-TB drugs kill the organism.

Note: For children less than 2 years old with miliary TB, TB meningitis should be evaluated regardless of the presence of Central Nervous Symptoms (CNS). If these children are not evaluated for TBM for any reason, an extension of treatment to 12 months may be considered.

The dosing for the 2HRZE/10HR regimen is the same as in the dosing table 28 though the duration for continuation is prolonged to 10 months. For the short 6-month TBM regimen (i.e. 6RHZ+Ethionamide), all drugs are to be given daily for the entire 6-month period. The table below is the dosing for the short TBM regimen.

Table 38: Recommended dosing for 6RHZ+Ethionamide regimen for TB meningitis in children and adolescents

Drug	Dosage (mg/kg)	
Isoniazid (H)	15-20	Higher end of dosing for younger children and lower end for older children.
Rifampicin (R)	22.5-30	
Pyrazinamide (Z)	35-45	
Ethionamide (Eto)	17.5-22.5	

The alternative regimen for TB meningitis in children is 2HRZE+Lfx/10RH with an increased dose of Rifampicin to 25-30 mg/kg as per the BMC trial. However, this regimen is not recommended yet by the WHO.

Recommended TBM regimen for children: 2RHZE+Lfx / 10RH (increase the dose of Rifampicin to 25 - 30 mg/kg).

8.7 Pyridoxine Supplementation

Isoniazid may cause symptomatic pyridoxine deficiency resulting in neuropathy, especially in severely malnourished children and children living with HIV on ART. Pyridoxine supplementation is given as standard therapy for all children at 2.5 mg/kg body weight, though certain situations may permit a higher dose of pyridoxine at 5-10mg/kg. These are.

8.8 Nutritional Support in Children

All children diagnosed with TB require nutritional counselling and support from children or caregivers. Apart from efforts to continue breastfeeding (until at least 24 months of age where possible) and ensuring adequate nutrient intake based on locally available and affordable foods, Nutrition assessment includes:

- Physical and clinical examination
- Dietary (24-hour recall for food type/frequency and household food security)
- Environmental and psychosocial
- Functional (ability to care for self, bedridden, etc.)

Nutritional Counselling & education should embrace:

- Benefits of maintaining good nutritional status for a child or adolescent affected by TB
- Benefits of having good nutrition for infants and children
- Identifying locally available foods accessed in their own context, food safety and food preparation
- Helping the client to plan meals and snacks with a variety of foods to meet their energy, high protein and nutrient needs and treatment plans
- Identifying any constraints, the child or adolescent may face and finding ways to minimize them
- Helping the child and or adolescent to understand the potential side effects and food interactions of the medicines they are taking, and help the client identify ways to manage these side effects
- Children with severe nutrition (MUAC <11.5 cm) should have nutritional therapy and a supplementary nutritional support package.

8.9 Adjuvant Steroid Therapy

Recommendations on the use of adjuvant steroid therapy are the same as for adults for the following conditions.

- TB meningitis (decreased consciousness, neurological defects, or spinal block).
- TB pericarditis (with effusion or constriction).

Steroids should be given after initiation of TB treatment with 1-2 mg/kg dose of dexamethasone or prednisolone tapered over 6-8 weeks. (See Table 16 for dosing steroids)

For the other conditions listed below, steroid use is beneficial, from expert opinions and experience in clinical practice.

- Massive TB pleural effusion (when large with severe symptoms).
- Hypoadrenalism (TB of adrenal glands).
- TB laryngitis (with life-threatening airway obstruction).
- Severe hypersensitivity reactions to anti-TB drugs.
- Renal tract TB (to prevent ureteric scarring).
- Massive lymph node enlargement with pressure

8.10 Treatment Monitoring

It is very important to make a treatment plan as soon as the child is initiated on treatment for each visit to the facility.

The treatment supporter should be informed of the child's treatment plan

- The child will visit the health facility at least once a month unless the child may have other needs that may require the visit to the facility earlier.

At each visit the child should be evaluated for:

- Adherence: emphasis should be made to the treatment supporter that treatment should be taken to completion even after the child feels and or looks well. Any factors that may influence adherence such as distance to the facility, lack or no social support or multiple caregivers should be addressed
- Drug toxicity
- Weight gain: weighing the child on every visit will enable the adjustment to the dosage as necessary
- New symptoms or resolution of previous symptoms and signs
- Follow-up sputum should be done at 2, 5 and 6 months to ascertain the sputum status
  In children who cannot expectorate, closely monitor clinically (weight gain, resolution of clinical signs and symptoms including extra-pulmonary signs and symptoms)

8.11 Poor Response to Treatment

Children respond well to TB treatment. They may show a response at 4-6 weeks of initiation to treatment. However, weight remains the most delicate indicator in terms of response to treatment marking the importance of weight monitoring.

Causes of poor response to treatment in children may include:

- Poor adherence
- Wrong diagnosis
- Concurrent undiagnosed co-morbidity such as diabetes, asthma and HIV
- Drug-resistant TB
- Malnutrition

Consider treatment failure or alternative diagnoses if despite good adherence the child:

- Remains sputum positive at the end of the 2nd month and on any other occasion if sputum was positive at baseline
- Has no weight gain or continues to lose weight
- Has worsening symptoms that cannot be attributed to immune reconstitution syndrome

8.12 Treatment of drug-resistant TB in children

Children with MDR-TB, especially in younger children, may not have bacteriological confirmation. In such cases, children diagnosed with MDR-TB clinically should be started on the same regimens as their contacts. The Bdq-Dlm-Lfx-Lzd-Cfz containing a regimen with a 6-month treatment duration can be used for the management of RR/MDR-TB including PreXDR TB in children. A 6-month BPaLM regimen can be used for RR/MDR-TB children 15 years old and above. If a child is not eligible for these two regimens, Bdq based 9-month regimen including a) Bdq-Mfx-Cfz-Z, b) Bdq-Lzd-Lfz-Cfz-Z, c) Bdq-Dlm-Lfx-should be considered for children with RR/MDR-TB for whom FQ-resistance has been excluded. For children with CNS TB and children who are not eligible for Bdd-Dlm-Lzd-Lfx-Cfz or BPaLM or 9-month Bdq-based regimens, individualized treatment regimen should be used (refer to the CNS TB section) and treatment duration should be at least 12 months. Whenever possible, child-friendly formulations or child-friendly dosing devices should be used for the administration of medication.

Monitoring responses to DR-TB treatment and adverse monitoring is the same as for adults. Since many children may be treated by clinical diagnosis, monitoring of clinical response (i.e. resolution of TB signs and symptoms, weight gain, CXR and other imaging in case of EP-TB) is important in children. Regular monitoring of growth and body weight at every visit is also important since children grow fast and the change of drug dose may be required depending on the weight gained. Though children are generally well tolerant to the treatment when the drugs are administered correctly according to the recommended dosage, some children experience adverse drug events. Therefore, the same adverse event monitoring procedures and management should be applied for children since late identification can leave the child with serious consequences (e.g. permanent disability due to optic neuritis/peripheral neuropathy, anaemic heart failure due to myelosuppression, etc.). Refer to the treatment monitoring of DSTB, DR-TB and aDSM chapter for the details of treatment monitoring procedures.

8.13 Management of a newborn from a mother with TB

- A baby born from a mother who has been on anti-TB treatment for at least 8 weeks before delivery is less likely to be infected as the woman is usually noninfectious at the time of delivery, but they should still be evaluated for TB symptoms.

- A newborn delivered within 8 weeks of the mother starting TB treatment, diagnosed with TB at delivery or soon thereafter is at a high risk of infection or disease with TB.
- The newborn should be immediately screened for TB.
- The presentation of TB symptoms may be nonspecific but signs of fever, feed intolerance, poor weight gain, and hepatosplenomegaly may be realized.
- Mothers diagnosed with TB should immediately after birth have the placenta and the baby carefully investigated for possible indication of congenital TB.
- Symptomatic neonates should be treated for TB and those who are without TB disease should be put on preventive treatment for 3 or 6 months and withhold BCG vaccination until two weeks after completion of TPT.
- If the BCG vaccine was given immediately before TPT was initiated, the BCG should be repeated following completion of treatment if there are no contraindications.

If the baby has been exposed to a mother with MDR-TB, consult an expert. The benefits of breastfeeding still outweigh the risks during this period. However, the mother should be carefully educated on infection prevention and control she can implement while at home to prevent TB transmission. These will include:

- Limiting contact with the neonate
- Covering her mouth and nose with a mask while breastfeeding and breastfeeding outside if possible
- Keep all windows wide open when indoors
- Spend a greater part of the day outdoors

8.14 TB preventive treatment in children

Children in contact with bacteriologically confirmed TB/DR-TB index cases should be put on TB preventive treatment after thorough contact investigation and exclusion of active TB disease. A shorter TPT regimen (3HR, 3HP, 1HP) should be used whenever the right formulation is available rather than 6-month Isoniazid preventive therapy. Refer to details of the TB preventive treatment chapter for TPT provision to eligible children including CLHIV.

Figure 23: TB screening algorithm for children less than 15 years old attending a health facility

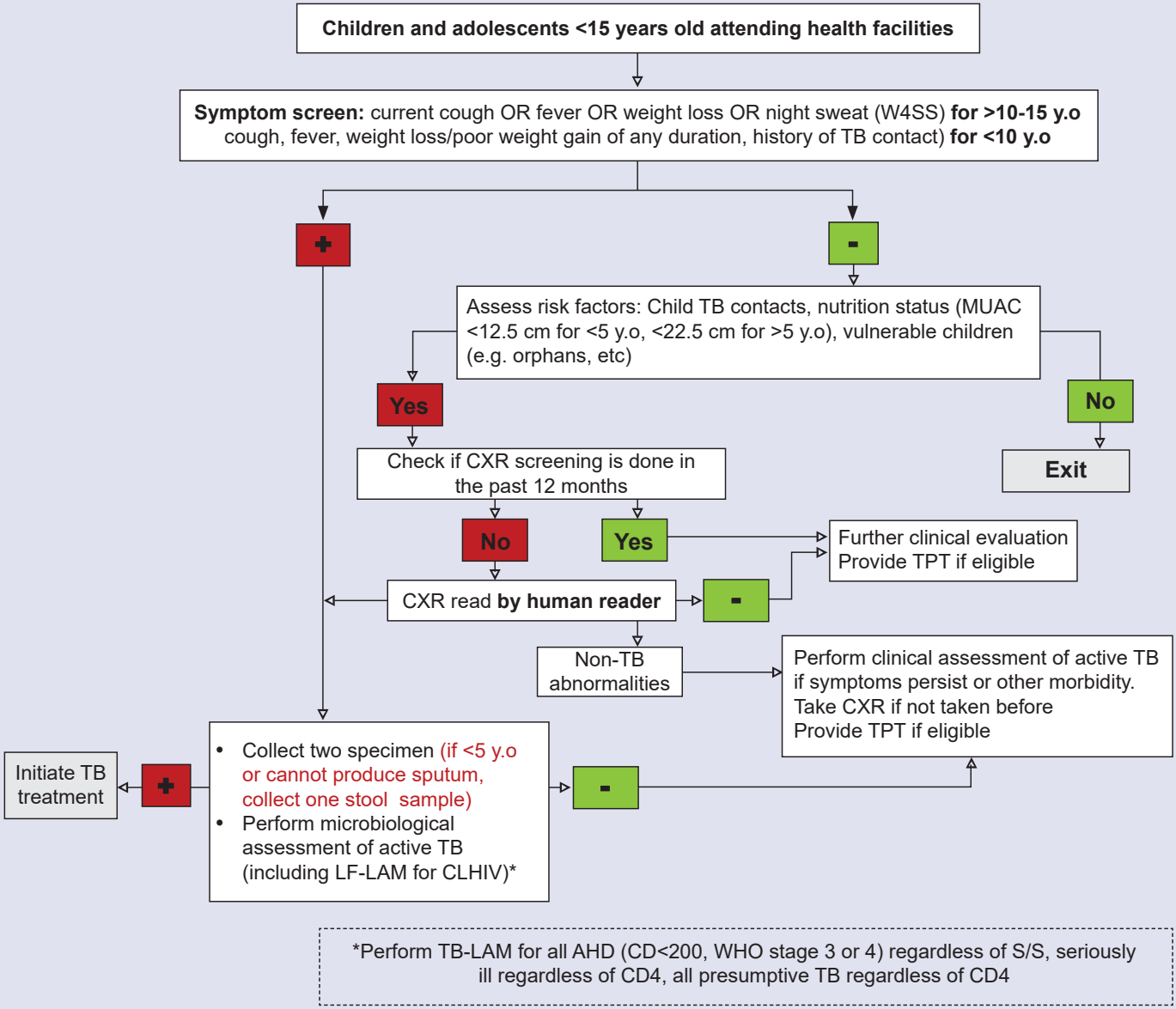
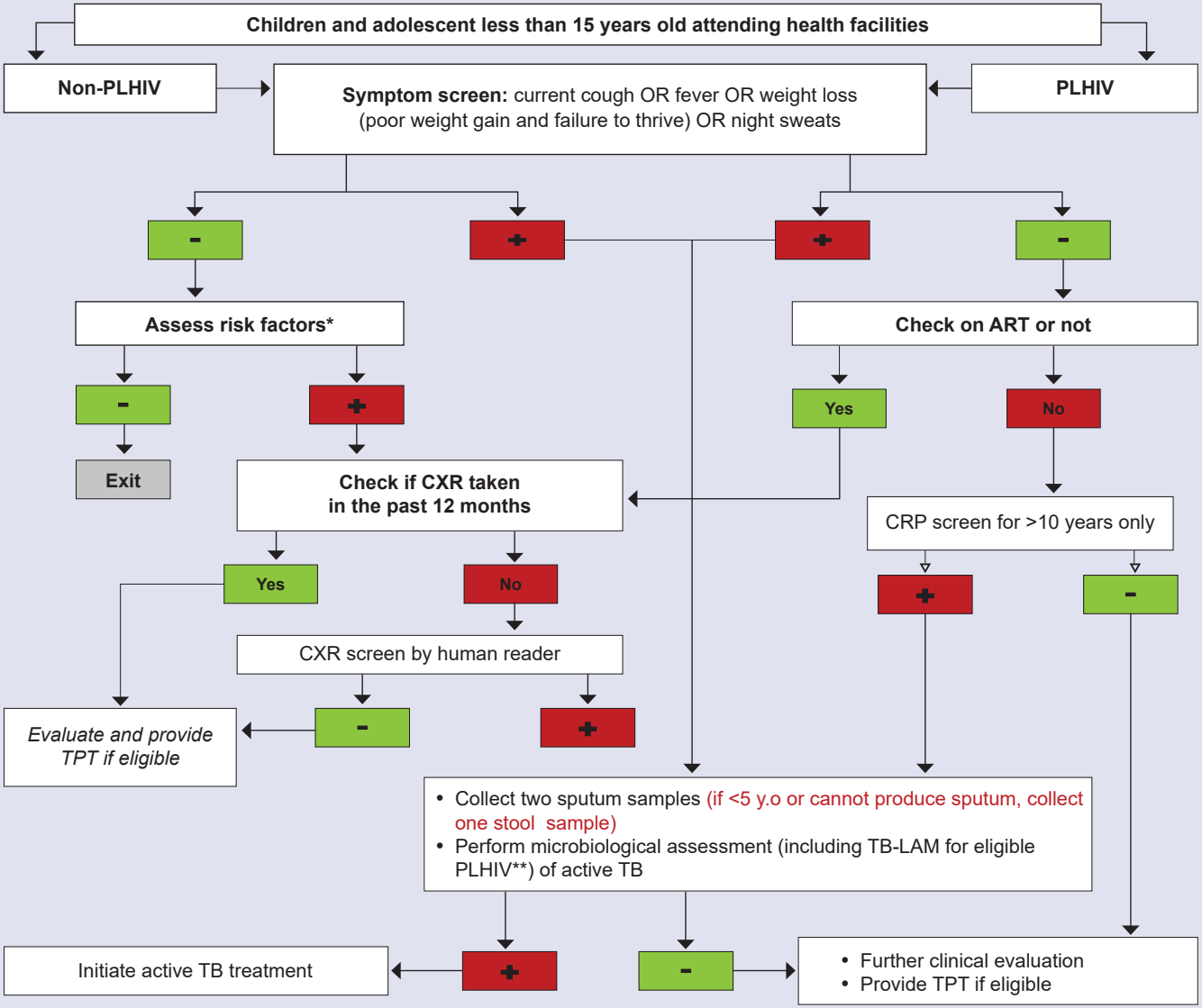


Figure 24: TB screening algorithm for PLHIV < 15 years old attending health facilities with access to Xray and CAD/AI and CRP



**Assess risk factors: Child TB contacts, nutrition status (MUAC <12.5 cm for <5 y.o, <22.5 cm for > y.o), vulnerable children (e.g. orphans, etc)*
***Perform TB-LAM for all AHD (CD4<200, WHO stage 3 or 4) regardless of S/S, seriously ill regardless of CD4, all presumptive TB regardless of CD4*

CHAPTER 9
PHARMACOVIGILANCE AND ADVERSE EVENT MANAGEMENT

9.1 Introduction

Pharmacovigilance is science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. It is a fundamental public health surveillance activity to inform the management of patient safety measures in healthcare. It is a facet of program monitoring, not too different from the way many countries operate routine surveillance of TB drug resistance based on diagnostic testing. The Kingdom of Eswatini has both active and passive pharmacovigilance. The former is used for the new MDR/XDR medicines while passive is used for the DS-TB medicines.

9.2 Definitions Used in PV

(a) **Adverse Drug Reaction (ADR):** is a response to a medicine which is noxious and is unintended and occurs at doses normally used in humans.

(b) **Adverse Event (AE):** any untoward medical occurrence that may present in a patient during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment.

(c) **Serious Adverse Event (SAE):** is an AE that leads to:
- Death or
- A life-threatening experience.
- Hospitalization or prolongation of hospitalization.
- Persistent or significant disability or
- A congenital anomaly.
- SAEs that do not immediately result in one of these outcomes but may require an intervention to prevent it from happening are included.
- SAEs may require drastic intervention, such as termination of the medicine suspected of having caused the event.

(d) **Adverse Event of Special Interest (AESI)*:** is an AE documented to have occurred during clinical trials and for which the monitoring program is specifically sensitized to report regardless of its seriousness, severity or causal relationship to the treatment. The centres that offer the intermediate and advanced packages of aDSM will include all AEs of special interest in their reporting.

(e) **Adverse event of clinical significance*:** is an AE which is either (i) serious, (ii) of special interest, (iii) leads to discontinuation or change in the treatment, or (iv) judged as otherwise clinically significant by the clinician. The centres that offer the intermediate package of aDSM will include all AEs of clinical significance in their reporting.

(f) **Adverse event leading to treatment discontinuation or change in drug dosage*:** is that which leads a clinician to stop, interrupt temporarily or change the dosage of one or more drugs, regardless of its seriousness, severity, or causal relationship to the TB treatment.

(g) **Causal relationship:** is a relationship between an exposure (A) and an event (B) in which A precedes and causes B. This may refer to the causal association between exposure to TB medicine and the occurrence of an adverse reaction.

(h) **Causality assessment:** the evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction.

(i) **Drug-safety profile*:** is a description of the benefits, risks and toxicity of a given medicine or regimen, specifying any known or likely safety concerns, contraindications, cautions, preventive measures and other features which the user should be aware of to protect the health of a patient.

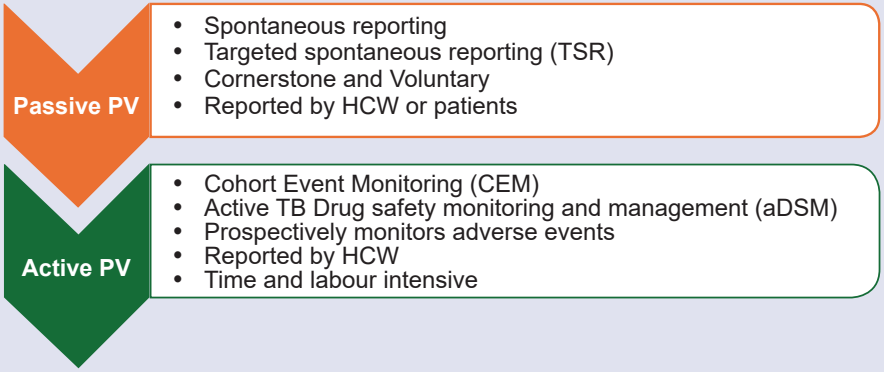
(j) **Signal:** is reported information on a possible causal relationship between an adverse event and TB medicine. The relationship may be unknown or incompletely documented previously or represent a new aspect of a known association. The information may arise from one or multiple sources that are judged to be of sufficient likelihood to justify verification.

(k) **Rechallenge:** the voluntary or inadvertent re-administration of a medicine suspected of causing an adverse drug reaction.

(l) **Dechallenge:** the withdrawal of a drug from a patient; the point at which the continuation, reduction or disappearance of adverse reaction may be observed.

9.3 Types of Pharmacovigilance

Figure 25: Type of Pharmacovigilance

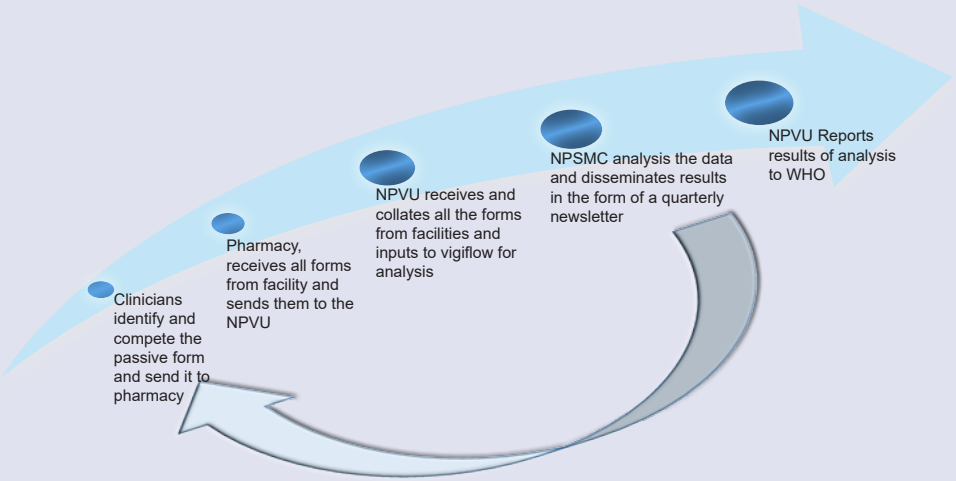


Process for recording and reporting ADRs due to TB medication:

In Eswatini clinicians are required to manage and report any adverse drug reaction that patients may experience because of the medication they are taking. There are two mechanisms of pharmacovigilance reporting in the country, i.e. passive and active surveillance. For any adverse drug reaction patients may experience that may be due to medicines for the treatment of DR-TB medicines and associated LTBI treatment, clinicians are required to use the active pharmacovigilance system to report the ADR). For any adverse drug reaction patients may experience that may be due to susceptible TB medicines and associated LTBI treatment, clinicians are required to use the passive pharmacovigilance system to report the ADR. **ALL** serious events must be reported within 24-48 hours including:

- Those requiring or prolonging hospital stay
- Those believed to have contributed to permanent disability, death, risk of death, congenital anomaly etc.

Figure 26: Pharmacovigilance reporting requires the clinician to follow the following process



9.4 Monitoring of TB Patients for Adverse Effects of Anti-TB Drugs

9.4.1 Drug-susceptible TB

Most TB patients complete their treatment without any significant adverse effects of drugs. However, a few patients do experience adverse effects. It is therefore important that patients be clinically monitored during treatment so that adverse events can be identified promptly and managed properly. Routine laboratory monitoring is not necessary.

Healthcare providers can monitor adverse events of drugs by educating patients about how to recognize common symptoms and adverse effects and to report if they develop such symptoms. Providers should also actively ask patients about common symptoms of adverse events at every clinical encounter.
Prevention of adverse effects of drugs

Healthcare providers can prevent some drug-related adverse events by providing prophylaxis, such as Pyridoxine supplements for Isoniazid (INH)-induced peripheral neuropathy (PN). IND-induced PN occurs more commonly in pregnant women and people with the following conditions: HIV infection, alcohol abuse, malnutrition, diabetes, and chronic liver disease. These patients should receive preventive treatment with pyridoxine, 10 mg daily, along with their anti-tuberculosis drugs.

Symptom-based management of adverse effects of anti-tuberculosis drugs

Adverse effects associated with anti-TB are classified as minor or major. In general, a patient who develops minor adverse effects should continue the TB treatment, sometimes at a reduced dose. The patient also receives

symptomatic treatment. If a patient develops a major side-effect, the treatment or the offending drug should be stopped. Further management depends on the nature of the adverse reaction. Patients with major adverse reactions should be managed in a hospital setting. Table 39 below provides a symptom-based approach to the management of adverse effects.

Table 39: Guide to management of side effects of first line

Side effects	Drugs (probably responsible)	Management
Major		
Generalized severe skin rash with or without itching	Isoniazid, Rifampicin, Pyrazinamide and Ethambutol	Stop anti-TB drugs and refer. Re-challenge once stable, starting with the least likely causative agent. Give antihistamines to manage pruritis
Deafness (no wax on otoscopy)	Injectable *	Stop Injectable and refer
Dizziness (vertigo and nystagmus)	Injectable *	Stop Injectable and refer
Jaundice (other causes excluded), hepatitis	Pyrazinamide, INH, Rifampicin	Stop anti-TB drugs and refer Re-challenge once stable starting with the least hepatotoxic agent
Confusion (suspect drug-induced acute liver failure if there is jaundice)	Most anti-TB drugs	Stop anti-TB drugs and refer
Visual impairment (other causes excluded)	Ethambutol	Stop Ethambutol and refer
Shock, purpura, acute renal failure	Rifampicin	Stop Rifampicin and refer
Decreased urine output (acute renal failure)	Injectable *	Stop Injectable and refer Adjust the doses of other renally-excreted drugs e.g. Ethambutol
Minor		
Anorexia, nausea, abdominal pain	Pyrazinamide, Rifampicin, INH	Give drugs with small meals or just before bedtime and advise the patient to swallow pills slowly with small sips of water. If the symptoms persist or worsen, or there is protracted vomiting or any sign of bleeding, consider the side-effect to be major and refer to the Clinician urgently.
Joint pains	Pyrazinamide	Aspirin or other non-steroidal anti-inflammatory drugs or Paracetamol.

Side effects	Drugs (probably responsible)	Management
Major		
Burning, numbness or tingling sensation in the hands or feet	INH	Give Pyridoxine 50-75mg daily Can go up to 100mg. Refer if no improvement or grade 3 or 4 neuropathy.
Drowsiness	INH	Reassure the patient. Give drugs before bedtime.
Orange/red urine	Rifampicin	Reassure patient. Patients should be informed about the urine change when initiating TB treatment.
Flu-like syndrome (fever, chills, malaise, headache, bone pain)	Intermittent dosing of Rifampicin	Reassure patient. When staring TB treatment, patients should be informed about the possibility of such occurring and that it is normal.

Source: Treatment of tuberculosis guidelines. 5thEdition. WHO/HTM/TB/2017

Table 40: When to stop anti-TB drugs

Reaction	Drug Responsible
Hearing loss or disturbed balance	Injectable
Visual disturbance (poor vision and colour perception)	Ethambutol
Renal failure	Injectable
Shock, or thrombocytopenia	Rifampicin
Hepatitis	Pyrazinamide

Management of skin itching and rash

In case of skin itching, it is necessary to determine if the reaction was present before initiation of anti-TB treatment, as many HIV-positive patients have itchy skin lesions because of HIV infection.

Other causes of itching should also be excluded, give antihistamines, continue anti-TB treatment, and observed closely. If a rash develops, anti-TB drugs should be stopped until the rash resolves. In case of a severe reaction, supportive treatment should be provided as appropriate.

Reintroduction of anti-TB drugs following drug reaction

A drug challenge should be done to identify the drug responsible for the reaction. The process should start with the anti-TB drug, which is least likely to be responsible for the reaction. The initial challenge should start with a small dose of the drug. If a reaction occurs to a small challenge dose, it will not be such a severe reaction as to a full dose. Gradually increase the dose over 3 days. Repeat the procedure, adding one drug at a time. A reaction after a particular drug is added identifies that drug as the one responsible for the reaction.

If the drug responsible for the reaction is pyrazinamide, ethambutol, or streptomycin, resume anti-TB treatment without the offending drug. If possible, replace it with another drug. It may be necessary to extend the treatment regimen. Consider the start of the resumed regimen as a new start of treatment. This prolongs the total time of TB treatment but decreases the risk of recurrence.

Table 41: Guide to performing anti-TB drug challenge and re-introduction

Drug	Likelihood of causing a reaction	Challenge doses		
		Day 1	Day 2	Day 3
Isoniazid	Least likely	50 mg	300 mg	300 mg
Rifampicin	↓	75 mg	300 mg	Full dose
Pyrazinamide	↓	250 mg	1 gr	Full dose
Ethambutol	↓	100 mg	500 mg	Full dose
Streptomycin	Most likely	125 mg	500 mg	Full dose

9.4.2 Drug-Resistant TB

Active TB drug-safety monitoring and management (aDSM)*: is the active and systematic clinical and laboratory assessment of patients on DR-TB treatment to detect, grade, manage, and report suspected or confirmed drug toxicities. Close monitoring of patients is necessary to ensure that the adverse effects of second-line drugs are recognized quickly by healthcare personnel. The ability to monitor patients for adverse effects daily is one of the major advantages of DOT over self-administration of DR-TB treatment. Most adverse effects are easy to recognize. If well-informed, patients will indicate when they are experiencing adverse events. However, it is important to have:

- A systematic method of patient interviewing since some patients may be unforthcoming about reporting even severe adverse events. (This is important because some patients may be distracted by one adverse effect and forget to tell the healthcare provider about others).

All DOT workers, hospitals, clinics or community health workers should be trained to screen patients regularly for symptoms and signs of common adverse events; manage adverse events and when to refer cases to a higher level. See Table 42 for common adverse events to commonly used second line medicines and Figure 28 - Figure 32 for suggested management of adverse events.

9.4.2.1 Objectives of aDSM

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

To achieve these objectives, the aDSM includes three essential activities:

- **Clinical monitoring:** Active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs.

- **Management of all AEs** detected promptly to deliver the best possible patient care.
- **Standardized data** should be **systematically collected and reported** for any SAE and AEs of special interest. This will eventually be used to characterize the types of AEs, assess the safety of treatment and inform future policy on the use of these medicines.

9.4.2.2 What and When to Monitor in aDSM?

All patients on 2nd line drugs should be regularly monitored for any adverse events through history, physical examinations and investigations as detailed in Table 23 in the monitoring section (8.5). The presence or absence of an AE should be documented in the chronic care file, including deranged laboratory and other investigations (e.g. ECG, audiometry, visual acuity). The AE should then be graded and patient management decided upon in line with the severity grading.

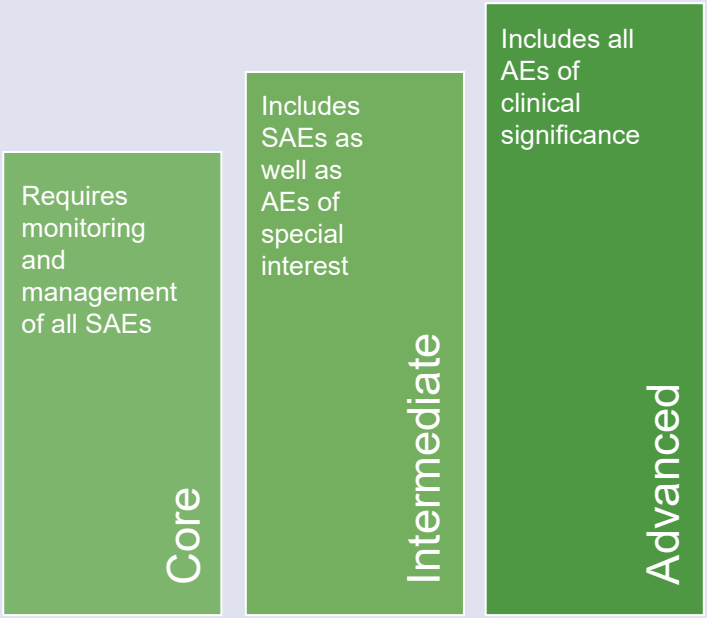
9.4.2.3 What and when to report in aDSM?

The NTCP recommends an intermediate package (see Figure 17) for all DR-TB patients. This package targets the systematic screening, recording, and reporting of SAEs and adverse effects of special interest (AESIs) listed below.

Adverse Events of special interest (WHO aDSM guide + DTG)

- Peripheral neuropathy (paraesthesia)
- Psychiatric disorders: anxiety, mood swings, psychosis, depression, suicidal ideation
- Central nervous system toxicity: headache, dizziness, insomnia, drowsiness, abnormal dreams or nightmares
- Optic nerve disorder (optic neuritis) or retinopathy
- Ototoxicity
- Myelosuppression
- Prolonged QT interval
- Lactic acidosis
- Hepatitis
- Hypothyroidism
- Hypokalaemia
- Pancreatitis
- Rash
- Fatigue
- Flatulence

Figure 27: The three packages/levels of monitoring in aDSM



All deaths are to be reported and as much relevant information on ascertainment of the cause of death should be consistently collected. Reporting of AEs and other events (e.g. pregnancy, lactation exposure) may be required, primarily based on what is known about the safety profile of the new agent and for other possible harm which has not yet been described.

All SAEs and Severe (Grade 3 or 4) AESIs detected should be reported to the NPVU within the medicine's regulatory unit of the MOH within 24-48 hours.

9.5 Management of Adverse Events

DR-TB can be deadly, but the drugs used to treat the disease can be harmful in many ways. All efforts should be made to promote patient safety and contribute to improving the quality of care during the treatment of drug-resistant TB, relieving unnecessary suffering.

The timely and intensive monitoring for, and management of, adverse effects caused by second-line drugs are essential components of DR-TB control programmes. Poor management of adverse effects increases the risk of treatment interruption or irregular adherence to treatment and may result in death or permanent morbidity. The ability to monitor patients for adverse effects daily is one of the major advantages of having a treatment supporter over self-administration of drug-resistant TB treatment.

Treatment of drug-resistant tuberculosis (DR TB) involves the use of multiple medications, and most patients will experience some difficulty tolerating them. As the response of an individual patient cannot be predicted, medications should not be withheld because of fear of a reaction. Patients should be well-informed and engaged as partners in their treatment.

Proper management of adverse effects begins with patient education. Before treatment initiation, the patient should be provided with details about the potential adverse effects that he/she may experience as a result of the prescribed drug regimen, and when to notify a health-care provider.

If the adverse effect is mild and not life-threatening, continuing the treatment regimen, with the help of ancillary drugs if needed, is often the best option. In patients with highly resistant TB, a satisfactory replacement drug may not be available, so suspending a drug will make the treatment regimen less potent. Some adverse effects may disappear or diminish with time, and patients may be able to continue receiving the drug if sufficiently motivated. The adverse effects of several second-line drugs are highly dose-dependent.

Prompt evaluation, diagnosis and treatment of adverse effects are extremely important, even if the adverse effect is not particularly dangerous, as this may influence adherence. Patients may have significant fear and anxiety about an adverse effect if they do not understand why it is happening. These emotions in turn may augment the severity of the adverse effect, as in the case of nausea and vomiting. Long periods without medical evaluation also promote feelings of isolation and abandonment by the healthcare system.

The following approach is recommended:

- **Before initiating a treatment regimen, it is essential to discuss the benefits and risks of therapy and obtain informed consent.**
  - ✓ The patient should understand the need for treatment, the importance of each medication in the treatment regimen, and the possible side effects and toxicities.
- **Psychosocial support** is an important component of the management of adverse effects. This is one of the most important roles played by DOT workers, who educate patients about their adverse effects and encourage them to continue treatment. Patient support groups are another means of providing psychosocial support to patients.
- **Assure patients that every possible attempt to make their treatment as easy as possible will be made but emphasize that having enough effective drugs in the treatment is essential to achieving a cure.**
  - ✓ While side effects will be addressed and treated as aggressively as possible, patients should be mentally prepared for the likely discomfort that they may experience and should brace themselves for the long road ahead.
- **Ensure measures to avoid breaks in treatment to maximize the effectiveness of treatment.**
  - ✓ Reported side effects of each patient should be given due attention. Most patients will be willing to continue medication despite symptoms when they understand the benefit of the medication, know that many of these symptoms improve after the first several weeks, and are assured that the HCWs are doing their best to evaluate and address their problems.

- ✓ Express appreciation for the patient's efforts to cooperate. This recognition often helps a patient to continue therapy.

- **Permanent** dose reduction or definitive elimination of a drug from the regimen is a serious step and should be considered only after all other possibilities have been exhausted, and should be used as a last resort, i.e., in cases of significant organ dysfunction or intractable symptom intolerance.
  - ✓ Ideally, any drug eliminated should be replaced with an equally effective drug so as not to compromise the overall effectiveness of the regimen.

It is often difficult to ascertain whether a side effect is due to a single medication, or the result of several drugs given simultaneously. If after following the various recommended treatment schemes, the patient remains intolerably symptomatic, a dose reduction or elimination of one of the drugs may be necessary.

- The dose of the most likely offending drug can be reduced for one week, to see whether the symptoms diminish or disappear; if symptoms persist, the drug is returned to its original dose and the same process is repeated for the other drugs in the regimen, until all potentially responsible drugs have been tested. This should be done systematically. For Cs and Eto, for example, a patient may be completely intolerant at one dose and completely tolerant at a slightly lower dose. Unfortunately, given the narrow therapeutic margins of these drugs, lowering the dose may also affect efficacy, so every effort should be made to maintain an adequate dose of the drug according to body weight. Lowering the dose by more than one weight class should be avoided.
- Systematic dose reduction of multiple drugs simultaneously would be the next option.

Pyridoxine (vitamin B6) should be given to all patients receiving Cs or Trd to help prevent neurological adverse effects. The recommended dose is 50 mg for every 250 mg of Cs (or Trd) prescribed.

Table 42: Common Adverse events to Second- Line Anti TB Drugs

Drug	Moderate to severe adverse events	Mild adverse events
Pretomanid	• Peripheral neuropathy • Acne • Anaemia • Nausea and vomiting • Hepatotoxicity (increase in ALT/AST) • Musculoskeletal pain	• Abnormal weight loss • Diarrhea (10%) • ECG QT prolonged (6%) • Insomnia (6%)
Bedaquiline	• Cardiotoxicity (QTcF prolongation): mean increase (10 ms at 8-12 weeks, then decreases*) • Hepatotoxicity (increase in ALT/AST)	• Nausea, anorexia, arthralgia, headache, increased blood lipase/ amylase, rash
Delamanid	• Cardiotoxicity (QTcF prolongation): 6-10 weeks after initiation, stable afterwards	• Nausea, vomiting, dizziness, anxiety, paresthesia, itchiness, tremor
Linezolid	• Anemia • Thrombocytopenia • Optic neuropathy • Peripheral neuropathy	• Avoid linezolid in combination with other serotonergic agents
Isoniazid	• Skin rash with mild itchiness, no mucous membrane involvement or blisters • Jaundice (yellow eyes or skin) • Hepatotoxicity (increase in ALT/AST) • Clumsiness or unsteadiness. • Nausea or vomiting. • Numbness, tingling, burning, or pain in hands and feet.	• Peripheral neuropathy • Skin rash with mild itchiness, no mucous membrane involvement or blisters
Clofazimine	• QTcF prolongation • Skin hyperpigmentation or discoloration (slowly reversible)	

9.6 Management of specific conditions

9.6.1 Management of Nausea and Vomiting

This may be due to the bulk of drugs and/or due to Eto, PAS, Z and E. While most patients experience nausea and/or vomiting as an adverse effect during DR TB therapy, these symptoms rarely prevent delivery of adequate therapy. The patient should take another dose if he/she vomits and the medication is visible in the vomitus. Volume and electrolyte management is also essential if vomiting is significant. Patients who complain of nausea or vomiting can be advised to take the drugs embedded in a banana/porridge, bread, etc. If vomiting persists, drugs will be administered one hour after one tablet of Domperidone and/or a course of proton pump inhibitor (Omeprazole)

or H2 receptor inhibitor (Cimetidine, Ranitidine). Other antacids are not usually given since they interfere with the absorption of fluoroquinolones. In case of severe vomiting, the hydration status of the patient should be monitored and rehydration therapy initiated if required. If the offending drug is Eto, the drug is more tolerable if it is administered with milk, after meals, or at bedtime to avoid nausea. If vomiting is severe, drugs can be withheld temporarily, and tests should be conducted to rule out other causes of vomiting like hepatitis.

The following approach is recommended in case of nausea and vomiting:

(a) Ask the patient's opinion about which drug may be responsible.
    (i) Patients may have strong ideas about which medication is causing them problems. Their opinions should be respected (even if no change can be made).
(b) Encourage the patient to continue to take the medication and assure them that for most patients many adverse reactions lessen over the first several weeks and may become tolerable or resolve entirely.
    (i) If signs of dehydration (thirst, dry mouth, sunken eyes, low blood pressure, orthostasis, weakness), aggressively rehydrate: Administer 1-2 litres of NaCl 0.9% over the first 6 hours. Consider hospitalization
    (ii) If jaundice, pruritis and right-sided abdominal pain, rule out Hepatitis
    (iii) If vomiting blood or emesis with the appearance of coffee grounds, consider possible gastrointestinal haemorrhage.
(c) If the drug suspected of causing the symptoms is Eto, PAS or Cfz, decrease the dose to see if the lower dose is better tolerated.
    (i) Advise the patient that this is a test to determine which drug is causing side effects and that the drug dose will be increased back to the therapeutic dose in a manner that will be better tolerated.
    (ii) The dose of medication can then gradually increase over the next 2 weeks. Both medications can be given in 2 or 3 doses over the day, which may improve tolerance. Many patients tolerate the higher dose of Eto better in the evening (Eto 250 mg in a.m., 500 mg at bedtime; or may only tolerate 500 mg at bedtime). The goal should be to increase the Eto dose to at least 500 mg daily and the PAS dose to at least 6 to 8 grams daily
(d) Treat gastritis or acid reflux. Proton pump inhibitors or H2-receptor blockers may be helpful in many patients.
(e) Minimize the use of non-steroidal anti-inflammatory drugs (NSAIDs).
    (i) This may be difficult if the patient also has arthralgia and myalgia from medications. Acetaminophen may be helpful but with caution given its potential risk of increasing isoniazid (INH) hepatotoxicity.
(f) Encourage hydration.
(g) Evaluate and monitor electrolytes, Urea and creatinine, and correct any imbalance.
(h) Refractory nausea and vomiting may suggest the need for further investigation, including addressing the possibility of liver involvement e.g. hepatitis.
(i) If the patient can be treated ambulatory, administer anti-emetics or antacids before medication or as needed. **Note:** Antacids cannot be given within 2 hours of fluoroquinolones.

The following are some specific options (adult dose):

- **1st option:** Metoclopramide 10 to 20 mg PO, IM or IV every 4 to 6 hours as needed, given 30 minutes before morning and/or afternoon dose of anti-TB drugs

- **2nd option:** Promethazine 12.5 to 25 mg PO, IV, or PRN 30 minutes before the dose and every 6 hours as needed
- **3rd option:** Ondansetron 8 mg PO 30 minutes before the dose and again 8 hours after the dose; for refractory nausea 24 mg 30 minutes before the dose can be tried

The medications should be spaced out during the day to lessen the pill burden or administer the drug in three doses.

Pregnancy should be considered as the possible aetiology of nausea and vomiting, especially if the symptoms occur after a period of initial tolerance.

9.6.2 Management of Diarrhoea

Diarrhoea is characterized by frequent watery bowel movements. Since many patients use the term diarrhoea to describe bowel movements that are more frequent or loose than normal, it is important to ascertain whether the stool is truly watery with frequency of more than three or four times a day.

PAS often causes diarrhoea with the initiation of medication. Inform patients that diarrhoea usually resolves or improves considerably after several weeks.

Fluoroquinolones can also cause loose stools or diarrhoea, along with increased flatulence. This can improve, but may persist in part for the duration of therapy

In the case of **mild to moderate** diarrhoea:

- Oral Rehydration Solution (ORS) should be administered as a first measure of tolerance; or
- Give Loperamide 4 mg stat dose orally, then followed by 2mg after each loose stool to a maximum of 10mg in 24 hours.
- The patient's fluid intake and hydration status should be evaluated.

In cases with **severe** diarrhoea:

- If accompanied by bloody stools, severe abdominal pain, or fever greater than 38.5°C, consider other causes such as acute bacterial enteritis, or pseudo-membranous colitis related to fluoroquinolones and treat according to the diagnosis.
- The electrolyte status should be checked
- Administer ORS or IV fluids to maintain the right hydration status.

9.6.3 Management of Gastritis

Gastritis covers a broad spectrum of entities that induce inflammatory changes in the gastric mucosa. Anti-TB drugs may potentially cause such inflammations which may result in symptoms like gnawing, burning epigastric pain or distress, occasionally accompanied by nausea and/or vomiting. The pain may improve or worsen with eating.

In the case of patients presenting with symptoms of gastritis, the following should be observed:

- Administer anti-tuberculosis medications with a small amount of food or after eating
- Evaluate possible gastrointestinal haemorrhage (blood or “coffee ground” emesis, black, tarry stools)
- Advise patient to avoid caffeine (coffee, tea, soda), cigarettes
- If symptoms occur in the morning, advise patients to eat before going to bed and sleep with their heads elevated.
- Administer gastric-acid suppressants such as omeprazole 20mg, once a day, before breakfast; If no improvement, administer antacids: - Calcium carbonate for patients who need a calcium supplement (elderly, pregnant women, etc.), aluminium hydroxide helpful in cases with diarrhoea, magnesium hydroxide may improve constipation.
- Advise patients to take fluoroquinolones at least 3 hours apart from antacids to minimize reduced fluoroquinolone absorption
- If no improvement and the patient is receiving Ethionamide and/or clofazimine, consider a dose reduction.
- IF REFRACTORY AND SEVERE SYMPTOMS, consider treatment for Helicobacter pylori.

9.6.4 Management of Hepatitis

Any signs or symptoms of hepatitis (including nausea, severe vomiting, scleral icterus, jaundice, dark urine, pale stool) merit immediate evaluation of serum liver tests.

The ALT (SGPT) is more specific for hepatocellular injury than the AST (SGOT). Elevations in the AST may indicate abnormalities in the muscle, heart, or kidney. If the ALT is elevated more than the AST, this is consistent with liver inflammation. When the AST is elevated more than the ALT, the possibility of alcohol-related elevation of the transaminase should be considered.

1. If the hepatocellular enzymes are < 3 times the upper limit of normal and there is no evidence of jaundice, continue the medications using strategies for managing nausea and vomiting and observe carefully.
2. If the hepatocellular enzymes are >3 and < 5 times the upper limit of normal with evidence of jaundice, stop the medications and observe carefully
   (a) If symptoms continue, consider repeating liver enzymes again to exclude hepatotoxicity.
   (b) If the bilirubin is increased but the hepatocellular enzymes are only mildly elevated, this could still represent significant drug-induced liver injury.
   (c) An evaluation of causes of direct and indirect hyperbilirubinemia should be done, and hepatotoxic medications should be stopped.
3. If the enzymes are more than 5 times the upper limit of normal, hold all potentially hepatotoxic medications. If at least 3 medications remain in the treatment regimen that are not hepatotoxic, then these can be continued. If not, then all anti-tuberculosis medications should be held.
   (a) Monitor the LFTs weekly.
4. If liver enzymes plateau or revert to normal and symptoms resolve, anti-TB drugs may be restarted sequentially beginning with the agents least likely to be hepatotoxic: Amikacin, Ethionamide, Fluoroquinolone and Cycloserine/ Terizidone.

(a) Carefully observe clinical reactions and repeat liver enzymes twice weekly until the medication has been taken for at least a week and enzymes are stable. The next medication can then be added to the regimen and monitored.
(b) All remaining medications should be reintroduced in this manner.

5. If the reintroduction of medication leads to clinical symptoms of hepatotoxicity and enzymes increase, stop that medication and eliminate it from the regimen.
6. Even if a medication is identified as causing hepatotoxicity, reintroduce each additional medication one at a time, because in some instances, more than 1 medication may be responsible for the hepatotoxicity.
7. Monitor liver enzymes at least monthly for the remainder of the treatment course.

Rule out other aetiologies, viral hepatitis, alcohol, and non-anti-tuberculosis drugs (e.g., antiepileptic, acetaminophen, sulpha drugs, griseofulvin, ketoconazole, fluconazole etc.)

9.6.5 Management of Peripheral Neuropathy

Peripheral neuropathy is characterized by symmetrical polyneuropathy in nearly all cases. The first symptoms are tingling, prickling, and burning in the balls of the feet or tips of the toes. With further progression, sensory loss can occur. Ankle reflexes may be lost and weakness of dorsiflexion of the toes may be present. Symptoms may progress centripetally and involve the fingers and hands. Unsteadiness of gait may develop due to proprioceptive loss.

The diagnosis can usually be made clinically. The drugs most implicated are INH, ethionamide, cycloserine/terizidone, and linezolid. Fluoroquinolones and ethambutol have rarely been associated with the development of neuropathy.

Prescribe 50mg of pyridoxine for every 250mg of cycloserine/terizidone used for all patients (including a proportionate weight dose for children) receiving treatment for MDR-TB which includes INH, ethionamide, cycloserine/terizidone, or linezolid.

If symptoms develop or progress, doses can be increased to 200mg. Caution should be exercised with individuals with end-stage renal disease, as pyridoxine may develop toxic levels in these cases and cause neurologic symptoms.

Additional interventions include:

- Correct nutritional deficiencies.
- Address additional medical problems (diabetes, alcoholism, vitamin deficiencies, HIV, hypothyroidism, uraemia, other drugs, etc.)
- Evaluate and correct electrolytes.
- Identify and change other medications that may cause peripheral neuropathy, if possible.
- Physical therapy may be helpful but is often not available.
- NSAIDs or acetaminophen may be helpful.
- A low dose of tricyclic antidepressant, amitriptyline 25mg PO at bedtime can be tried if there are no contraindications. The dose of amitriptyline may be increased (25mg each week to 150mg maximum) if lower doses are not helpful.

(Linezolid cannot be given with tricyclic drugs or selective serotonin reuptake inhibitors [SSRIs] due to its mild monoamine oxidase (MAO) activity contributing to the risk of serotonin syndrome.)

- Carbamazepine orally at 100 to 600mg twice daily can be given.
- As Blood dyscrasias and elevated liver function may complicate therapy, a complete blood count (FBC) and liver function should be routinely monitored in patients on this medication.
- Patients who fail to respond to a tricyclic may respond to gabapentin. Adults should be treated initially with a single dose of 300mg PO on Day 1, increased to 300mg twice a day on Day 2, and 300mg 3 times a day on Day 3. The dose may be titrated up to 1800 mg as needed for relief. Gabapentin is also associated with a wide range of adverse effects, including nausea and vomiting, as well as arthralgia and CNS symptoms. Decrease dosage with renal insufficiency.
- Consider whether the dose of ethionamide, cycloserine/terizidone, isoniazid, and linezolid can be reduced without compromising the regimen, and resume normal dose once the pain is controlled.

Rarely, medication may be discontinued, but only if an alternative drug is available or the regimen is not compromised.

9.6.6 Management of Psychosis

Psychosis refers to a constellation of symptoms that reflect a disintegration of personality or a loss of contact with reality. Visual or auditory hallucinations, paranoia, catatonia, delusions, and bizarre behaviour are hallmarks of psychosis.

Cycloserine/Terizidone is the medicine most commonly associated with psychosis; however, H, fluoroquinolones, and thioamides have also been associated with it. Other causes could be psychosocial stressors, depression, hypothyroidism, and other medications (benzodiazepines, certain antidepressants), as well as illicit drug and alcohol use.

A prior history of psychiatric disease is not a contraindication to the use of the above agents, though psychiatric side effects are more likely. Some patients may need anti-psychotic medication throughout anti-TB therapy, though side effects are generally reversible upon discontinuation of treatment.

Once psychosis has been diagnosed, other possible causes should be ruled out (especially in HIV-positive patients with low CD4, consider Cryptococcosis!).

Twenty-four-hour surveillance and possible hospitalization should be considered for all patients with florid psychosis and/or suicidal or homicidal tendencies.

In the cases of acute psychosis:

- If the patient is at risk of harming himself/herself or others:
- Urgent hospitalization
- Give haloperidol 2.5 mg orally or intramuscularly.
- If there is no improvement after 20 minutes, give 2.5 mg and if there is no improvement after 20 minutes, give 5 mg.
- If there is no response and/or risk of harming herself or others, use Chlorpromazine 25 mg intramuscularly (IM) up to 100 mg total dose until the patient is calm.
- If a good response, start haloperidol 2.5mg orally once daily and increase pyridoxine to 300 mg/day. Haloperidol may be increased by 2.5mg per day to control symptoms, to a maximum dose of 10 mg orally per day.
- Risperidone is effective and causes less extrapyramidal effects than haloperidol, therefore it can be used instead of haloperidol: start with 0.5mg to 5mg twice or three times per day. The usual dose is 2-10 mg per day.
- **Note:** that Haloperidol has anticholinergic as well as anti-dopaminergic effects. If a patient develops symptoms of neuroleptic syndrome, they must discontinue haloperidol immediately.
- If patients develop dystonia, Parkinsonism, or EPS, administer with diphenhydramine 25 mg PO QD or biperiden or benztropine
- Withhold Cycloserine or Terizidone and reintroduce with careful observation when symptoms are resolved.
- If no alternative drug is available, Cs/Trd may be tried at a low dose. If any recurrence of psychotic behaviour occurs, promptly and permanently discontinue Cs/Trd.
- When the patient has stabilized, all medications have been successfully restarted, and all symptoms have resolved, the antipsychotic drugs can be tampered with careful observation of the patient.

9.6.7 Management of Seizures

A seizure is an episode of neurologic dysfunction caused by abnormal neuronal or electrical activity of the brain that results in a sudden change in behaviour, sensory perception, or motor activity. The clinical spectrum of seizures includes simple and complex focal or partial seizures and generalized seizures.

Certain anti-TB drugs have been associated with seizures. However, a prior history of seizures is not a contraindication to DR-TB treatment if the condition is well controlled on anti-convulsive therapy. Seizures are not a permanent sequel of treatment.

The goal of seizure management is to stabilize the patient during an acute episode and the prevention of seizure recurrence.

In general, clinical evaluation is sufficient unless there is suspicion of infectious, malignant, vascular, or metabolic causes present. However, the following should be observed:

- Rule out other likely causes for seizure (e.g. meningitis, encephalitis, illicit drug use, alcohol withdrawal, hypoglycemia, hyper- or hyponatremia, hyper- or hypocalcemia, cerebrovascular accident, or space-occupying lesion)

- Consider checking blood chemistries and laboratory studies (including serum liver tests, urea, creatinine, glucose, electrolytes, calcium, HIV serology).
- Suspend Cs/Trd and isoniazid if the patient is receiving these medications
- Consider suspension of fluoroquinolone.
- Always check serum creatinine for new-onset seizures as acute renal failure is associated with the rapid increase in serum Cs/Trd levels, which induces seizures.

If actively fitting:

- Place the patient in the lateral decubitus position, remove objects nearby that can cause danger for the patient, protect the tongue with a soft object too large to be swallowed, and observe until the patient stops seizing.
- Ensure the airway is protected and not obstructed.
- Give diazepam 5 mg intravenously or intramuscularly immediately, followed by a loading dose of phenytoin (20 mg/kg intravenously, diluted in 200 ml NaCl 0,9%, and not 5% Dextrose solution). Diazepam may be repeated once in 10 minutes if seizures do not cease.
- Monitor the patient carefully for signs of respiratory depression.

If the seizure has already stopped at the time of initial evaluation and the patient is postictal:

- Do not give diazepam but give phenytoin loading dose as described above.
  - ✓ In both instances, begin a phenytoin maintenance dose of 300 mg/day (3-5 mg/kg/day) once the loading dose has been administered.

If seizures recur:

- Phenytoin may be increased to a maximum of 500 mg/day, or a second agent (valproic acid, phenobarbital) may be added.
- Increase pyridoxine to 300 mg/day in all cases.
- Initiate anti-epileptic treatment for the remainder of MDR TB therapy
  - ✓ Phenytoin (3-5 mg/kg/d) – Potential adverse effects: ataxia, incoordination, confusion, skin rash, cerebellar dysfunction, hepatotoxicity, gingival hyperplasia, lymphadenopathy, hirsutism. Levels increased by H, R, and FQs.
  - ✓ Valproic acid (750-1250 mg/d) – Potential adverse effects: ataxia, sedation, tremor, hepatotoxicity, bone marrow suppression, GI upset, weight gain
  - ✓ Carbamazepine (600-1200 mg/d) – Potential adverse effects: ataxia, dizziness, diplopia, vertigo, GI upset, hepatotoxicity, skin rash
  - ✓ Phenobarbitol (60-120 mg/d) – Potential adverse effects: sedation, ataxia, confusion, dizziness, decreased libido, depression, skin rash – Enhances metabolism of other drugs, including H.
  - ✓ Once stabilized, consider reinitiating the suspected drug at a lower dose

9.6.8 Hypothyroidism

Hypothyroidism may be asymptomatic but commonly manifests as a slowing in physical and mental activity. Symptoms and signs of this disease are often subtle and neither sensitive nor specific. Classic signs and symptoms, such as cold intolerance, puffiness, decreased sweating, coarse or dry skin, muscle pain, emotional lability, impaired memory, blurred vision, and hoarseness of voice.

Individuals can also present with obstructive sleep apnoea (secondary to macroglossia) or carpal tunnel syndrome. Women can present with galactorrhea and menstrual disturbances. Consequently, the diagnosis of hypothyroidism is based on clinical suspicion and confirmed by laboratory testing.

Some second-line anti-TB medications are associated with the causation of hypothyroidism of which the likely agents include: PAS, Prothionamide and Ethionamide (particularly when given in combination).

When hypothyroidism is suspected:

- Assess baseline thyroid function before the start of DR TB treatment for patients starting PAS and/or Prothionamide/ Ethionamide and correct if needed.
- Assess thyroid function every 2 months for the first 6 months for patients on PAS and or Prothionamide/ Ethionamide unless clinical assessment indicates the need to evaluate sooner.

Conduct monthly clinical assessments for hypothyroidism:

  - ✓ Clinical assessments may be a better indicator of thyroid function than laboratory values.
  - ✓ Enquire about fatigue, weakness, cold intolerance, decreased appetite, constipation, loss of energy, depression, and inability to concentrate.
  - ✓ Check physical signs e.g. enlarged thyroid, dry skin, coarse hair, and weight gain.
- Check TSH level if suggestive symptoms or signs are present.
  - ✓ If the TSH level is greater than 10, then symptomatic hypothyroidism is likely and therapy should be given.
  - ✓ Levothyroxine therapy should be initiated at a dose of 50 µg daily (or 25 µg daily for patients older than 65 years), increasing the dose by 25 µg and checking a TSH level every 4 weeks until a normal level is attained.
  - ✓ Thereafter TSH should be checked every 4 months until the patient's course of anti-TB therapy has been completed. If TSH testing is not available, discontinue levothyroxine after two to three months and follow the symptoms.
  - ✓ If symptoms do not improve, lower Eto dose by 250 mg or decrease PAS to 4 gm once daily. Discontinue the drug(s) if the above measures are ineffective and an equally effective drug can be substituted.
  - ✓ Continue to follow TSH until the treatment is completed, and discontinue levothyroxine according to TSH results.
  - ✓ **Note:** do not give levothyroxine at the same time as antacids or phenytoin, as these impair GI absorption
- Hypothyroidism is reversible upon discontinuation of PAS and/or Eto, i.e., the TSH level is expected to normalize after 2-3 months.

9.6.9 Management of myalgia and arthralgia

Pain and tenderness of the muscles and joints are relatively common side effects associated with a variety of drugs used to treat drug-resistant TB patients. One or more of the following drugs may be implicated: PZA, fluoroquinolones, INH, and ethionamide. Electrolyte disturbances associated with the aminoglycosides and Capreomycin may also cause muscle pain and cramping. Hypothyroidism may also contribute.

Serum uric acid levels may be elevated, but this is of little clinical relevance and anti-hyperuricemia therapy is of no proven benefit in these patients.

Therefore:

- Do not discontinue medications.
- If moderate to severe, NSAIDs may be given (indomethacin 50 mg orally twice daily or ibuprofen 400-800 mg orally thrice daily).
- If mild, Paracetamol 500-1,000 mg orally 2- 4 times daily may provide some relief
- If acute swelling, erythema, and warmth are present, evaluate for the presence of inflammatory diseases:
  - ✓ Aspirate joint for diagnosis if fluid is present
  - ✓ Evaluate for infection
  - ✓ Evaluate hypothyroidism or hyperthyroidism.
  - ✓ Draw serum electrolytes, calcium, and magnesium. Correct deficiencies.

9.6.10 Management of electrolyte abnormalities

All of the aminoglycosides and capreomycin can cause electrolyte disturbances due to renal tubular waste of potassium, magnesium, and calcium salts. These effects are most pronounced with capreomycin. Chloride and hydrogen losses may also occur with resulting alkalosis. A defect in renal tubular resorption of chloride may be caused by these drugs. Nausea, vomiting, and diarrhoea may also contribute to electrolyte abnormalities.

Although often asymptomatic, low serum potassium and magnesium may present as fatigue, myalgia, cramps, paraesthesia, lower extremity weakness, behaviour or mood changes, somnolence, and confusion. More severe disturbances can lead to tetany, paralysis, and life-threatening cardiac arrhythmias.

9.6.10.1 Hypokalemia – Hypomagnesemia:

- Mild-to-moderate hypokalemia (i.e., 2.5 < K < 3.5 mEq/L, asymptomatic) and mild hypomagnesaemia (1.4 < Mg < 1.8 mg/dl, asymptomatic) can be treated with oral supplements, with repeat monitoring in 24-48 hours.
- Where it is not possible to measure magnesium if a patient has hypokalemia, it should be assumed that he also has some degree of hypomagnesaemia. Untreated hypomagnesaemia may lead to a syndrome of “resistance” to the correction of hypokalemia.
- Severe hypokalemia (K < 2.5 mEq/L or symptomatic) and moderate-to-severe hypomagnesaemia (Mg <1.4 mg/dl or symptomatic) should be treated with parenteral or combined parenteral/oral supplementation, with repeat monitoring in 6 - 24 hours depending on the severity of the symptoms.

Table 43: Blood Potassium levels and recommended monitoring protocol

Potassium level mEq/L	Quantity of KCL 1mEq I. V=1mmol I.V 8mEq=600mg tablet	When to do the next control (sooner if the patient has vomiting or diarrhoea)
4.0 or more	None	Monthly
3.7 – 4.0	None	Monthly
3.4 – 3.6	20 - 40 mEq (1500-3000mg)	Monthly
3.0 – 3.3	60 mEq (4500mg)	Two weeks
2.7 – 2.9	80 mEq (6000mg)	One week
2.4 – 2.6	60 mmol IV and 6000 mg orally every 6 hours for 24 hours	
2.0 – 2.3	60 mmol IV and 7500 mg orally	Every 6 hours with aggressive IV replacement. Consider holding injectable until >2.4

Source: Guidelines for Programmatic Management of Drug-resistant Tuberculosis. Emergency update 2008. WHO/HTM/TB/200.402.

Note:

- Every tablet of Slow K 600 mg contains 8 mEq of K
- Every tablet of Magnesium contains 150 mg of Magnesium oxide
- **Potassium IV Supplementation:** should NOT exceed more than 20 mmol/hr of KCl. Normal preparation is 40 mmol in 1 litre of NaCl 0.9%, maximum preparation is 60 mmol/L.
- **Magnesium IV Supplementation:** maximum concentration: 5 g of MgSO4 in 1 litre of NaCl 0.9% or dextrose 5%. Do NOT exceed 150 mg per minute. If not emergency: 2 g in 100 ml administered over 1–2 hours or 4 g in 250 ml administered over 2–4 hours
- Amiloride or spironolactone are useful in resistant cases.

9.6.10.2 Hypocalcaemia:

Symptomatic hypocalcaemia should be treated on an emergency basis with 2 grams of calcium gluconate (180 mg elemental calcium or 20 ml 10% calcium gluconate) IV over 10 minutes, followed by an infusion of 6 grams calcium gluconate in 500 ml D5% over 4–6 hrs.

- The IV infusion should be tapered.
- The initial oral dose during the transition from IV to oral therapy is 1–2 g elemental calcium three times a day.
- For long-term therapy the typical dose is 500mg to 1g orally administered thrice daily.
- Hypomagnesemia must be treated if present.
- Total serum calcium levels need to be adjusted for low albumin (ionized levels of calcium do not need to be adjusted). The total serum calcium can be corrected by adding 0.8 mg/dL for every 1 g/dL decrease of serum albumin below 4 g/dL. By doing this calculation one can determine if true hypocalcaemia is present: Corrected calcium for hypoalbuminemia = 0.8(4.0 -measured albumin) + reported calcium

9.6.11 Management of Nephrotoxicity

All the aminoglycosides and capreomycin can cause nephrotoxicity. Ongoing assessment of renal function is therefore important.

Concurrent medical conditions such as diabetes or chronic renal failure are not a contraindication to DR-TB treatment, though greater caution must be exercised in such circumstances.

9.6.11.1 Acute renal failure: Creatinine clearance < 30 ml/min

- Suspend nephrotoxic TB medications (S, Am).
- Refer to **Swaziland HIV guidelines** for dose adjustments of ART medications.
- Check electrolytes including K, Mg and HCO3. Consider checking Ca and phosphorus.
- Rule out other causes of renal failure (e.g., diabetes, dehydration, congestive heart failure, urinary obstruction, urinary tract infection, prostatic hypertrophy, other medications such as NSAIDs, ACE inhibitors, sulpha drugs, diuretics)

Treatment

- Follow serum urea and creatinine and clinical exam for signs of improvement.
- Consider inpatient management (hospitalization) in patients with severe renal failure.
- Treat symptoms, and fluid and electrolyte disturbances as needed.
- Follow up clinical improvement and normalization of serum urea and creatinine before considering re-initiation of injectable medications.
- Once symptomatic improvement and documented stabilization of renal function; if the patient is receiving an aminoglycoside, it should be substituted with non-nephrotoxic drugs.
- If a change from aminoglycoside cannot be made, reduce the dose of the injectable according to creatinine clearance.

Adjust the dose of all TB medications according to creatinine clearance

- Follow serum urea and creatinine every 2-4 week thereafter.
- Maintain close surveillance for treatment failure and/or resistance amplification if there is a period of irregular therapy during acute management

9.6.12 Management of ototoxicity

Ototoxicity refers to damage of cranial nerve VIII, usually manifested by hearing loss and/or tinnitus. Other vestibular symptoms such as nystagmus, ataxia, and disequilibrium can also occur.

All of the aminoglycosides and capreomycin are toxic to the eighth cranial nerve and can cause both vestibular and auditory toxicity.

Although hearing loss is irreversible, progression can be prevented once the offending agent is discontinued. However, continuation of injectable therapy despite hearing loss may be warranted in patients with significant resistance and/or disease. In such cases, capreomycin may replace an aminoglycoside agent if the infecting strain is susceptible.

Using the injectable three times a week can also be considered.

9.6.12.1 In Vestibular Toxicity

- Observe the patient closely.
- If tinnitus and unsteadiness develop and these are attributed to vestibular toxicity, reduce or stop the injectable agent, according to the severity of the symptoms.
  - ✓ This is one of the few adverse reactions that cause permanent intolerable toxicity and, sometimes, necessitate discontinuation of a class of agents. Drug-induced vestibular toxicity is not reversible.
- At least monthly, assess vestibular toxicity.
- Fullness in the ears and intermittent ringing in the ears are early symptoms of vestibular toxicity.
  - ✓ When these are reported, it is sometimes possible to change the dosing to the lowest by weight for the patient but avoid changing the frequency of dosing in patients with normal renal function.
- Watch the patient carefully. Toxicity is related to the total dose and is cumulative. It is impossible to predict for an individual patient what dose is tolerated.
- A degree of disequilibrium can be caused by cycloserine, fluoroquinolones, ethionamide, INH, or linezolid.
  - ✓ Before stopping the injectable agent, evaluate whether these and/or other medications are causing the symptoms.
  - ✓ Stopping the injectable should be done after carefully excluding other causes of the symptoms.
  - ✓ Other drugs or all drugs can be held for several days to see if the symptoms improve. Symptoms of vestibular toxicity generally do not improve withholding medication.

9.6.12.2 Auditory Toxicity

Some degree of loss occurs in nearly all patients treated for drug-resistant TB. High-frequency loss usually occurs first. The effects are cumulative, and hearing loss may be reversible or permanent.

In case of suspected auditory toxicity:

- Perform a baseline audiogram and repeat monthly, for patients on IP.
- Substituting injectables with non-ototoxic drugs.
- Avoid loop diuretics (furosemide) because they increase eighth nerve toxicity.
- Streptomycin has less auditory toxicity, but more vestibular toxicity.
- Resistance to streptomycin is common and should be excluded before substituting it for another injectable.

The decision to continue therapy with an injectable when significant hearing loss occurs should be discussed with the patient and relatives.

9.6.13 Specific toxicities due to Bedaquiline

Monitoring specific toxicities is based on target organs defined in preclinical toxicity studies. For monitoring the specific toxicities related to second-line TB drugs, the NTCP guidelines should be followed, e.g. eye care, and audiometry. Management of patients with AST and/or ALT elevations, amylase and/or lipase elevations, musculoskeletal system and cardiac muscle abnormalities, cardiac rhythm disturbances, gastrointestinal system disorders or other toxicities is enumerated below.

9.6.13.1 Management of AST and/or ALT elevations

Management will be at the discretion of the physician, according to generally accepted medical practice standards.

- **Grade 1** (>1.0 to <2.0 x ULN), or **Grade 2** (>2.0 to <3.0 x ULN) AST or ALT elevation:
  - ✓ Patients may continue BDQ.
  - ✓ Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.
- **Grade 3** (>3.0 to <8.0 x ULN), or **Grade 4** (>8.0 x ULN) AST or ALT elevation:
  - ✓ Patients are allowed to temporarily discontinue treatment of the suspected causative agent (usually Eto, Z or PAS).
  - ✓ AST, ALT and serum bilirubin should be monitored as frequently as necessary to manage the patient's condition.
  - ✓ If ALT and AST do not return to baseline, BDQ may be temporarily withheld for up to 2 weeks. Additional tests should be performed to evaluate the cause of hepatitis (e.g. hepatitis A, B, C). Liver enzymes, including serum bilirubin, should be monitored as frequently as necessary to manage the patient's condition.
  - ✓ If the LFT improves, then the rest of the dosages of BDQ can be given. For patients who fail to show improvement in the clinical course and to return to baseline values of AST and ALT, it is recommended that the patient discontinue BDQ.

9.6.13.2 Management of Amylase and/or lipase elevation

Management will be at the discretion of the physician, according to generally accepted medical practice standards.

- **Grade 1** (>1.0 to <1.5 x ULN), or **Grade 2** (>1.5 to <2.0 x ULN):
  - ✓ Patients may continue to BDQ and should be carefully evaluated and followed closely.
- **Grade 3** (2.0 to <5.0 x ULN), or **Grade 4** (> 5.0 x ULN):
  - ✓ For asymptomatic grade 3 amylase elevations with no history or concomitant disease of pancreatitis, patients may continue BDQ but should be carefully evaluated and followed closely.
  - ✓ For confirmed grade 4 elevations of amylase and confirmed grade 3 or 4 elevations of lipase, it is recommended that the patient discontinue BDQ.

Musculoskeletal system and cardiac muscle abnormalities – myalgia

- Grade 1 (mild with no limitation of activity):
  - ✓ Patients may continue to BDQ and should be carefully evaluated and followed closely.
- Grade 2 (muscle tenderness at a site other than the injection site or with moderate impairment of activity), Grade 3 (severe muscle tenderness with marked impairment of activity) or Grade 4 (frank myonecrosis):
  - ✓ It is recommended that the patient discontinue BDQ.

9.6.13.3 Cardiac Rhythm Disturbances

QT Interval Monitoring

An ECG should be obtained before initiation of treatment and every two weeks for the first month, then monthly. ECGs should be done at least weekly throughout the BDQ course if other QT-prolonging drugs like FQ (Mfx) or Cfz are included in the regimen. Other drugs with additive or synergistic QT prolongation observed when BDQ is co-administered are those with serotonin 5-HT3 receptor antagonist (ondansetron), prokinetics (Cisapride), azole agents (ketoconazole, itraconazole, fluconazole), common ART drugs, antimalarials (chloroquine and quinine sulphate), some drugs used for psychiatric disorders (chlorpromazine, haloperidol, thioridazine) and drugs known to lower serum electrolytes. If possible, avoid the use of QT-prolonging drugs with BDQ. If it is necessary to include a QT-prolonging drug, increase ECG monitoring as described earlier.

QT prolongation can result in ventricular arrhythmias (Torsades de Pointes) and sudden death. It is therefore imperative that ECGs be used to monitor the QT interval regularly during BDQ use.

- **Grade 1** (asymptomatic) or Grade 2 (asymptomatic, transient rhythm abnormality not requiring any treatment) cardiac rhythm disturbances:
  - ✓ Patients may continue to BDQ and should be carefully evaluated and followed closely.
- **Grade 3 (recurrent, persistent, symptomatic arrhythmia requiring treatment) or Grade 4** (unstable dysrhythmia requiring hospitalization and treatment) cardiac rhythm disturbances:
  - ✓ It is recommended that the patient discontinue BDQ.

A normal value for the corrected QTcF interval is less than 0.45 seconds (450 ms). Whenever an abnormal QTc value is found, the ECG and calculations should be repeated.

- A value greater than 450 ms is considered prolonged.
- A value between 450 – 500 ms: Rule out other causes of prolonged QTc and manage accordingly, monitor closely (i.e. weekly ECG) until it reaches <480 ms
- A value greater than 500 ms (or an increase of greater than 60 ms from baseline) should trigger the following actions:
  - ✓ Repeat ECG to confirm prolongation
  - ✓ Check for serum K+, Mg2+ and Ca2+ and correct the levels if found to be abnormal. Identify other causes of QTc prolongation (e.g. hypothyroidism, drug-induced – e.g. psychotropic drugs, antiemetics, macrolides, etc.) and manage accordingly.
  - ✓ Once other possible causes of the QTC prolongation have been excluded, repeat the ECG.
  - ✓ If repeated ECG confirms QTC>500ms.
  - ✓ Hospitalize patients.
  - ✓ Withhold suspected causative drugs until the electrolytes have normalized. If the QTc interval is between 480 and 500 ms, the patient is stable and electrolytes are within normal values, repeat weekly ECGs to confirm that the QTc interval is stable.

- ✓ BDQ and all other QTc-prolonging drugs are to be discontinued if the patient develops a clinically significant ventricular arrhythmia (Torsade de points). Hospitalize patient. If BDQ is stopped for QTc prolongation, monitor ECGs at least weekly to confirm that the QTcF interval has returned to baseline. If syncope occurs, obtain an ECG to detect QT prolongation. Because of the long half-life of BDQ, if the ECG has QTc prolongation at week 24, ongoing weekly monitoring should take place until the QTc interval normalizes (even though the drug is no longer being given).
- ✓ If a core drug from the BPaLM/BPaL regimen is to be stopped permanently, change to the individualized regimen.

9.6.13.4 Gastrointestinal system disorders

Patients with grade 4 elevation of gastrointestinal parameters should be hospitalized and monitored closely. In case of grade 4 nausea (hospitalization required) or grade 4 vomiting (physiological consequences requiring hospitalization or requiring parenteral nutrition), the patient's BDQ treatment should be discussed with the DR-TB Clinical Expert committee.

Other toxicities

- **Grade 1 or 2:**
  - ✓ Patients who develop grade 1 or 2 AE or laboratory toxicity may continue intake of BDQ.
- **Grade 3 or 4:**
  - ✓ Patients who develop grade 3 or 4 AE or laboratory toxicity should be carefully evaluated by the physician.
  - ✓ Patients may discontinue their intake of BDQ if, in the opinion of the physician, the AE or laboratory toxicity poses a significant risk for the patient in the case of continued treatment.
  - ✓ Patients should be followed as appropriate until resolution of the AE or toxicity.

Refer to DAIDS criteria for grades.

Patients should be monitored for the common side effects of concomitant TB therapy, including decreased hearing, tinnitus, vision changes, dizziness, psychosis, depression, tremors, nausea, vomiting, diarrhoea, joint pain and renal function.

For the detailed algorithm for management of common side effects, please refer to section 9.9 (Figure 28 -Figure 32)

Table 44: Commonly used ancillary medications in managing side effects of second-line anti-TB drugs

ADRs	Suggested Drugs to manage the ADR
Nausea, vomiting, abdominal upset	***Metoclopramide, ondansetron,*** dimenhydrinate, prochlorperazine, ***promethazine***, bismuth subsalicylate
Heartburn, acid indigestion, sour stomach, ulcer	H2-blockers (***ranitidine***, cimétidine, etc.), proton pump inhibitors (***omeprazole***, etc.) Avoid antacids because they can decrease the absorption of fluoroquinolones.
Oral candidiasis (non-AIDS patient)	***Fluconazole, clotrimazole lozenges***
Diarrhoea	***ORS, Loperamide where necessary***
Depression	Selective serotonin reuptake inhibitors (fluoxetine,), tricyclic antidepressants (amitriptyline)
Severe anxiety	***Diazepam, clonazepam***
Insomnia	***Dimenhydrinate***
Psychosis	***Haloperidol***, risperidone (consider ***benztropine*** to prevent extrapyramidal effects)
Seizures	Phenytoin, ***carbamazepine***, valproic acid, phenobarbital
Prophylaxis of neurological complications of Cycloserine	***Pyridoxine*** (vitamin B_6)
Peripheral neuropathy	Amitriptyline, Gabapentin
Vestibular symptoms	Meclizine, prochlorperazine, promethazine
Musculoskeletal pain, arthralgia, headaches	Ibuprofen, paracetamol, paracodeine
Cutaneous reactions, itching	Hydrocortisone cream, calamine, caladryl lotions
Systemic hypersensitivity reactions	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisone, dexamethasone)
Bronchospasm	Salbutamol, Inhaled beta-agonists (salbutamol, albuterol, etc.), inhaled corticosteroids (beclomethasone, etc.), oral steroids (prednisone), injectable steroids (dexamethasone, methylprednisolone)
Hypothyroidism	Levothyroxine

Source: Adapted from Guidelines for Programmatic Management of Drug-resistant Tuberculosis. Emergency update 2008. WHO/HTM/TB/200.402.

9.6.14 Prevention of impairments leading to TB-associated disability

Timely assessment should be carried out to identify and manage impairments that with interaction with personal and environmental factors might result in disability. Disability grading should be carried out to support patient management and monitor program objectives. The overall disability grade for a patient is determined by the highest grade assigned to any body part impaired. For example, if the hands, feet, and left eye are graded 0, but the right eye is graded 2, the patient's overall grade would be 2.

9.7 Data Collection for aDSM

Clinicians involved in the treatment of DR-TB patients using new medicines, and/or novel treatment regimens are required to record and report SAEs and other AEs that are of clinical significance or special interest using the paper-based Active Pharmacovigilance Data Collection Form.

To facilitate data sharing and data analysis, as well as generating indicators, the completed paper-based active pharmacovigilance forms are consolidated into an electronic database at NPVU. This electronic database is called Vigiflow. The active surveillance data for DR-TB patients treated with new medicines, and/or novel regimens will also be captured in the WHO Global database for TB active drug safety monitoring (WHO Global aDSM Database).

In addition to the identification of signals and causality assessment, indicators will be useful to assess the coverage of aDSM activities and to summarize the overall AE experience of monitored patients. The ultimate purpose of systematic data collection within aDSM is to enable causality assessment for SAEs, determine their frequency (rates) and detect signals. Even though clinicians skilled in MDR-TB management already attempt to assess relationships between drugs and ADRs and take appropriate clinical action. Nevertheless, formal causality assessment is a separate process that requires the involvement of other experts and is not within the scope of these guidelines.

9.8 Structure and coordination of active pharmacovigilance in Eswatini

The responsibility for the coordination of pharmacovigilance at the national level in Eswatini has been assigned to the National Pharmacovigilance Unit (NPVU) with the guidance of the National Patient Safety Monitoring Committee (NPSMC) and support from public health programs. The NPSMC is responsible for promoting the optimum safety of medicines used in the country.

Reports from facilities are collated and consolidated into a database (Vigiflow) at the NPVU after which analysis (CA) is done by the aDSM committee and the NPVU then results are reported to the WHO Global aDSM Database as well as disseminated to the health care workers.

9.9 Algorithms for management of adverse events with Second-line Anti-TB Drugs

Figure 28: Management of QTc Prolongation

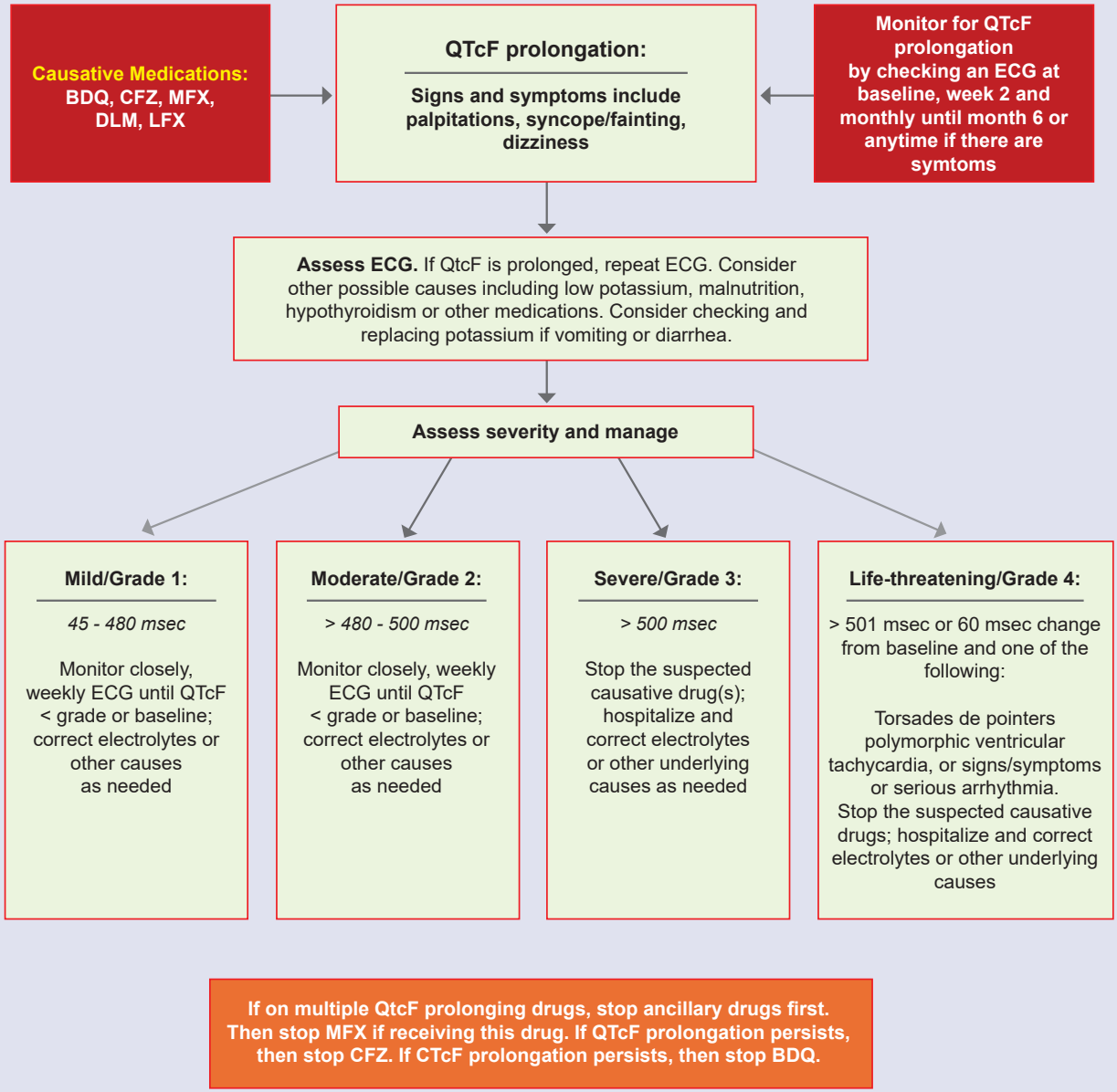


Figure 29: Management of Peripheral Neuropathy

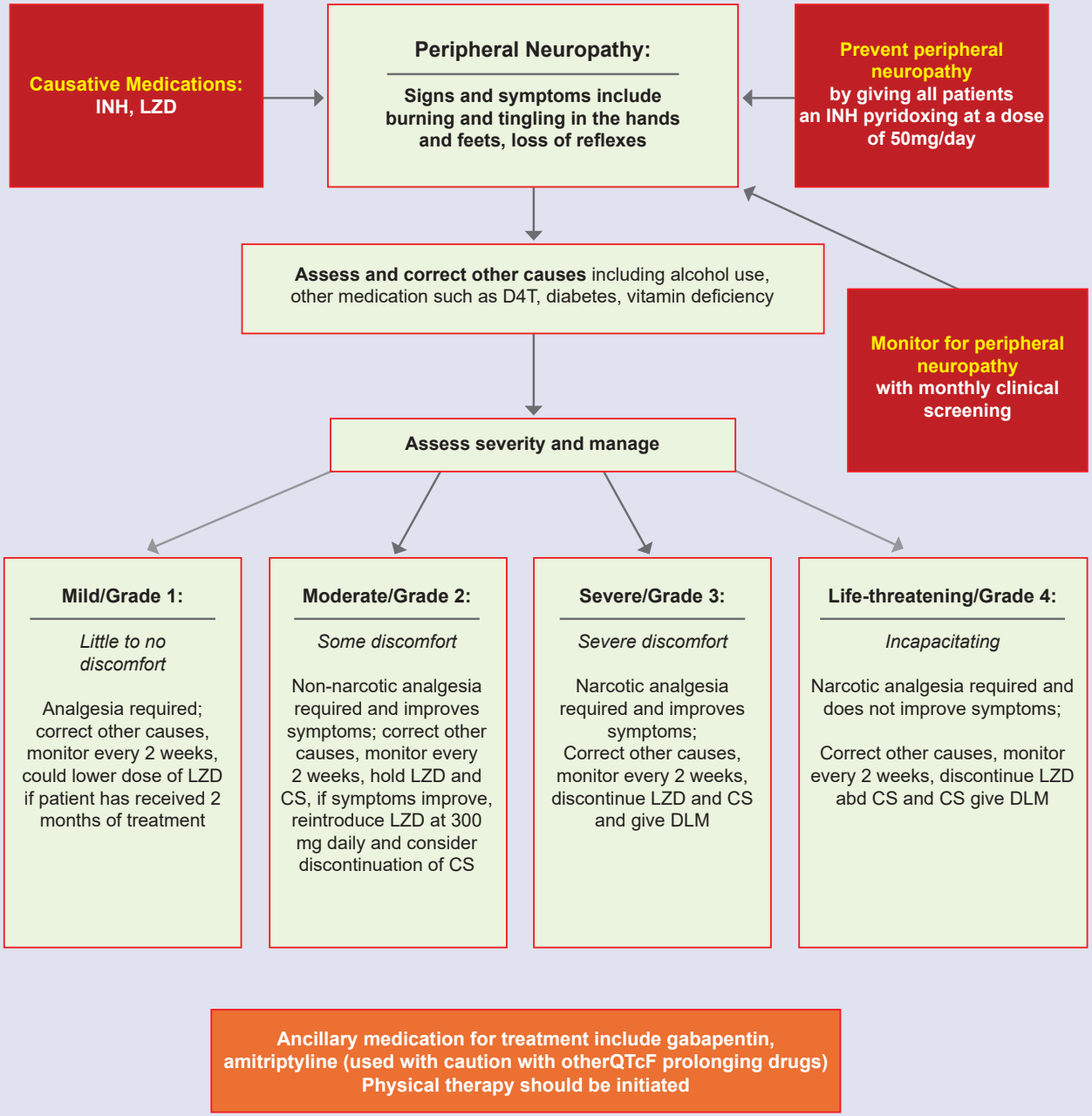


Figure 30: Management of Optic Neuropathy

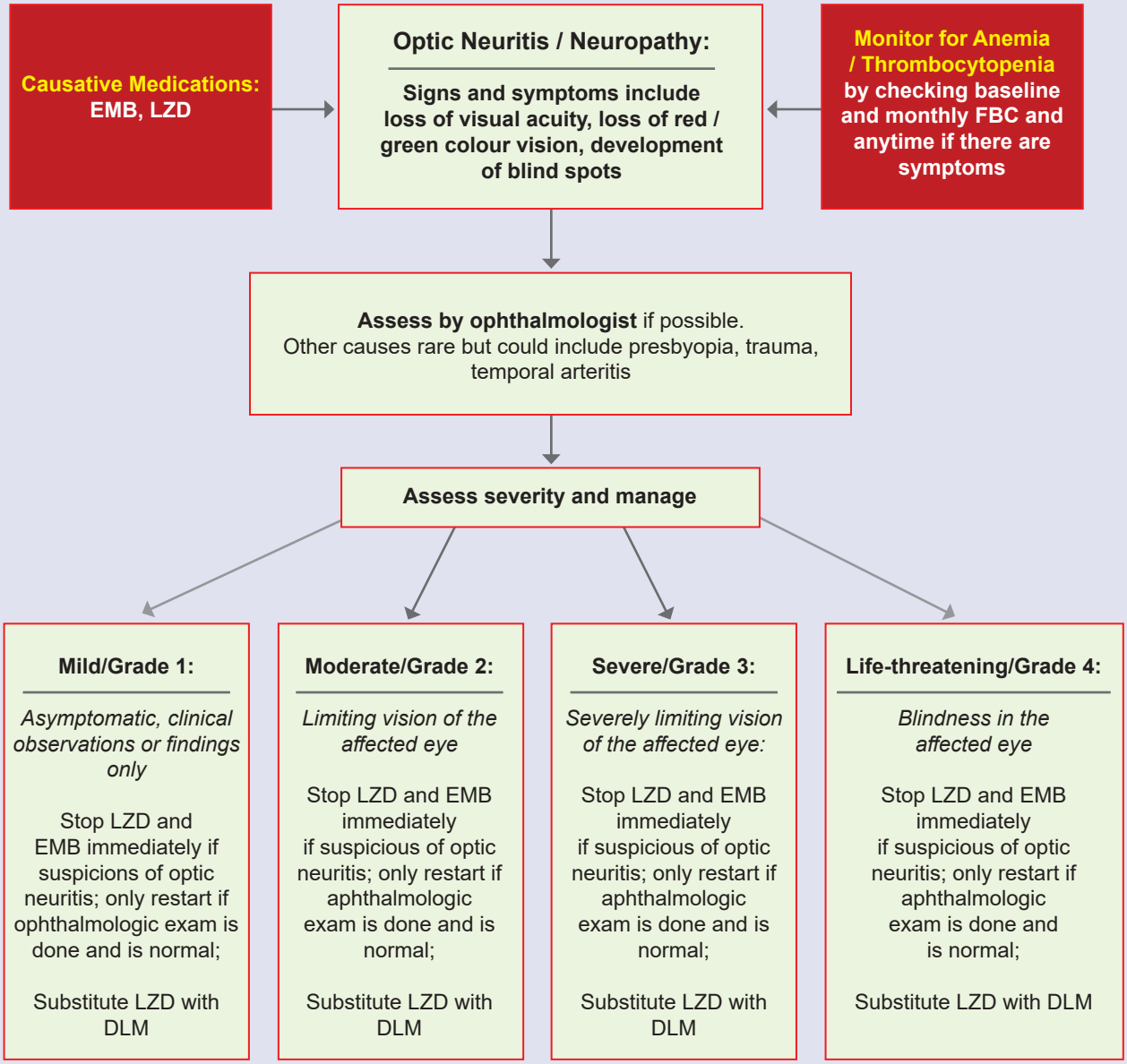
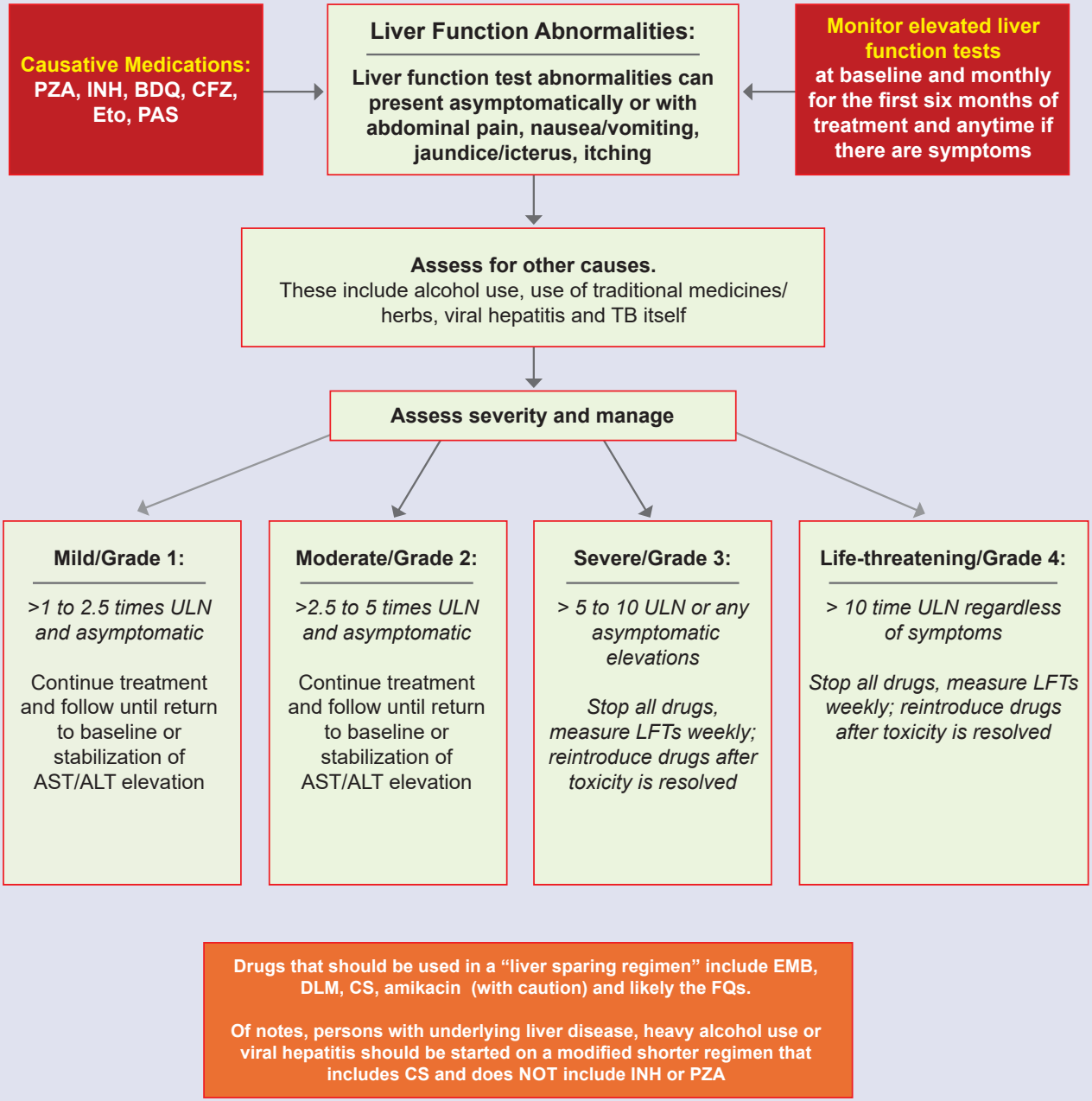


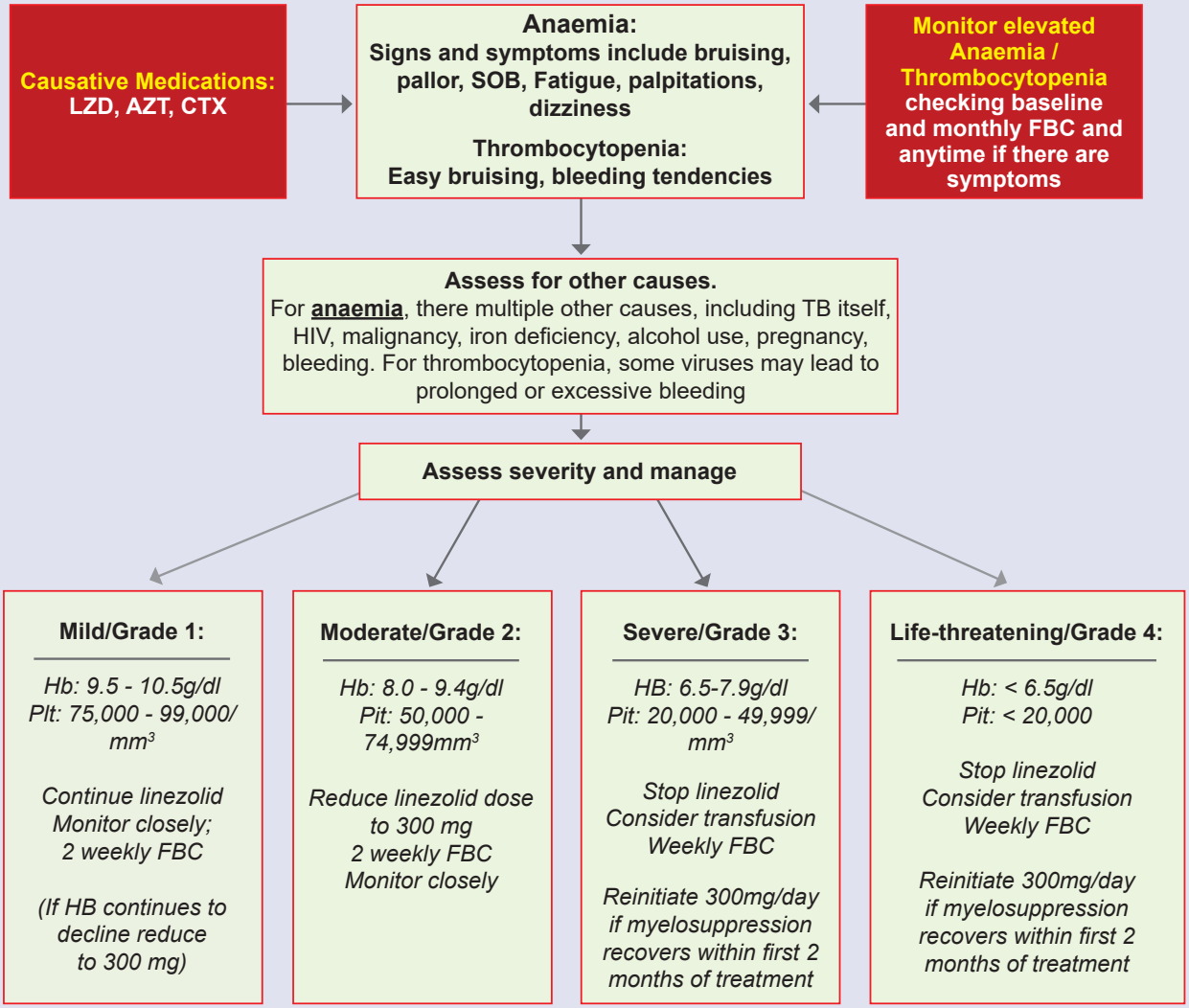
Figure 31: Management of Liver Function Abnormalities



Drugs that should be used in a "liver sparing regimen" include EMB, DLM, CS, amikacin (with caution) and likely the FQs.

Of notes, persons with underlying liver disease, heavy alcohol use or viral hepatitis should be started on a modified shorter regimen that includes CS and does NOT include INH or PZA

Figure 32: Management of Anaemia/ Thrombocytopenia



Patient with baseline anaemia of all grades can be treated with LZD. They should have more frequent FBC monitoring (i.e. every 2 weeks). This is true even of patients with Grade 3 or Grade 4 anemia, provided they are started on therapy as inpatients and that they have weekly FBC checked.

CHAPTER 10
TB AND HIV COLLABORATIVE ACTIVITIES AND ADVANCED HIV DISEASE

This chapter gives guidance on the management of TB patients co-infected with HIV and Advanced HIV disease (AHD), adopted from the national policy guideline on TB/HIV collaborative activities, 2015. The focus would be on the 2nd and 3rd objectives of the policy, to reduce the burden of HIV in patients with presumptive and diagnosed TB and to reduce the burden of TB in People living with HIV.

10.1 TB/HIV interaction and the comprehensive package of care

TB remains the leading cause of death among PLHIV and HIV remains the most potent risk factor for developing TB disease in Eswatini. TB can occur at any point during the progression of HIV infection and the risk rises with worsening immune status. The risk of developing TB among people living with HIV (PLHIV) is 20 times higher than the risk in the general population (range 17-23).

A comprehensive package of HIV prevention, treatment and care services should be provided to all TB patients, and these include HIV prevention interventions, HIV testing services, care for opportunistic infections, early ART initiation and psychosocial support. Likewise, a comprehensive care package for TB prevention, treatment, and care services should be provided for PLHIV, including TB screening services, TB preventive treatment services, and infection prevention and control measures in ART sites.

10.1.1 HIV prevention interventions for patients with presumptive and confirmed TB

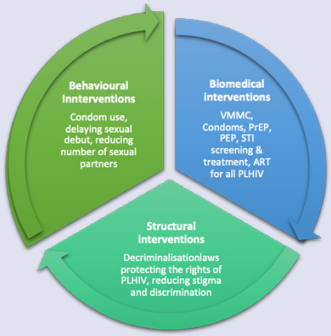
In line with the national integrated management of HIV guidelines (2022), the NTCP will prioritize high-impact combinations of behavioural, biomedical and structural prevention interventions to accelerate the reduction of new HIV infections among presumptive and diagnosed TB patients. The following HIV Prevention interventions should be provided to all HIV-negative people with presumptive TB and confirmed TB:

Behavioural interventions

- Condom use
- Delaying sexual debut
- Reducing the number of sexual partners

Biomedical Interventions

- Voluntary Male Medical Circumcision (VMMC)
- Condoms
- Pre-Exposure Prophylaxis (PrEP)
- Post-Exposure Prophylaxis (PEP)
- Sexually Transmitted Infections (STIs) screening and treatment
- ART for PLHIV



Combined HIV Preventive Interventions

Structural Interventions

- Decriminalization laws: Protecting the rights of PLHIV
- Reducing stigma and discrimination

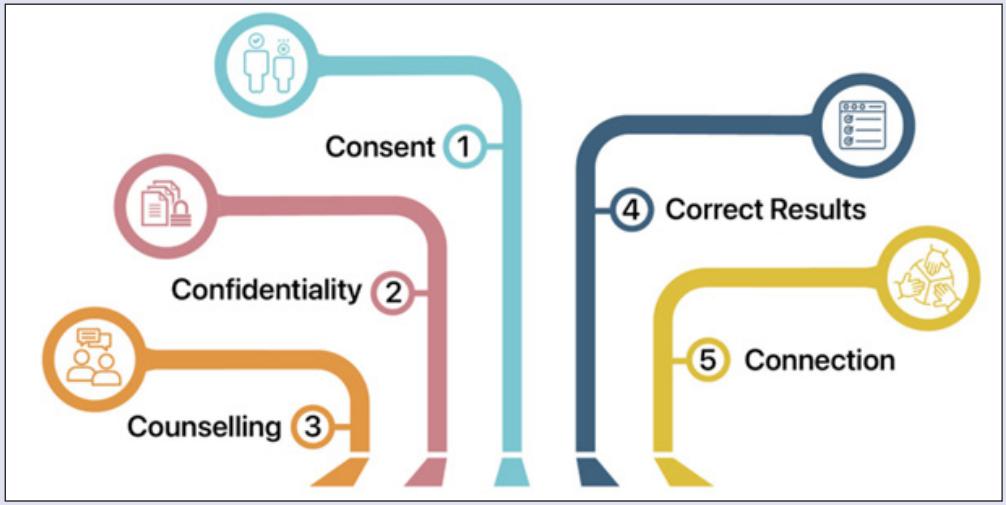
10.1.2 HIV testing services (HTS) for people with presumptive TB and confirmed TB

TB is often the first clinical indication that a person may have an underlying HIV infection; hence the importance of HIV testing services as an entry point to HIV prevention, care and treatment.

- Offer HIV testing and counselling services to all patients of all ages who present with signs or symptoms suggestive of tuberculosis or have confirmed TB.
- Employ Index-based provision of HIV Testing Services (HTS), such that once a client has been diagnosed with HIV, every effort should be made to provide HTS for immediate family members and significant others including sexual partners.
- Ensure appropriate post-test counselling, with a strong focus on HIV prevention for HIV-negative clients, and immediate enrollment in ART for newly diagnosed HIV clients in the absence of any reasons to delay the ART treatment initiation.
- Properly document the results of HIV testing in the appropriate columns of the CMIS/presumptive TB and TB treatment registers.

The guiding principles of HTS ("5 Cs as shown in Figure 33") must be respected and adhered to by all HTS providers even in TB settings (for details, refer to the Swaziland Integrated HIV Management Guidelines 2022).

Figure 33: The guiding principles of HTS ("5 Cs)



10.1.3 Care for opportunistic Infections in PLHIV with active TB disease

10.1.3.1 Cotrimoxazole Preventive Therapy

TB disease in a person infected with HIV should be viewed as a sign of Advanced HIV Disease (AHD) (a WHO Clinical Stage III or IV disease depending on site). PLHIV with advanced immuno-suppression are at high risk of opportunistic infections (OIs) such as recurrent bacterial infections e.g. Pneumocystis pneumonia (PCP) and malaria. Cotrimoxazole preventive therapy (CPT) substantially reduces morbidity in HIV-positive TB patients by reducing the risk for such OIs.

- Provide CPT to all TB/HIV co-infected patients throughout the anti-tuberculous therapy.
- Check CD4+ cell count and viral load (VL)at the end of the TB treatment course
- If the CD4+ cell count is > 350 cell/µl and VL is undetected stop CPT and continue with ART

TB/HIV co-infected patients should continue taking CPT until they have a CD4+ cell count >350 cell/µl and an undetectable viral load

10.1.4 ART for PLHIV with presumptive TB and confirmed TB

Antiretroviral therapy (ART) improves survival in HIV-positive patients. Additionally, ART reduces the risk of TB infection by 65% in PLHIV and this protective effect of ART against TB is seen irrespective of the CD4 counts at which people started taking antiretroviral treatment. ART should be initiated for all PLHIV with presumptive and confirmed TB irrespective of CD4+ cell count.

- Referral of TB/HIV clients to ART Clinics for HIV care and treatment is not recommended by the NTCP.
- Every effort should be made to ensure a “One Stop Shop” approach to service provision for TB patients with co-morbid conditions, including but not limited to HIV
  - ✓ Eswatini has prioritized fixed-dose combinations and once-daily dosing for ART to facilitate better adherence, tolerance, and viral suppression.
  - ✓ The recommended first-line ART regimen for drug-susceptible adults and adolescent TB patients co-infected with HIV is a fixed-dose combination of:

TDF (tenofovir 300 mg) + 3TC (lamivudine 300 mg) + DTG (dolutegravir 50mg bd (12 hours apart))

10.1.5 When to start ART?

Starting ART during TB treatment may be complicated by overlapping toxicities, drug-to-drug interactions, immune reconstitution disease, as well as high pill burden, which may negatively affect adherence to both TB and HIV treatment. On the other hand, delaying ART may lead to prolonged or worsening immune suppression. Clinicians need to balance these risks when deciding when to initiate concomitant ART and TB treatment.

Table 45: Recommended periods to start ART in PLHIV with presumptive TB and confirmed TB

Patient Category	When to start ART
Among PLHIV who are presumptive for TB	Initiate ART while rapidly investigating for TB, with close follow-up within seven days to initiate TB treatment if TB is confirmed
Among PLHIV on ART and diagnosed with TB	Continue ART and initiate anti-TB treatment as soon as diagnosed, may need to adjust ART regimen/dosage if required
For newly diagnosed PLHIV/returnees who also have been diagnosed with TB	Initiate ART as soon as possible preferably within 2 weeks of initiating tuberculosis treatment (including same-day anti-TB and ART treatment if clinically stable) regardless of immune status
Patients with TB meningitis	Delay ART to 4 weeks post-initiation of anti-TB treatment

10.1.6 What ART regimen to start on?

Table 46: Recommended Adult ART Regimens for TB/HIV Co-infected patients

Client Category	Recommended ART regimen	Comments
Clients already on TB treatment presenting for ART initiation	TDF (300mg)/3TC (300mg) once daily + DTG (50mg twice daily)	• Start ART as soon as possible with increased DTG dosing of 50mg twice daily • Return to standard DTG dosing 50mg once daily two weeks after the completion of TB treatment
Clients developing TB while on a DTG based ART regimen	Increased DTG dose to 50mg twice daily	For Clients must return to DTG 50mg once daily 2 weeks after completing TB treatment.
Developing DS-TB while on an EFV-based ART regimen.	TDF/3TC+EFV 400mg (once daily)	• Check VL at the end of treatment. If VL is undetectable, the client can be transitioned to a once-daily FDC of TDF+3TC+DTG two weeks after completion of TB treatment • If VL is detectable immediately switch to the second line and continue adherence support refer to the ART section
Developing DS-TB while on Protease inhibitor (PI) based ART regimen	Consult an experienced HIV clinician or snapthirdline@mohcoag.org before choosing these options: **TB patient on LPV/r** • Super boost LPV/r to 400mg/400mg by adding 300mg Ritonavir and continue until 2 weeks after completion of TB treatment	

Client Category	Recommended ART regimen	Comments
	• Double-dose of LPV/r to 800 mg/200 mg twice daily. Double dosing is only for clients >10yrs of age and continues until 2 weeks after completion of TB treatment. • If evidence of VL suppression in the past 3-6months, switch to a DTG-based second-line regimen and continue twice daily DTG until 2 weeks after completion of TB treatment **TB patient on ATV/r or DRV/r:** • Do not combine with RIF • Change to DTG twice daily if DTG naive or LPV/r with adjustments as stated above if DTG experienced **Patients who may be failing ART** • Follow guidance on managing treatment failure	
For Clients with Multidrug-Resistant TB		
EFV and Bedaquiline (BDQ)	• EFV should not be used with BDQ. • EFV induces CYP3A activity and co-administration with BDQ may result in reduced BDQ exposure and loss of BDQ activity. • DTG is the preferred INSTI for clients receiving BDQ.	
Delamanid (DLM) and ARVs	• DLM is generally considered safe to administer with ART. • Evidence shows safety with EFV, TDF and LPV/r. • No LPV/r dose adjustment is needed for TB patients on DLM No long-term studies have been done on potential drug-to-drug interactions with DLM and ARV DTG is the preferred INSTI for clients receiving DLM	

For all clients, maintain the same NRTI backbone provided there is no dose adjustment necessary, and the client is virally suppressed.

10.1.7 Drug-Drug Interactions

- Consider whether ART needs to be modified because of drug interactions or to reduce the potential for overlapping toxicities
- Consider whether the presentation of active TB in a patient on ART constitutes ART failure that requires a change in the ART regimen (Refer to the *Swaziland Integrated HIV Management Guidelines*).

Table 47: TB treatment/ART Drug Interactions

Drug combination	Considerations
Rifampicin and (LPV/r)	• LPV/r can be used with Rifampicin • Super boost the LPV/r (1:1 lopinavir and ritonavir) by adding ritonavir. • Closely monitor the client for toxicity (especially gastrointestinal intolerance) and virological failure
Rifampicin and Oral Contraceptive Pill	• Oral contraceptive pills may not be effective when administered with RIF. • Women of childbearing age should either receive a contraceptive pill containing a higher dose of oestrogen (50µg) or use another form of contraception (e.g., medroxyprogesterone). • Emphasize concomitant condom use during this period
DTG and all TB treatments	• Preference is for clients to be maintained on a fixed dose combination of TDF+3TC+EFV for the duration of TB treatment. • Check VL at the end of TB treatment. If the VL is undetectable: the client can be transitioned to a once-daily FDC of TDF+3TC+DTG two weeks after completion of TB treatment. If the VL is detectable, immediately switch to the second line and continue adherence support. • If the client is on a DTG regimen, the DTG does need to be given as 50mg twice daily until at least 2 weeks after the client has completed TB treatment. This may increase the occurrence of DTG side effects.

10.1.8 Managing side effects of concurrent TB/HIV treatment.

Patients on concurrent anti-tuberculous therapy and ART may experience overlapping toxicities due to both treatments. These patients should therefore be closely monitored especially for evidence of drug-induced hepatic damage through monthly measurement of transaminases.

10.2 Care and support for people with TB/HIV treatment

People with TB/HIV coinfected face challenges taking concomitant treatment for TB and HIV including (ART and treatment for opportunistic infections and other NCDs), In addition, TB/HIV coinfected have a higher risk of mental health conditions, especially depression. Due to pills-burden and drug-drug-potentiated adverse events, they pose a challenge with treatment adherence and the risk of developing drug resistance. There comprehensive care and support should be provided throughout treatment to ensure treatment adherence for TB, HIV and other comorbidities. It is recommended that all TB/HIV clients receive the following treatment-supportive interventions.

- Treatment education and counselling for TB, HIV and comorbidities
- Mental health screening using the People Health Screening 9 tool (PHQ9) at every visit and management/referral for further management at psychologist/psychiatrist
- Psycho-social counselling support

- Provision of supplemental food package monthly if available. Recommended indications for supplemental food packages are.
  - ✓ Children with MUAC <125 cm or Weight for height/age Z score <-2
  - ✓ Adolescents with MUAC <22.5 cm or BMI <18.5, adults BMI<18.5
- Provide medication adherence support intervention by HCWs, trained community cadre and digital adherence technology (e.g. smart pillbox, video-observed therapy) to clients (caregivers in case of children or who need assistance e.g. elderly) if available.

Daily medication administration should be provided by a treatment supporter who documents the administration of each dose of therapy on the medication administration record card (i.e. DOT card). The importance of patient education and empowerment around taking medication is a key part of improving adherence.

10.3 TB Prevention, treatment and care services for PLHIV

10.3.1 TB screening and diagnosis in PLHIV

PLHIV should be systematically screened at each clinical visit to a health facility to early detect TB disease. The standard TB symptoms screening tools should be used at every visit as follows: insert national TB screening tool. Annual TB screening with Chest X-ray with computer-aided detection software should be complemented to symptom-based screening wherever available.

10.3.2 TB Treatment in PLHIV

Treatment of TB is essentially the same for HIV-co-infected and HIV-negative TB patients, for both drug-susceptible and drug-resistant TB. Care should be taken however when combining anti-TB medicines and anti-retroviral medicines due to some drug-drug interactions which may compromise the effectiveness of either therapy. While every effort should be made to ensure that TB/HIV co-infected patients receive effective treatment for both TB and HIV, where this may not be possible due to the availability of alternative drugs, the effective treatment of TB disease takes precedence. Refer for detailed management of TB/HIV to the National Integrated HIV Management Guidelines, Chapter 1.6.4.

TB treatment is the same for HIV co-infected patients and HIV negative patients for both drug susceptible and drug-resistant TB (see Chapter 6 &7)

10.3.3 TB Preventive Treatment and Infection Prevention and Control in PLHIV

TB preventive treatment (TPT) or TB infection Treatment should be given to every new PLHIV (and old PLHIV on ART who may have been missed) after exclusion of active TB disease. For details on TPT management for PLHIV, refer to National Integrated HIV Management Guidelines and Chapter 11 of these guidelines.

10.4 Monitoring patients on concurrent ART and TB treatment

10.4.1 Clinical Monitoring

- Following ART initiation, clinical assessments should be conducted by a doctor or nurse at 2 weeks, 4 weeks and then monthly thereafter, until the patient has completed anti-TB treatment.
  - ✓ Following completion of anti-TB therapy, the follow-up of ART clients is as per the ***Swaziland Integrated HIV Management Guidelines (2022)***, with emphasis on Differentiated Service Delivery (DSD).
  - ✓ A focused history and physical examination should be performed during routine visits.

Table 48: Important features of regular clinical assessments should include:

• **Monitoring weight (done at <u>every</u> visit) height (in children, done every 3 months)** • **Head circumference (in children < 3 years of age, measured every 3 months)** • **Developmental status in children nutritional status in children**	• **Medication review** • **Side effects** • **Adherence and dosing** • **Other medications, including traditional medicines and other medications that may interact with ARVs**
• **Diagnosis and management of interim or new illnesses** • **Opportunistic infections (OIs) that may suggest immune reconstitution inflammatory syndrome (IRIS) or treatment failure.** • **Other co-morbidities, including STIs, Hepatitis B, substance abuse, psychiatric illness**	• Early diagnosis of pregnancy • Changes in social situation that might affect adherence to ART and anti-TB therapy

10.4.2 Laboratory Monitoring

Laboratory monitoring should complement clinical assessments. Baseline laboratory tests help in identifying co-morbid conditions such as chronic Renal Failure, chronic hepatitis and other conditions which may need an adjustment to the ART regimen a person should be initiated on. While the collection of samples for baseline investigations should be routine, the absence of the capacity to perform laboratory testing on-site should not delay a person from being initiated on ART.

Where possible, the following baseline laboratory investigations should be obtained before initiating ART:

Table 49: Baseline Laboratory Investigations

• **CD4 count, or percentage (in children < 5 years)** • **Full blood count (FBC)** • **ALT and AST** • **RBS (random blood sugar)** • **Pregnancy test in all women of childbearing age**	• **Serum Creatinine, followed by calculation of the rate of Creatinine Clearance (for details of calculation method for Creatinine clearance, please refer to TB treatment in special situations in the chapter on TB treatment and monitoring)**

10.4.2.1 Routine Laboratory Investigations

The following laboratory tests should be performed routinely depending on the specific ARVs that are included in the patient's regimen:

- If on Tenofovir (TDF), Serum Creatinine (and rate of Creatinine Clearance) should be checked 6 months after initiation, and every 6 months thereafter.
- If on AZT, Haemoglobin (Hb) should be checked at 1 month, 2 months, 3 months, 6 months, and every 6 months thereafter.
- If on NVP, ALT should be checked at 1 month, 2 months, 6 months, and every 6 months thereafter. If the CD4 count at initiation is between > 250 cells/mm3 in females or > 400 cells/mm3 in males, there is an increased risk of hepatotoxicity, so additional ALT testing is recommended at 2 weeks and 3 months.
- Viral Load (VL) should be monitored at 6 months, 12 months and then yearly if determined to be an undetectable post-ART initiation. VL is the most sensitive tool for determining treatment response and should be routinized for all ART clients.
- CD4+ cell counts should be checked at 6 months and 12 months, as an adjuvant to determine the efficacy of treatment. However, if the 6 and 12-month VL are undetectable, CD4+ cell count monitoring can be discontinued except in patients with advanced immunosuppression (CD4+ cell count < 350 cells/mm).

Additional laboratory tests can be requested depending on the results of the clinical assessments but should only be done if the result is required to further guide management. These include, but are not limited to:

- Lactate measurement, if the patient is on an NRTI (especially d4T or AZT) for > 4 months losing weight, and/or having other symptoms that suggest lactic acidosis
- Glucose and lipid measurements, if the patient is taking a Protease Inhibitor, such as Lopinavir/ritonavir (Kaletra) or Atazanavir/ritonavir.

10.5 Immune Reconstitution Inflammatory Syndrome (IRIS) among patients with HIV-related TB

The term "immune reconstitution inflammatory syndrome" (IRIS) describes a collection of inflammatory disorders associated with paradoxical worsening of pre-existing infectious processes occurring during the first 6 months after initiation of Antiretroviral Therapy (ART) in HIV-infected individuals.

10.5.1 Tuberculosis-associated IRIS: Two Main Syndromes:

A paradoxical reaction after the start of ART in patients receiving tuberculosis treatment (here termed paradoxical tuberculosis-associated IRIS)

Antecedent requirements

Both of the following requirements must be met:

1. Diagnosis of TB: the TB diagnosis was made before starting ART and this should fulfil WHO criteria for diagnosis of smear-positive PTB, smear-negative PTB or extrapulmonary TB
2. Initial response to TB treatment: the patient's condition should have stabilized or improved on appropriate TB treatment before ART initiation – e.g. cessation of night sweats, fevers, cough, and weight loss.

(**Note:** this does not apply to patients starting ART within 2 weeks of starting TB treatment since insufficient time may have elapsed for a clinical response to be reported.)

A new presentation of tuberculosis that is "unmasked" in the weeks following initiation of ART with an exaggerated inflammatory clinical presentation or complicated by a paradoxical reaction (here termed unmasking tuberculosis-associated IRIS).

Clients with advanced immunodeficiency (advanced disease) are at greater risk for IRIS when initiating ART and should be closely monitored. They usually present with the following clinical manifestations:

- Fever
- New or worsening adenitis - peripheral or central nodes
- New or worsening pulmonary infiltrates, including respiratory failure
- New or worsening pleuritis, pericarditis, or ascites
- Intracranial tuberculomas, worsening meningitis
- Disseminated skin lesions
- Epididymitis, hepato-splenomegaly, soft tissue abscesses

  Note: *Dolutegravir (DTG) has been associated with a higher risk of IRIS due to the rapid viral suppression and the accompanying immune reconstitution. Clients initiating DTG should be closely monitored for the first 6 months.*

10.5.2 Management of TB associated with IRIS

Treatment for TB-associated IRIS depends on the presentation and disease severity. Once other infectious etiologies have been excluded, standard anti-TB therapy should be continued as the clinical situation dictates. Most patients present with non-life-threatening presentations which respond to symptom-based therapy.

a. Since the pathogenesis of the syndrome is an inflammatory one, systematic corticosteroid or non-steroidal anti-inflammatory drugs can be used to alleviate symptoms.
b. Treatment can include prednisone 20-70 mg/day for 5-12 weeks or intravenous methylprednisolone 40 mg every 12 hours in severe situations.
c. Other studies showed that prednisolone prophylaxis of -40 mg per day for 14 days followed by 20mg per day for 14 days may prevent IRIS in high-risk populations (Meintjes et al., 2010).
d. Interruption of ART is rarely necessary but could be considered in life-threatening situations, especially those with neurological symptoms.
e. Refer to the Doctor at a Health Center or Hospital

10.6 Management of TB in children living with HIV

There is an increased risk of death for children with HIV-associated TB. It is therefore imperative that a comprehensive approach is employed in the management of these diseases. It is much more advisable and is of greater benefit if treatment for both these diseases is offered in the same location. HIV infection increases the risk of the development of tuberculosis by:

- Reactivating latent TB
- Quickening the progression of TB infection to TB disease and
- Increasing the risk of recurrent TB after successful treatment
- Increasing the risk of TB exposure and infection

10.6.1 Treatment of TB in a HIV-infected Child

There is an increased risk of drug-drug interactions and overlapping of toxicities between ARVs and anti-TB medicines that forward additional management challenges such as overlapping toxicities between these two classes of medications and a high pill burden. For instance, rifampicin interacts with both PIs, NNRTIs (NVP) and INSTIs by reducing their blood levels and hence their effectiveness, thus treatment for TB/HIV co-infection may require adjustments.

10.6.2 Principles of Tuberculosis Treatment in an HIV-infected Child

The principles of treatment in an HIV-infected child are the same as the principles in an uninfected child and the same regimens are used. However, the literature suggests that early initiation of ART in TB-infected children reduces TB-related morbidity and mortality with no excess adverse events.

Any child with TB should start treatment immediately and can start ART as soon as the TB treatment is tolerated, such as no experience of nausea, vomiting or any other adverse effects-usually 2 weeks into TB therapy.

9.5.3 ART in HIV-infected Children with TB

HIV infection increases the risk of progression to primary tuberculosis in a child and reactivation of latent TB in older children. This increases the pill burden, requiring intensive adherence and support. It is at this time that even the risk of adverse reactions is increased, and it is for that reason that a full clinical history is imperative at each clinic visit. Symptoms suggestive of adverse drug reactions, particularly liver toxicity in a child should be immediately evaluated or referred to. Severe drug intolerance or issues of erratic adherence may require consideration for interrupting ART. Resumption of treatment may occur once the problem is completely addressed.

Table 50: TB/HIV Simplified Treatment Table

Treatment of HIV-associated TB in children	
Patients Initiating ART while on TB Treatment	
Weight	**Initial Regimen (NRTIs based on HIV guidelines)**
< 10 Kg	LPV/r with 1:1 ritonavir boosting1,6 (recommended) or ABC-3TC-AZT2,3 (recommended if ritonavir is not available) or NVP2,3,4,5
10-20 Kg	EFV (recommended) or LPV/r with 1:1 ritonavir boosting1,6 or ABC-3TC-AZT2,3
> 20 Kg	DTG7 twice daily (recommended)

Modifications to ART when initiating TB Rx in patients on ART		
Weight	**Current ART Regimen**	**Suggested Modification**
< 10 Kg	NVP	Continue NVP2,3,4,5
	LPV/r	LPV/r with 1:1 ritonavir boosting1,6 (recommended) or ABC-3TC-AZT2,3 (recommended if ritonavir not available) or NVP2,3,4,5
10-20 Kg	NVP or EFV	EFV8
	LPV/r (1st Line ART)	LPV/r based with 1:1 ritonavir boosting1,6 (recommended) or EFV (recommended if VL undetectable in last 6 mo) or ABC-3TC-AZT2,3.
	LPV/r (2nd Line Treatment)	LPV/r with 1:1 ritonavir boosting6 (recommended) or ABC-3TC-AZT2,3
> 20 Kg	NVP or EFV	EFV8,9
	ATV/r or LPV/r (1st or 2nd Line Treatment)	LPV/r Double dose 6 or DTG7 twice daily (If VL confirmed undetectable at TB treatment initiation)
	DTG	Twice daily DTG7

Guiding Principles

- Always immediately check a viral load and CD4 in a patient on ART who is diagnosed with TB to assess for treatment failure
- If the viral load is detectable avoid one drug change and manage it as a treatment failure considering ART/ATT drug interactions
- Consider ART and PMTCT history when changing and selecting ART regimens
- NRTI companion drugs should be based on HIV guidelines considering weight, comorbidities and prior NRTI exposure
- Consult with TB/HIV experts through NTCP, ENAP or Partners with questions and for patients failing second-line ART or failing a PI

Footnotes

1. *See Dosing Table **** for 1:1 LPV/r (ritonavir solution and capsules)*
2. *NEVER continue ABC-3TC-AZT or NVP-based regimen for more than 2 weeks after rifampicin is discontinued*
3. *Consider ABC-3TC-AZT or NVP if intolerant to LPV/r*
4. *Avoid NVP if prior exposure to PMTCT or ART*
5. *Start at full dose and increase the dose to 200 mg/m2/dose if formulation allows when coadministered with rifampicin 6. LPV/r can be administered as a double dose instead of 1:1 in children swallowing LPV/r tablets, reduced to standard dosing 2 weeks after rifampicin discontinued*
7. *DTG must be given twice daily while on TB treatment and continued twice daily for two weeks after rifampicin is discontinued*
8. *NVP can be continued during TB treatment instead of EFV if intolerance or cannot swallow EFV (see above box)*
9. *Plan to change to DTG from EFV following completion of ATT (two weeks after rifampicin is stopped) if viral load is undetectable*

10.6.3 Cotrimoxazole Preventive Therapy (CPT)

CPT prophylaxis has been confirmed to reduce morbidity in children who are living with HIV. If a diagnosis of TB is made, provision of CPT should be ensured.

Table 51: Dosing of Cotrimoxazole for prophylaxis therapy by body weight

Weight	Child suspension	Single strength adult tablet (b400mg/80mg)	Double strength adult tablet (800mg/160mg)
<5	2.5 ml	1/4 tablets	-
5-15	5ml	1/2 tablets	-
15-30	10ml	One tablet	1/2 tablets
>30	-	Two tablets	One tablet

10.7 Management of TB in patients with advanced HIV disease

Despite progress in ART initiation and improved access to HIV testing and treatment, approximately half of PLHIV continue to present to care with advanced HIV disease. People presenting with advanced HIV disease are at high risk of death, even after being initiated on ART with the risk increasing as the CD4 cell count decreases, especially with CD4 cell count <200 cells/mm^3. Refer to Chapter 6.2 of the National Integrated HIV Management Guidelines, 2022 for details management of Advanced HIV disease.

10.7.1 Advanced HIV Disease Definition

- Advanced HIV disease is defined by WHO as having a CD4 cell count <200cells/mm^3 or WHO stage 3 or 4 event at presentation for care (for adults, adolescents and children older than five years) or (a CD4 count of less than 25% for children).
- All children younger than five years old living with HIV and who have not been in treatment for at least 12 months are a high-risk group and are therefore managed as having advanced HIV disease.
- Children above 2 years who have been on ART, and are stable, for at least one year may not be considered as having AHD.

10.7.2 Advanced HIV assessment

- CD4 count is the gateway to AHD screening.
- Semi-quantitative CD4 count (e.g., VISITECT) can be used to assess AHD
- In the absence of a CD4 count, clients with WHO stage 3 or 4 should be managed as having AHD

10.8 Advanced HIV Package of Care

A defined package of care interventions includes screening, treatment and prophylaxis for major opportunistic infections, rapid initiation of ART and intensified treatment adherence support, for people presenting to care with Advanced HIV disease to reduce HIV-associated morbidity and mortality.

10.8.1 Diagnosis of TB in patients with advanced HIV

In persons with AHD, the signs and symptoms of TB are atypical or may not manifest. Therefore LF-LAM test with a urine sample should be performed for TB diagnosis regardless of TB signs and symptoms. Xpert MTB/Rif test with sputum sample should be performed for all LF-LAM positive cases to exclude rifampicin resistance. If the Xpert test is negative, a culture should be performed for a drug susceptibility test. For details of diagnosis, refer to the Chapter on TB and DR-TB diagnosis.

10.8.2 ART initiation in TB patients with AHD

In TB-diagnosed clients, ART should be started within 2 weeks of starting TB treatment when the client can tolerate treatment. After ART initiation, clients need to be monitored closely for the following:

1. Adverse events
2. Clinical response
3. Development of IRIS
4. Non-adherence to ART

10.8.3 Cryptococcal Infection and Meningitis

Clients with cryptococcal infection may present with symptoms (symptomatic) or without symptoms (asymptomatic) of meningitis. Cryptococcal meningitis (CCM) has a high mortality rate. It is important to treat cryptococcal infection before CNS involvement to reduce morbidity and mortality (pre-emptive treatment). Clients with symptoms of meningitis should be referred to a medical doctor for further management as soon as the condition is suspected.

For the details on management of cryptococcal infection and meningitis, refer to National Integrated HIV Management Guidelines Chapter 6.2.2

10.8.4 Histoplasmosis

Histoplasmosis is caused by a kind of fungus called Histoplasma capsulatum through inhalation of fungal spores. In immune-compromised individuals, severe infection may result from the dissemination of fungus from the lungs. Signs and symptoms of histoplasmosis are Fever, Cough, Fatigue (extreme tiredness), Chills, Headache, Chest pain and Body aches. These signs and symptoms mimic that of TB. Histoplasmosis screening (serology test) should be performed for individuals with AHD age 5 years old and above and managed accordingly if the test is positive (For the details, refer to National Integrated HIV Guidelines Chapter 6.2.3).

Table 52: Components of the package of care for people with advanced HIV disease

	Intervention	CD4 Cell Count	Adults	Adolescents	Children <10 years
Diagnosis	Xpert MTB/Rif Ultra as the first test for TB diagnosis among symptomatic patients	Any	Yes	Yes	Yes
	Urine LF-LAM for TB diagnosis among people who are seriously ill or have symptoms and signs of TB	Symptomatic patients: All patients regardless of CD4 count with TB signs and symptoms Seriously ill patients*: All patients regardless of CD4 count or of TB signs and symptoms Inpatient setting: CD4	Yes	Yes	Yes
	Cryptococcal antigen CrAg screening	CD4 ≤ 100 cells/ml	Yes	Yes	No
		CD4 ≤ 200 cells/ml	May be considered**	May be considered**	No
	Histoplasma antigen test	ALL PLHIV	Yes	Yes	Yes
Prophylaxis	Cotrimoxazole prophylaxis	CD4 ≤350 cells/mm^3 or WHO clinical stage 3 or 4	Yes	Yes	Yes
	TB-preventive treatment	Any	Yes	Yes	Yes
	Fluconazole pre-emptive therapy for cryptococcal antigen-positive people without evidence of meningitis	<100 cells/mm^3	Yes	Yes	No
		≤200cells/ml	May be considered as above	May be considered as above	No
	Itraconazole prophylaxis for Histoplasma antigen-positive patients	Any CD4 count until 12 months or stable on ART and virally suppressed	Yes	Yes	Yes
ART initiation	Rapid ART initiation	Any	Yes	Yes	Yes
	Defer ART initiation if signs and symptoms of TB, CCM or CNS histoplasmosis	Any	Yes	Yes	Yes
Adapted adherence support	Tailored counselling to ensure optimal adherence to the advanced disease package, including home visits, if feasible	≤200 cells/ml	Yes	Yes	Yes

Source: WHO guidelines for the management of advanced HIV disease, 2022.
**Seriously ill patients (adults): any one of the following: respiratory rate >30 per minute, temperature > 39°C, heart rate >120 beats per minute, or unable to walk unaided. This excludes danger signs that can be explained or are a result of other diagnosed conditions e.g., cardiac failure, other bacterial infections, malaria etc. **May be considered in high cryptococcal antigenemia settings with adequate testing capacity.*

CHAPTER 11
TUBERCULOSIS PREVENTIVE TREATMENT

11.1 Introduction

In high-burden TB countries, most people may have TB infection (TBI). The prevention of active TB disease through treatment of TBI, also known as TB Preventive Treatment (TPT), is a critical component of the WHO End TB Strategy. Studies have proven that the efficacy of TPT ranges from 60% to 90%. In high-risk group populations, the benefits of TPT are likely to exceed the harm due to medication.

TB infection refers to a state of persistent immune response to stimulation by M. tuberculosis antigens with no evidence of the clinical manifestations of TB disease. This is also at times referred to as “latent TB infection”. There is no gold standard test for direct identification of M. tuberculosis infection in humans. Most infected people have no signs or symptoms of TB but are at risk for progression to active TB disease.

11.2 The difference between TB infection and TB disease

The difference between TBI and TB disease is distinguished below in Table 53.

Table 53: Difference between TB infection and TB disease

Characteristics	Tuberculosis Infection	Tuberculosis Disease
Symptoms	None	Most present with one or more of the following symptoms: cough, weight loss or poor weight gain, in children (failure to thrive), fever, night sweats, chest pain, hemoptysis, fatigue, and decreased appetite.
Tuberculin skin test or Interferon Gamma Release Assays (IGRA)	Usually Positive	Usually Positive
Bacteriological status	Negative	Respiratory specimens are usually positive on smear microscopy, mWRD, and culture. However, may be negative in people with extrapulmonary disease or minimal or early pulmonary disease.
Chest X-RAY	Normal	Usually, abnormal
Infectiousness	No	Often infectious (before treatment)
Tuberculosis Case	No	Yes
Preferred Management	Preventive treatment	Tuberculosis treatment

11.3 TPT implementation strategies

The key TPT implementation strategies include:

- Identifying individuals eligible for TBI treatment
- Delivering effective, safe treatment in such a way that the majority of those on TPT will complete it with no or minimal risk of adverse events.
- Regular monitoring and evaluation of the process and outcomes

11.4 Identification of individuals eligible for TPT

TPT will be the most beneficial for the population groups at high risk of getting infected and Progressing to TB disease, The targeted high-risk groups for TPT are:

- People living with HIV
- Household contacts (HHC) of bacteriologically confirmed TB cases include children under 5 years old, children above 5 years old, adolescents and adults. Within household contacts, the following people are more vulnerable:
  - ✓ Children <5 years old
  - ✓ Adult >60 years old
  - ✓ Diabetics
  - ✓ Smokers
  - ✓ Alcoholics
  - ✓ Substance abusers
  - ✓ Malnourished
- Individuals who have silicosis
- Persons with Immuno-suppressive medical conditions.
  - ✓ Chronic Kidney Disease with or without dialysis
  - ✓ Anti-TNF treatment
  - ✓ Transplantation (including candidates)
  - ✓ Person on immune-suppressant drugs (e.g. on long steroid therapy, chemotherapy for cancer)
- Healthcare workers
- Offenders

To identify eligible persons for TPT, contact investigation among HHC and identification of other risk groups in health facilities are crucial.and drug-resistant TB (see chapter 6 &7)

Health workers (skilled, lay and support staff), offenders and correctional facility staff should periodically be screened for TB to identify and treat active disease and provide TPT after active TB is ruled out, regardless of HIV status. HIV testing should, however, be encouraged. **Note:** Tests of TB infection could be done, if possible, to learn about the risk of transmission to healthcare workers - in those who test negative at baseline.

11.5 TB infection Testing

There are two types of TB infection tests: Skin tests including the Tuberculin Skin Test (TST) the new antigen-based skin test (TBST), and Interferon Gamma Release Assay (IGRA).

TBI testing by TST (or the new antigen-based skin test) or IGRA is not a requirement for initiating preventive treatment in people living with HIV or children with household contacts aged < 10 years old in Eswatini. **For the procedure of performing the TBI test, refer to section 11.5.**

If IGRA or TST is available, the following HIV-negative risk groups are recommended for TBI testing.

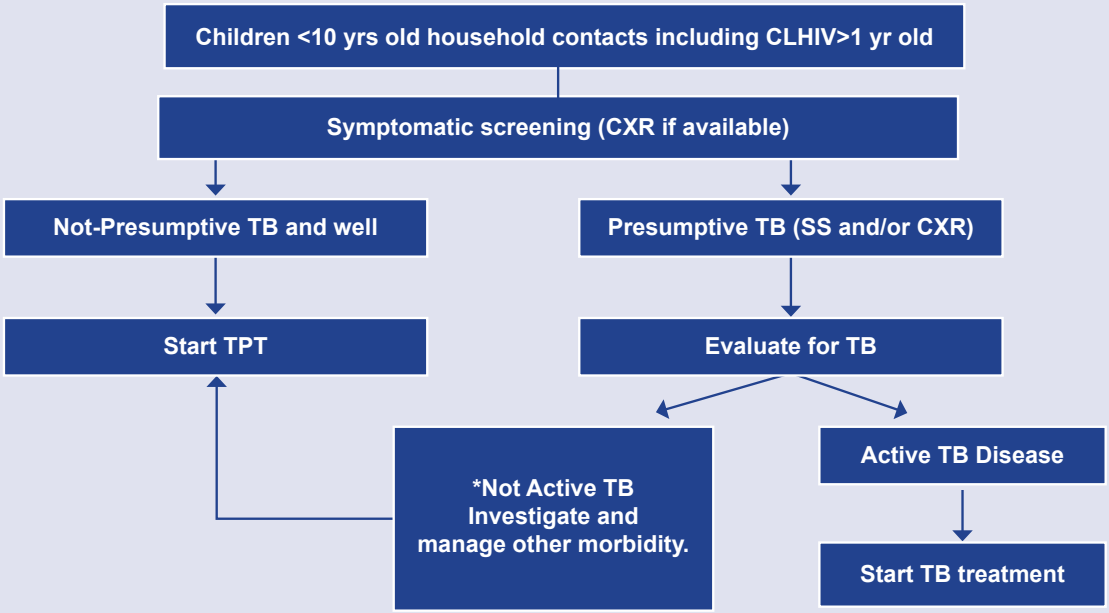
- Household (BC-TB/DR-TB index case) contacts of >10 years old
- Household (CD-PTB/DR-TB) contacts (index case did not have access to bacteriological diagnosis)
- People with silicosis
- People with immuno-suppressant medical conditions:
  - ✓ Chronic Kidney Disease with or without dialysis
  - ✓ Anti-TNF treatment
  - ✓ Transplantation (including candidate)
  - ✓ Person on immune-suppressant drugs (e.g., on long steroid therapy, chemotherapy for cancer)
- Healthcare workers
- Offenders

11.6 Ruling out active tuberculosis disease (TB/DR-TB)

For children 0-10 years old household contacts including CLHIV

- Assess TB signs and symptoms (any fever, cough, weight loss or poor weight gain or failure to thrive, tiredness – less playfulness, less active, history of contact with TB)
- *Poor weight gain is defined as reported weight loss, very low weight-for-age (< –3 z-score), underweight (weight-for-age < –2 z-score), confirmed weight loss (> 5%) since the last visit or growth curve flattening*
- Take CXR if available
- Start TPT, if there are no TB signs and symptoms and the child is doing well (or CXR not suggestive of TB)
- If there are TB signs and symptoms, exclude active TB/DR-TB disease as per the national TB diagnostic algorithm (sputum/stool test with Xpert MTB/Rif, clinical diagnosis if bacteriological test is negative).
- In the event of active TB/DR-TB disease diagnosed bacteriologically or clinically by the discretion of the clinician, start TB/DR-TB treatment.
- If there is no active TB/DR-TB disease, investigate for other morbidity and manage accordingly and start TPT if the symptoms are resolved.
- If there is still a concern with active TB disease due to incomplete resolution of symptoms, follow up after two weeks. If symptoms are resolved and TB is excluded/no longer a concern, start TPT.

Figure 34: Algorithm for ruling out active TB/DR-TB disease in children 0-10 years old including CLHIV



***If there is still a concern with active TB disease due to incomplete resolution of symptoms, follow-up after two weeks. If symptoms resolve, start TPT.**

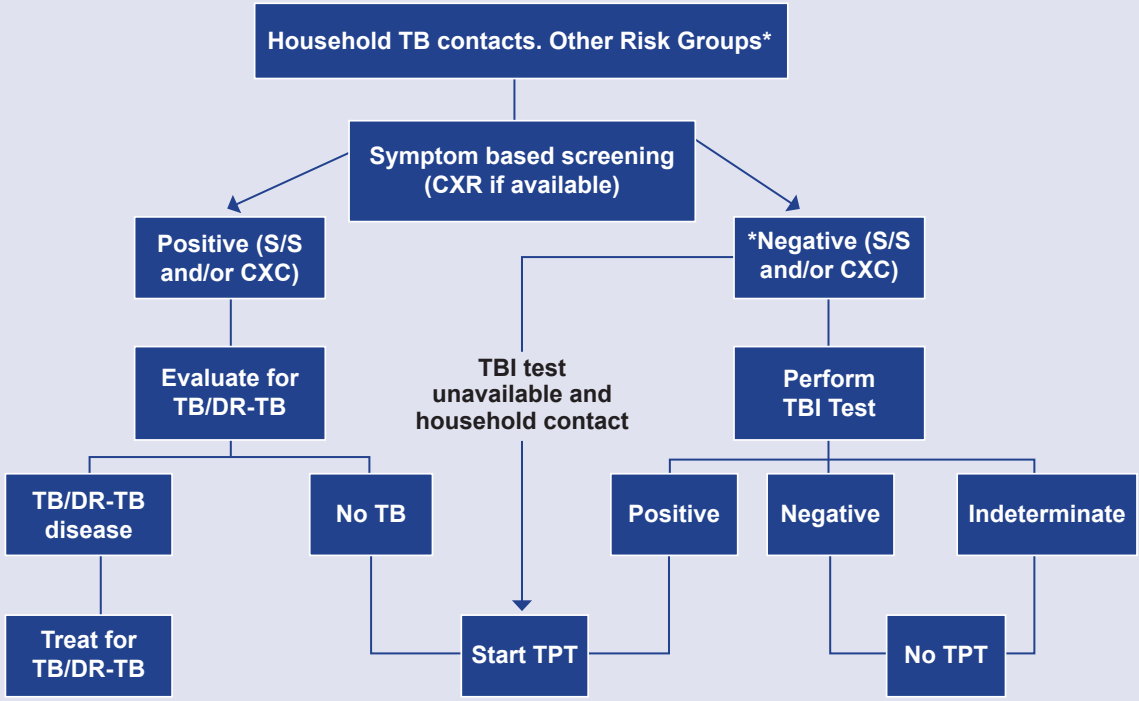
Infants living with HIV who are < 1 year of age should be given TBI treatment only if they have a history of household contact with a TB case and active TB has been excluded in investigations.

For HIV-negative>10 years old adolescents and adult's household contacts and other risk groups

- Assess TB signs and symptoms (any fever, cough, night sweat, weight loss, history of contact with TB/DR-TB)
- Take CXR if available
- Perform TBI test if available for eligible risk groups
- Exclude active TB/DR-TB disease for individuals determined as presumptive TB as per TB diagnosis chapter.
- In the event of active TB/DR-TB disease diagnosed bacteriologically or clinically by the decision of the clinician, start TB treatment.
- If there is no active TB/DR-TB disease, investigate for other disease and manage accordingly and start TPT after assessing eligibility.
- If there is still a concern with active TB disease due to incomplete resolution of symptoms, follow-up after two weeks. If symptoms are resolved and TB is no longer a concern, start TPT.

Neither CXR norTBI test is mandatory to make a decision to start TPT

Figure 35: Algorithm for ruling out active TB/DR-TB disease in HIV negative household contacts >10 years old and other risk groups



Other risk groups include people with silicosis, person on immune-suppressant drugs (e.g. on long steroid therapy, chemotherapy for cancer), anti-Tumor Necrosis Factor (Anti-TNF) treatment and transplantation (including candidates), health care workers and offenders.

For exclusion of active TB disease in PLHIV prior to TPT

- The algorithm for evaluation of TB in PLHIV, Figure 18 (Page 55) details the exclusion of active TB disease in PLHIV before TPT.
- Refer to Chapter 6, National Integrated HIV Guidelines, 2022 for the details of the procedures, TPT initiation and management of clients on TPT.

Ineligibility to TPT include acute or chronic hepatitis, peripheral neuropathy (if isoniazid used), and regular and heavy alcohol consumption

- For PLHIV on DS-TB treatment, TPT should start immediately after completion of TB treatment.
- For PLHIV on DR-TB treatment, perform post-treatment follow-up. If there is any exposure to TB (e.g. a household member has TB), consider giving TPT after exclusion of active TB disease depending on the index case TB type (e.g. if it is DS-TB, give TPT for DS-TB and if it is DR-TB without FQ resistance, give DR-TB TPT with Levofloxacin for 6 months).

11.7 Preparation before TPT initiation

Education and counselling for people eligible for TPT

- Education about TB infection, TB disease, benefits of TPT and potential adverse events (AE)
- Agree on the TPT delivery plan (e.g., through a treatment partner, by family members, or the patient themselves).
- Counsel on adherence plan including:
  - ✓ Preferred time and day to ensure doses are remembered (e.g., in the early morning with a light meal every Friday).
  - ✓ If multiple family members are taking TPT, all family members set one time and remind each other.
  - ✓ Set an alarm clock or use a calendar with pop-up messages on a mobile phone or smartwatch or simply tick in a physical calendar.

Baseline assessment

- Perform baseline clinical examination focusing on underlying conditions that could increase the risk of AEs from TPT.
- Pregnancy test for women at reproductive age, if unsure of pregnancy status
- Baseline liver function test if risk factors for hepatotoxicity present which include:
- History of chronic liver disease (cirrhosis, hepatitis B or hepatitis C, or liver cancer)
- Regular use of alcohol
- Pregnancy
- Within 3 months postpartum
- Age >60 years
- Check age and HIV status to determine the TPT regimen to be given.
- Check body weight and prescribe the right dosage of TPT by following the dosing table.
- Give pyridoxine (Vitamin B6) prophylactic dose for peripheral neuropathy (PNP), for those on isoniazid-containing regimen: o adults and children over 1 yr: pyridoxine 10 to 25 mg/day o Infants: pyridoxine 5-10 mg/day

11.8 TPT Regimens and Dosing

Shorter treatment regimens for DS-TB TPT are available, and they are preferred over 6-month isoniazid therapy. Key characteristics of TPT regimens and dosages for both DS-TB and DR-TB TPT regimens are described in Tables 54 and 55 respectively.

Table 54: Key characteristics of TPT regimens

Characteristics	6H	3HP	3HR	4R	1HP	6H(+CPT+B6)	6Lfx
Drug (s)	Isoniazid	Isoniazid + Rifapentine	Isoniazid + Rifampicin	Rifampicin	Isoniazid + Rifapentine	Isoniazid + Cotrimoxazole + Pyridoxine	Levofloxacin
Duration (mths)	6	3	3	4	1	6	6
Frequency	Daily	Weekly	Daily	Daily	Daily	Daily	Daily
Total No. of doses	182	12	84	120	28	182	182
Pill burden per dose (total per regimen), person weighing 50kg using adult formulations[a]	1(182)	6 singles (72) or 3 with FDC (36)	3(252)	3(360)	3(84)	1(182)	1(182)
Children	All ages: child-friendly (dispersible) formulation available preferred for children with HIV on LPV/r or NVP	All ages: child-friendly (dispersible) formulation available	All ages: child-friendly (dispersible) formulation available	All ages: no child-friendly formulation available, not generally feasible for children < 25kg	≥ 13 years	Adults and adolescents; no child-friendly formulations available	All ages: child-friendly (dispersible) formulation available
Pregnant women	Safe for use[c]	Not known	Safe for use[c]	May be safe, although no safety or efficacy data available for this population	Not known	Safe for use[c]	May be safe, although no safety or efficacy data available specifically in this population
Interactions with ART	No restriction	Contraindicated: All protease inhibitors (PIs), nevirapine (NVP), doravirine and etravirine, tenofovir alafenamide (TAF) Use: tenofovirdisoproxil fumarate (TDF), EFV, DTG, RAL	Contraindicated: All PIs, NVP, doravirine and etravirine Use with caution: TAF Adjust dose: DTG, RAL Use: TDF, EFV	Contraindicated: All PIs, NVP, doravirine and etravirine, TAF Adjust dose: DTG, RAL Use: TDF, EFV	Contraindicated: All PIs, NVP, doravirine and etravirine, TAF Use: TDF, EFV, DTG, RAL	No restriction	No restriction (may interfere with lamivudine clearance)
Toxicity	Hepatotoxicity (more), peripheral neuropathy, rash, gastrointestinal upset	Flu-like syndrome, hypersensitivity reactions, gastrointestinal upset, orange discolouration of body fluids, rash, hepatotoxicity (less)	Hypersensitivity reactions, hepatotoxicity (less), rash, gastrointestinal upset, hypo-prothrombinaemia, orange discolouration of body fluids	Rash, gastrointestinal upset, hepatotoxicity (less), hypo-prothrombinaemia, Orange discolouration of body Fluids	Hepatotoxicity (more), hypersensitivity reaction, rash, gastrointestinal upset, orange discolouration of body fluid	Hepatotoxicity, rash, gastro-intestinal upset	Diarrhoea, nausea and bloating, arthralgia, inflamed or torn tendons, muscle pain or weakness, prolonged QTc interval, mood or behaviour changes, insomnia

Characteristics	6H	3HP	3HR	4R	1HP	6H(+CPT+B6)	6Lfx
Absorption	Best absorbed on an empty stomach; up to 50% reduction in peak concentration with a fatty meal	Oral rifapentine bioavailability is 70%; peak concentration increased if given with a meal	Rifampicin absorption is rapid but may be delayed or decreased by high-fat meals.		Same as 3HP	Same as 6H	Absorption is not influenced by food. Concomitant steroid use may increase risk of tendon rupture. Multivalent cation containing products includ-ing antacids (may contain aluminium), mineral supple-ments (e.g. iron or magnesium) or multivitamins may decrease absorption. Effect of warfarin may be enhanced

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 monotherapy; B6, pyridoxine; CPT, cotrimoxazole; DTG, dolutegravir; EFV, efavirenz; FDC, fixed-dose combination; H, isoniazid; LPV/r, lopinavir–ritonavir
NVP, nevirapine; P, rifapentine; PI, protease inhibitor; H + CPT + B6 (Q-TIB), isoniazid- cotrimoxazole-pyridoxine combination; R, rifampicin; RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate a H-300 mg; P-300 mg; H-300 mg/P-300 mg FDC; R-150 mg/H-75 mg FDC; R-300 mg/150 mg; Lfx-500 mg

Table 55: TPT regimen and drug dosing

TPT regimens and drug formulations	No. of tablets or quantity of solution 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
Three months of weekly rifapentine plus isoniazid (3HP)													
Isoniazid 100mg dt	0.6 (6 mL[a])	0.7 (7 mL[a])	1	1.5	2.5	3	4.5	4.5	6	6	7.5	7.5	9
Isoniazid 300mg tab	–	–	–	–	–	1	1.5	1.5	2	2	2.5	2.5	3
Rifapentine 150mg dt	0.5 (5 mL[d])	0.7 (7 mL[d])	1.5	1.5	2	3	4	4	5	6	6	6	6
Rifapentine 300mg tab	–	–	–	–	–	1.5	2	2	2.5	3	3	3	3
Rifapentine 300 mg and Isoniazid 300 mg FDC tab	–	–	–	–	–	–	–	–	–	–	–	–	3
One month of daily rifapentine plus isoniazid (1HP)[e]													
Isoniazid 300mg tab	–	–	–	–	–	–	–	1	1	1	1	1	1
Rifapentine 30 mg tab	–	–	–	–	–	–	–	2	2	2	2	2	2
Six months of daily levofloxacin (6Lfx)													
Lfx 100mg dt	0.5	1	1	1.5	2	2.5	3	3.5	–	–	–	–	–
Lfx 250mg tab	0.25 (2.5 mL[d])	0.5 (5 mL[d])	0.5 (5 mL[d])	1 (10 mL[d])	1	1.5	–	2	2	2	2	2	3
Lfx 500mg tab	–	–	–	–	–	–	–	1	1	1	1	1	1. 5

1HP, 1 month of daily rifapentine plus isoniazid, 3HP, 3 months of weekly rifapentine plus isoniazid; 3 months of daily rifampicin monotherapy; 6H or 9H, 6 or 9 months of daily isoniazid monotherapy; 6L fx, 6 months of daily levofloxacin monotheraphy; dt, dispersible tablet; FDC, fixed dose combination; kg milligrammer; mL, millilitre; tab, tablet

Please note different weight bands are used in the two parts of this table; a process of weight-band harmonization is on-going

[a] Solution with a concentration of 10 mg/mL (one 100 mg isoniazid dispersible tablet in 10mL water)

[b] A triple bill combination of isoniazid 300 mg + pyridoxine 25 mg _ sulfamethoxazole 800 mg + trimethoprim 160 mg (scored) can be used for people with HIV

[c] A quality of 0.5 can be achieved by adding a 150-mg capsule of rifampicin

[d] Solution with a concentration of 15 mg/mL (one 150-mg rifapentine dispersible tablet in 10 mL water

[e] For indiduals aged < 13 years

Table 56: TPT dosing by body size

TPT regimens and drug formulations	No. of tablets or quantity of solution by body weight band								
	4-7.9 kg	8-11.9 kg	12-15.9 kg	16-24.9 kg	25-29.9 kg	30-34.9 kg	35-49 kg	50-64.9 kg	≥ 65 kg
Six or nine months of daily isoniazid monotherapy (6H or 9H)									
Isoniazid 100 mg dt	0.5 (0.5 mL[a])	1	1.5	2	–	–	–	–	–
Isoniazid 300 mg tab[b]	–	–	–	–	0.5	1	1	1	1.25
Four months of daily rifampicin monotherapy (4R)									
Rifampicin 150 mg cap	–	–	–	–	2	3	4	4	5
Rifampicin 300 mg cap[c]	–	–	–	–	1	1.5	2	2	2.5
Three months of daily rifampicin plus isoniazid (3HR)									
Isoniazid 300 mg tab	–	–	–	–	0.5	1	1	1	1.25
Rifampicin 300 mg cap[c]	–	–	–	–	1	1.5	2	2	2.5
Rifampicin 75 mg and Isoniazid 50 mg FDC dt	1	2	3	4	–	–	–	–	–
Rifampicin 150 mg and Isoniazid 75 mg FDC dt	–	–	–	–	2	3	4	4	5

Note: For 3HP regimen, when Rifapentine 150 mg formulation or individual molecule of Isoniazid and Rifapentine are not available, a 3HR (50/75 mg) regimen will be used for children who are less than 25 kg. For children and adults whose weight is>25 kg, 2 tablets of 3HP (300/300 mg) for body weight band 25-29.9 kg, 2.5 tablets for 30-34.9 kg and 3 tablets for those above 35 kg (see table below)

Table 57: Dosing of DS-TB TPT regimens for HIV not infected when Rifapentine 150 mg or individual molecules of Isoniazid and Rifapentine are not available

Group	TPT Regimen	Dosing	
		Weight	HR (50/75)
Children less than 25 kg	3HR (50/75)	4-7.9	1
		8-11.9	2
		12-15.9	3
		16-24.9	4
		Weight	HP (300/300)
Children and adults >25 kg	3HP (300/300)	25-29.9	2
		30-34.9	2.5
		>35	3
		Weight	Lfx (100 d.t)
Children <30 kg	Lfx (100) dispersible tablet (d.t)	3-5.9 (<3Mth old)	0.5
		3-5.9 (<3Mth old)	1
		6-9.9 (<6Mth old)	1
		6-9.9 (>6Mth old)	1.5
		10-14.9	2
		15-19.9	2.5
		20-24.9	3
		25-29.9	3.5
		Weight	Lfx (250) tablets
Children <20 kg	Lfx (250)	3-5.9 (<3Mth old)	0.25 (2.5 ml)*
		3-5.9 (<3Mth old)	0.5 (5 ml)*
		6-9.9 (<6Mth old)	0.5 (5ml)*
		6-9.9 (>6Mth old)	1 (10 ml)*
		10-14.9	1 (10 ml)*
		15-19.9	1.5
		Weight	Lfx (500) tablets
Children and adults > 25 kg	Lfx (500)	25-29.9	1
		30-34.9	1
		35-39.9	1
		40-44.9	1
		45-49.9	1
		>50	1.5

*250 mg Lfx tablet is to be used when child friendly formulation of 100 mg dt is not available. The 250 mg tablet is to be crushed and the powder is dissolved with 10 ml of clean water.

Table 58: TPT regimens and dosing table for PLHIV

<table>
<tr><th>Population Group</th><th>Preferred Regimen</th><th>Alternative Regimen</th></tr>
<tr><td>Individuals
≥ 12 years and ≥ 25kg</td><td>3HP*
Weekly Isoniazid plus Rifapentine for 3 months (Rifapentine 300mg/ Isoniazid 300mg per tablet, 12 doses)
3 tablets weekly plus 25 or 50 mg plus Vitamin B6 weekly</td><td>1HP (when available)
Daily Isoniazid plus Rifapentine for 1 month
Dosage: 300 mg of Isoniazid and 600 mg of Rifapentine daily plus 25 mg of Vitamin B6 daily</td></tr>
<tr><td>Children <14 years or Weight < 30 kg</td><td>6H
6 months of daily isoniazid plus Vitamin B6 25 mg daily
Dosing
<table><tr><th>Age</th><th>Dosage</th></tr><tr><td><10 yrs</td><td>10 mg/kg/day</td></tr><tr><td>>10 yrs</td><td>5 mg/kg/day</td></tr></table></td><td>3HP/1HP may be used for ³ 2 years old when a Child-friendly formula is available.</td></tr>
<tr><td>Pregnant women</td><td>6H
6 months of daily isoniazid plus Vitamin B6 25 mg daily
(dosing: 5 mg/kg/day, maximum dose 300 mg/day)
PNP prophylaxis for INH-containing regimen: Vitamin B6- 10-25 mg/day</td><td></td></tr>
</table>

3HP is not recommended for the following individuals.

- PLHIV who are taking antiretroviral medications with clinically significant or unknown drug interactions with Rifapentine
- People are presumed to be infected with isoniazid (INH/H) or rifampicin (RIF/R) resistant *M. tuberculosis*.

Note: In infants receiving NVP for prevention of maternal-to-child HIV transmission 6H should be the preferred regimen for TB prevention. Further, caregivers of exposed infants who have completed PMTCT should be counselled that if their infant's HIV status were to become positive, their TB preventive therapy may need to be changed from 3HR to avoid drug interactions.

Which TBI treatment regimen option to give?

Providers should choose the appropriate regimen based on the following:

- Potential for drug-drug interactions
- Age
- Pregnancy status
- Drug susceptibility results of the presumed source case if known
- Coexisting medical conditions
- Adherence status

Ineligibility for TPT

- Active TB
- CLHIV <12 months with no history of TB contact
- Acute/ chronic liver disease
- Excessive consumption of alcohol (defined as alcohol intake of >21 units per week for men/boys or 14 units per week for women/girls)
- One unit of alcohol equals 10ml or 8g of pure alcohol. It can be measured by using the following formula. Strength (alcohol by volume or ABV) x the volume of the drink (in milliliters)/1,000 = the total number of units in a drink.

For example, to work out the number of units in a pint (568ml) of strong lager beer (ABV 5.2%):

5.2 (%) x 568 (ml) ÷ 1,000 = 2.95 units

- Peripheral neuropathy grade 2 or above:
  - ✓ Grade 1: Tingling but no neurological deficits.
  - ✓ **Grade 2: Some sensory alterations or weakness.**
  - ✓ **Grade 3: Interfering with the activities of daily living.**
  - ✓ **Grade 4: Life-threatening and disabling paralysis.**

Repeat Course of TPT

The exact duration of TPT durability is not known. A repeat course of TPT should be considered among HIV-positive or HIV-negative persons who previously completed a course of TPT but have been thereafter a household or close contact of a TB patient after careful assessment of the intensity of exposure and balance between benefits and harms should guide the decision to administer a repeat course of TPT

11.9 Concerns of drug-resistant with large-scale use of TPT

Multiple trials have failed to find scientific evidence of a significant association between TB drug resistance and the use of isoniazid or rifamycin for TPT. Nonetheless, **active TB disease must be excluded before TBI treatment is initiated,** and **regular follow-up** is required to ensure early identification of people who develop active TB while receiving TB preventive treatment.

1. **ALL** patients should be informed of the importance of visiting their healthcare provider immediately, should they develop signs and/or symptoms of active TB.
2. If a person on TBI treatment develops symptoms suggestive of TB disease, promptly evaluate for TB including drug susceptibility test.
3. If active TB disease is confirmed, discontinue TBI treatment and promptly start treatment for TB disease.

Key point: Common beliefs that large-scale use of TPT will fuel drug resistance are not supported by reliable evidence and represent the type of barriers that withhold vulnerable populations from access to interventions that can protect them and their communities from avoidable TB disease and death.

11.9.1 Evidence of drug resistance after IPT

(a) Isoniazid resistance after TPT

In a systematic review of 13 published studies since 1951, which included 18 095 people on IPT and 17 985 controls, there was no suggestion of increased risk of isoniazid-resistant TB after IPT; these results were similar when stratified for HIV. In addition, in the Thibela study cohort from South Africa, proportions of TB episodes with drug resistance among patients who had received IPT did not significantly differ from those in comparison groups.

(b) Rifamycin resistance after TPT

In an analysis of six randomized control trials of rifamycin-containing regimens for TPT versus active control or placebo showed that the occurrence of rifampicin-resistant cases was 0.09% in 6808 individuals receiving rif-based TPT vs 0.01% in 7415 individuals receiving alternate regimens (RR = 3.45, 95%CI 0.72–16.56; P = 0.12). In three of these studies where intermittent rifamycin-based TPT was used, there were two cases of rifampicin resistance among 4673 individuals on intermittent rifamycin-containing regimen compared to one case with rifampicin resistance among 4427 individuals from control regimens (RR = 3.89; 95%CI 0.44–34.56; P = 0.22). In placebo-controlled trials, there were no cases of rifampicin resistance among participants receiving rifamycin-containing regimens whereas several cases of rifampicin resistance occurred in those on placebo (RR 0.20, 95% CI 0.02–1.66) (130).

11.10 Drug interaction, safety in pregnancy and toxicity of TPT regimens

- Regimens containing rifampicin should be prescribed with caution to people living with HIV who are on ART because of potential drug interactions.
- These regimens should not be administered to people receiving protease inhibitors or nevirapine.

The safety of rifapentine use in pregnant women and children under two years old remains unknown. Hence rifapentine containing regimens (i.e. 3HP and 1HP) are not yet recommended for these groups.

Inibitors, NVP = nevirapine, P = rifapentine, Pla = protease inhibitors, R =rifampicin, RAL = ralteegravir, TAF = tenofoir alafenamide, TDF = tenofovir disoproxil fumarate.

(a) Average available adult formulations: H-300 mg/150 mg, R-300 mg, P-150 mg.
(b) For women living with HIV (as well as HIV- negative) receiving rifamycin-based TPT and oral contraceptives, consider additional barrier contraception methods to prevent pregnancy.
(c) One randomized trial has shown high risk of poor birth outcomes for mothers taking isoniazid during pregnancy; however, several other studies have shown benefits of IPT; hence caution is required.
(d) Bleeding attributed to hypoprothrombinaemia has been reported in infants and mothers taking isoniazid during pregnancy. Vitamin K is recommended for both the mother and the infant postpartum if rifampicin is used in the last few weeks of pregnancy (FDA).
(e) Indicate that drug interaction has been studied in adults and not children; applies to adults taking DTG or RAL only.

11.11 Monitoring and management of Adverse events

It is important to regularly screen for AEs during regular follow-ups (at a health facility or in the community by trained community cadre, see in community-based TPT delivery session) in person or by phone when someone on TPT cannot come in (e.g. due to work, school schedule, or travel restrictions). The documented adverse events are listed in Table 59.

Table 59: Documented adverse events with drug used for TPT

Drug	Known Adverse Event	Uncommon Adverse Event
Isoniazid	Asymptomatic elevation of serum liver enzyme titres Hepatitis Peripheral neuropathy (paraesthesia, numbness, limb pain) Skin rash Sleepiness and lethargy	Convulsions Pellagra Arthralgia Anaemia Lupoid reactions
Rifampicin	Gastrointestinal reactions (abdominal pain, nausea, vomiting) Hepatitis Generalized cutaneous reactions Thrombocytopenic purpura Discolouration of body fluids	Osteomalacia Pseudomembranous colitis Pseudo adrenal crisis Acute renal failure Shock Haemolytic anaemia Influenza-like syndrome Hypoprothrombinemia
Rifapentine	Gastrointestinal reactions (abdominal pain, nausea, vomiting) Hypersensitivity reactions (influenza like symptoms) Hepatitis Discoloration of body fluids	Hypotension or syncope Decrease in white and red blood cell counts Decreased appetite Hyperbilirubinemia Hypoprothrombinemia

Drug	Known Adverse Event	Uncommon Adverse Event
Levofloxacin	Diarrhoea Nausea and bloating Arthralgia	Inflamed or torn tendons Muscle pain or weakness Peripheral neuropathy Mood or behaviour changes Insomnia Prolongation of the QTc interval Altered taste and smell

Clinicians should assess the severity of adverse events, and underlying causes and plan for management strategies by applying the following steps.

- How severe is the adverse event (mild, moderate, severe)?
- How serious is the event (likely to lead to death or life-threatening, hospitalization or prolongation of hospitalization required; persistent significant disability; congenital anomaly)?
- What should immediate management consist of (reassurance, symptomatic relief, discontinuation of TPT or intervention to avert a severe outcome)?
- What is the underlying cause (the drug, other factors)?
- How will the adverse event affect future adherence (tolerability, consideration of substitution with an alternative regimen)?
- What is the next step (continue or restart, substitute, follow up and reassess definitive halt)?
- Recommended management strategies for adverse events of TPT are as in Table 60

Table 60: Management strategies for adverse events of TPT

Adverse event	Responsible drug	Management
Flu-like signs and symptoms	Rifapentine, rifampicin	• Advise to stay hydrated by drinking plenty of water and juice. • Prescribe Paracetamol which may be taken every 4 to 6 hours. Leave at least 4 hours between doses. (Dosage 500mg tab for adults, for children 3 months- 6 years 120mg/5ml suspension, children 6 years of age and adults 250mg/5ml suspension.) • If severe and not tolerated to 3HP/3HR regimen, consider switching to an alternate regimen (6H)

Adverse event	Responsible drug	Management
Nausea and vomiting	Rifapentine, rifampicin, isoniazid	• Prescribe 10 mg of metoclopramide bid (twice a day) or tid. • Advise patients to stay hydrated by drinking plenty of water and juice. • Avoid spicy and greasy foods. • Prescribe oral rehydration solution if mild dehydration is present.
Hepatotoxicity	More with INH than rifapetine and rifampicin)	• If people on TPT have signs and symptoms of hepatotoxicity, perform LFT. • If aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) are >3 but <5 times upper limit of normal (ULN) without signs and symptoms of hepatitis, continue TPT and repeat AST and ALT weekly. • If AST and/or ALT >3 times ULN with signs and symptoms of hepatitis or if AST and/or ALT >5 times ULN with or without signs and symptoms of hepatitis, stop TPT and do not reintroduce.
Peripheral neuropathy	Isoniazid	• Use brief peripheral neuropathy scoring system (BPNS) to screen and assess the severity of peripheral neuropathy. • If mild: give 100 to 150 mg of pyridoxine in adults and 50 mg in children. • If not better or worsened with an increased pyridoxine dose, stop the H-containing regimen and consider switching to 4R.
Skin hypersensitivity reaction	Rifampicin, Rifapentine, Isoniazid	• If itchiness and localized mild rashes occur, give calamine lotion or steroid cream to apply bid on the affected area; chlorpheniramine 8 mg tid or bid orally may be given. • If itchiness, generalized rashes, or swelling of oral or nasal mucosa with or without fever, withhold TPT. • For mild or moderate hypersensitivity reaction, desensitization may be attempted with a low dose re-challenge once the rash resolves starting with isoniazid alone at 1/6 normal dose on day 1, then full dose on day 2 and subsequently monitoring closely, especially on the completion of antihistamines (at least weekly to 2-weekly for the first month then monthly). • If a rash does not recur, continue isoniazid monotherapy ensuring that the client gets a total of 180 doses.

Adverse event	Responsible drug	Management
		If rash recurs, do not rechallenge with isoniazid. Alternative regimen 4R may be considered by re-introduction with a low dose (1/6 of the dose) on day 1 and then a full dose on day 2. • If desensitization cannot be performed, an alternative regimen (e.g. 4R or 6H) may be considered • Never reintroduce after severe hypersensitivity reaction or Stevens-Johnson syndrome.
Orange-red discoloration of body fluid (tear, saliva, urine, milk, urine)	Rifampicin, rifapentine	• Reassure that it is just the staining from a drug in the regimen and is harmless. Advice to continue TPT.
Any occurrence of TB signs and symptoms		• Investigate for active TB disease or other diseases. • If there is no active TB disease, continue TPT. • If active TB disease, stop TPT and provide DS-TB or DR-TB treatment, as appropriate.

How to manage TPT regimen if switched for severe AE

- Prescribe the new regimen to continue for the proportion of time remaining to complete treatment.

An example of the calculation of time remaining after switching TPT regimen for severe AE

A person who completes 3 doses of HP (i.e., 3 doses out of 12 doses), has finished 25% of the 3HP regimen and needs 75% of the total doses to complete a full course of TPT. This is equivalent to 4.5 months (6 months-1.5 months. 135 daily doses) of the 6H regimen. Therefore, if this person switches from 3HP to 6H at 3 weeks, another 4.5 months of daily isoniazid is required after stopping 3HP.

11.12 Support to TPT Adherence

Adherence to the full course and completion of treatment are important determinants of clinical benefit to individuals and to the success of programmes. Interventions to ensure adherence and completion of treatment should be tailored to the specific needs of risk groups and the local context. These include but are not limited to offering community-based TPT (see next session) and proper individual and group education of patients (and treatment supporters where applicable) on:

- Benefits of TBI treatment.
- Duration of TBI treatment.
- How medication is taken: dose, time etc.
- What to do in the event of side-effects (see above).

- Importance of DOT (by a parent, treatment supporter, lay health worker or skilled health worker where feasible), especially for children.
- Importance of adherence aids such as cell phones, TV, calendar or radio reminders: The client should select one.
- Importance of appointment keeping.

Messages to motivate adherence should be repeated when patients come for refills.

Fixed-dose combinations such as co-trimoxazole plus isoniazid plus B6 and isoniazid plus rifampicin, Isoniazid and rifapentine, **can be used where possible** to reduce the number of pills to be taken.

11.13 TPT completion and management of TBI treatment interruption

It is required to complete at least 80% of the recommended dosage whereas 90% for the 3HP regimen. In the event of treatment interruption, treatment duration may be extended to a maximum of an additional 33% of additional days to administer compensatory doses (see Table 61).

Table 61: Minimum requirement of TPT completion (doses) and extended duration

TPT regimen	Total duration (in month)	Expected No. of doses	80% of recommended doses (days)	Extended time for treatment completion (days) Total duration +33% additional time
3HP (weekly)	3	12	10	112
3HR (daily)	3	84	68	120
6H (daily)	6	182	146	239
4R (daily)	4	120	96	160
1HP (daily)	1	28	23	40
6Lfx	6	182	146	239

In the event of a missed dose or treatment interruption, follow the guide in Table 62 below

Table 62: Management of TPT interruption or missed dose

TPT regimen	Duration of treatment interruption	Next Steps
3HP	1 weekly dose missed	If the missed dose is remembered within the next 2 days, continue to take the remaining doses according to the original schedule. 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.

TPT regimen	Duration of treatment interruption	Next Steps
	More than 1 weekly doses missed	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. If ≥ 4 weekly doses are missed, consider restarting the full TPT course. If an individual has difficulty adhering to a weekly routine, consider dis continuing 3HP and offering an alternative regimen with daily dosing.
1HP	Less than 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)
	More than 7 doses missed	If < 7 consecutive doses were missed, consider restarting the complete course of the 1HP regimen. If > 7 doses were missed intermittently, continue and complete the remaining doses, thus prolonging the total treatment duration to a maximum of 6 weeks (42 days from starting TPT)
3HR, 4R, 6H, 6Lfx	Less than 2 weeks	Resume TPT and add the number of missed doses to the total treatment duration. 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.
	More than 2 weeks	If treatment interruption occurs after more than 80% of doses in the regimen have been taken, continue and complete the remaining treatment as per the original plan. 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. If < 80% of doses in the regimen were taken, and the treatment course cannot be completed within the expected time, consider restarting the full TPT course. A shorter regimen would be preferable.

11.14 PLHIV participating in Differentiated Service Delivery (DSD) models

DSD participation should not exclude eligible PLHIV from receiving TBI treatment.

- TBI treatment must be incorporated into facility DSD models including fast-track, treatment clubs, teen clubs etc. Treatment initiation should be conducted by skilled health workers.
- TBI treatment may be incorporated into community models as follows:
  - ✓ Initiation and refill as part of community outreach.
  - ✓ Initiation and refill for community ART groups (CAGs) of not more than 3 people to ensure clinical visits at least every 3 months following TBI treatment initiation.
  - ✓ Align TPT refill with the ART refill schedule

11.15 TPT Outcomes

Individuals who are initiated on TBI should be monitored throughout treatment until they are evaluated at the end of treatment. Table 63 shows the definitions of TBI treatment outcomes.

Table 63: TPT treatment outcomes definition

Outcome	Definition
Completed treatment	Received the full course of daily INH within 6 to 9 months or weekly Rifapentine-INH or daily Rif-INH within 3-4 months.
Lost to follow up	▪ Has taken isoniazid monotherapy. then interrupted for ≥ 60 days or ▪ Has taken Rifampicin and Isoniazid. then interrupted for >30 days or ▪ Has taken Rifapentine and Isoniazid. then interrupted for >30 days.
Died	Death from any cause while on TBI treatment.
Failed treatment	Develop active TB while on TBI treatment.
Transferred out	Transferred to another facility to continue treatment.
Treatment discontinued	Treatment is stopped by a healthcare worker due to adverse effects or any other reason.

11.16 Community-based care and support for people taking TPT

- Trained community cadres will provide care and support to people taking TPT with:
  - ✓ Education and counselling about TPT
  - ✓ Refilling TPT drug supply
  - ✓ Monitoring adverse events and TB signs and symptoms and
  - ✓ Prompt referral if there is any occurrence of adverse events or TB signs and symptoms
- Health facility staff will convey the list of clients initiated on TPT and the copy of their TPT cards to community cadres
- Community cadres will visit clients' houses every month. During the visit, the following tasks will be carried out
  - ✓ Checking any occurrence of potential adverse events using the checklist (see Table 64 below)
  - ✓ Checking any occurrence of TB signs and symptoms
  - ✓ Measure weight for those <25 kg for whom adjustment may be needed if there is substantial weight gain. Inform health facility staff if the weight band crosses over the initial body weight to adjust the dosage.
  - ✓ Health education and adherence counselling include pill-counts checking.
  - ✓ Counsel and encourage clients to continue taking TPT if there is any treatment interruption that occurs in less than 1 month.
  - ✓ Refer clients to health facilities promptly in the event of:
    - Clients having adverse events
    - Clients who interrupted TPT for more than 4 weeks

Table 64: The checklist for monitoring adverse events and TB signs and symptoms

Checklist	Yes	No
Flu-like signs and symptoms: Fever, headache, runny nose, joint pain, etc		
Nausea and vomiting		
Abdominal pain, and yellow colouration of eye and skin		
Burning sensation, tingling, and numbness in the feet and/or hands		
Skin itchiness, rashes		
Any occurrence of TB signs and symptoms (cough, fever, weight loss, night sweat)		
Any "Yes", refer to health facility		
If referred to health facility, specify the name of the health facility		

11.17 Recording, reporting and monitoring of TPT implementation

At the health facility level, record:

- The screening of individual clients in the CMIS or TB Screening Register
- Contact Investigation (CI) in the CMIS or CI Register
- TPT initiation
- Follow-up includes treatment outcomes in the CMIS or TPT treatment card and TPT register

At the facility level a cascade analysis should be conducted weekly or at least biweekly as per the cascade below (table 65) and action should be taken if there is any leakage across the cascade (e.g. identifying the contacts that are not traced and screened, intensifying contact investigation and tracing eligible clients for TPT in collaboration with community cadres).

The national and regional TB/HIV team should conduct at least monthly data analysis and produce reports using cascade analysis, identify contributing factors to leakage across the cascade and take quality improvement activity as required.

Table 65: TPT cascade for regular review and timely action

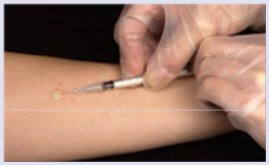
Parameter	No
Total number of TB cases diagnosed	
Number of BC-PTB and CD-PTB cases	
Number of index cases identified for contact investigation	
Number of contacts (as enumerated by identified index cases)	
Number of contacts screened for TB	0

Number of contacts who screened negative for active TB	0
Number of contacts tested for TBI	0
Number of contacts tested positive for TBI	
Number of contacts eligible for TPT (for population who do not need TBI test: e.g. PLHIV, Children <5 y.o)	
Number of contacts initiated TPT	0
Number of contacts who completed TPT	0

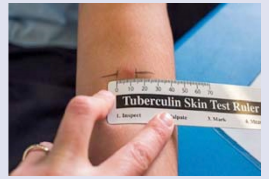
11.18 Performing TB Infection Tests

11.18.1 Performing Tuberculin Skin Test

Tuberculin skin tests can be performed using conventional purified derivative (PPD) reagents or a new TB antigen-based skin test (TBST). Either 5-TU (Tuberculin Unit) or 2-TU PPD can be used for TST or TB antigen reagent. The test is performed by injecting 0.1 mL of PPD intradermally into the inner surface of the forearm with a tuberculin syringe, the needle bevel facing upward. If the injection is done correctly, it will produce a pale elevation of the skin (a wheel) from 6 to 10 mm in diameter. The skin reaction should be read between 48 and 72 hours and measured in millimeters of the induration (palpable, raised, hardened area or swelling) but not erythema (redness). The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis). The induration of ≥10 mm is considered a positive result generally, but ≥5 mm for those with immunocompromise such as severe malnutrition or advanced HIV.



Administration and reading of TST (Source: CDC.gov)



The new TBST test is similar to the conventional TST with intradermal injection of mycobacteria antigen, namely early secreted antigenic target 6kD (ESAT-6) and culture filtrate protein 10 (CFP-10) antigens that are specific to M*tb* and stimulate T-cell release of IFN-γ.

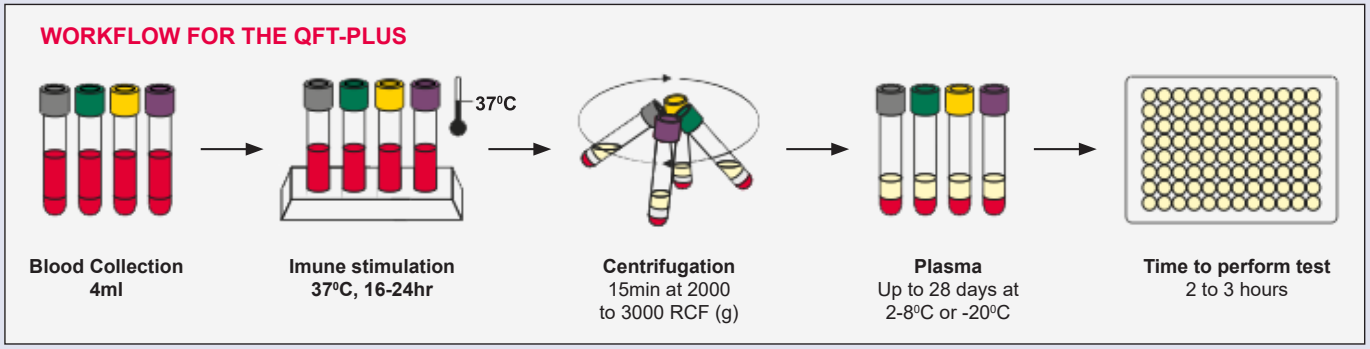
11.18.2 Performing IGRA Test

- Collect whole blood specimens into each of the four QFT-Plus blood collection tubes. The tubes differ by which antigens or controls have been dried onto the walls of the tube. Alternatively, blood may be collected in a single vacutainer tube that contains heparin as the anticoagulant and then transferred to the QFT-Plus blood collection tubes.
- The Nil tube adjusts for background (e.g. excessive levels of circulating IFN-γ or presence of heterophile antibodies). The IFN-γ level of the Nil tube is subtracted from the IFN-γ level for the TB Antigen tubes and Mitogen tube.
- The Mitogen tube is a positive control for the ability of the lymphocytes to produce IFN-γ and also serves as a control for correct blood handling and incubation.

- The TB1 tube contains long peptides from ESAT-6 and CFP-10 that are designed to stimulate IFN-γ production from CD4+ T-helper lymphocytes.
- The TB2 tube contains the same CD4 antigens of TB1 and an additional proprietary set of short peptides designed to stimulate IFN-γ production from CD8+ cytotoxic T lymphocytes.
- The contents of the QFT-Plus blood collection tubes must be thoroughly mixed with the collected blood to ensure that the antigens on the tube walls are completely dissolved.
- Then incubate the tubes in an upright position at 37°C for 16 to 24 hours, during which time the immune stimulation occurs.
- The samples are then centrifuged, the plasma is removed and the amount of IFN-γ (IU/ml) is measured by ELISA.

11.18.3 Workflow of QTF-Plus Test

Figure 36: Workflow for the QFT plus



11.18.4 Interpretation of IGRA results (QuantiFERON GlodPlus)

A QFT-Plus assay is considered positive if the IFN-γ response to either TB antigen (TB1 or TB2) tube is significantly above the Nil IFN-γ IU/ml value; if the Nil value is ≤ 8.0 IU/ml and either TB antigen tube minus the Nil IFN-γ value is ≥ 0.35 IU/ml and at least 25% of the Nil value, irrespective of the mitogen minus Nil value. The plasma sample from the Mitogen tube serves as an IFN-γ positive control for each specimen tested. The test is considered indeterminate if the mitogen response is <0.5 IU/ml, together with both TB antigen responses <0.35 IU/ml or ≥0.35 IU/ml and <25% of Nil value, or the Nil response >8.0 IU/ml.

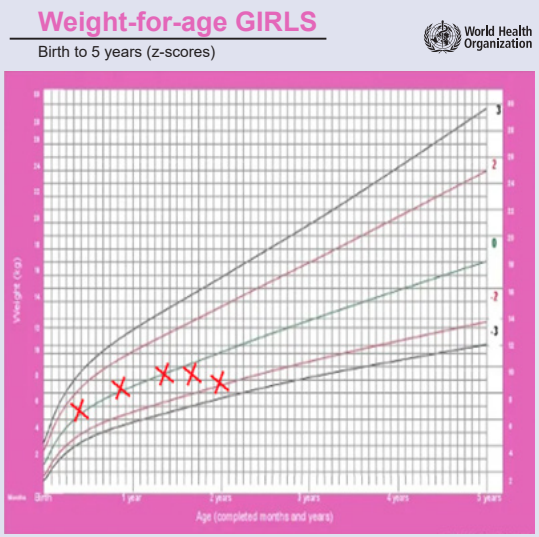
Table 66: Interpretation of IGRA results (QuantiFERON GlodPlus)

Results	Nil	TB Response	Interpretation
Positive	≤8.0	TB1 and/or TB2 minus Nil ≥0.35 and ≥25% of Nil	TBI is likely
Negative	≤8.0	Mitogen minus NIL <0.5, TB1 and TB2 minus NIL <0.35 or ≥0.35 and ≥25% of Nil	TBI is not likely
Indeterminate	>8.0 ≤8.0	Any TB1 and TB2 <0.35 or ≥0.35 and ≥25% of Nil and Mitogen minus Nil <0.5	The likelihood of TBI cannot be determined

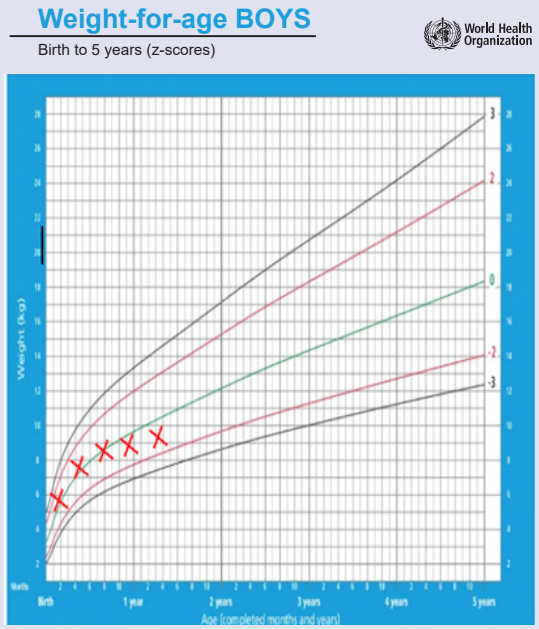
Note: The NTP may introduce an Interferon-Gamma Release Assay (IGRA) in the future. The IGRA test measures the response of immune cells to simulated TB proteins when they are mixed with a small amount of whole blood. Currently, there are two types of commercially available and WHO-recommended IGRA tests: QuantiFERON(R) TB Gold in Tube and T-SPOT(R) TB.

11.19 Example of Drawing Growth Curve

Figure 37: Child Growth Monitoring Charts



2 years old girl with 14kg weight = -2 Z score (underweight)



A 1.5 year old boy on failure to thrive (poor weight gain underweight)

WHO Child Growth Standards

CHAPTER 12
TB INFECTION PREVENTION AND CONTROL

12.1 Introduction

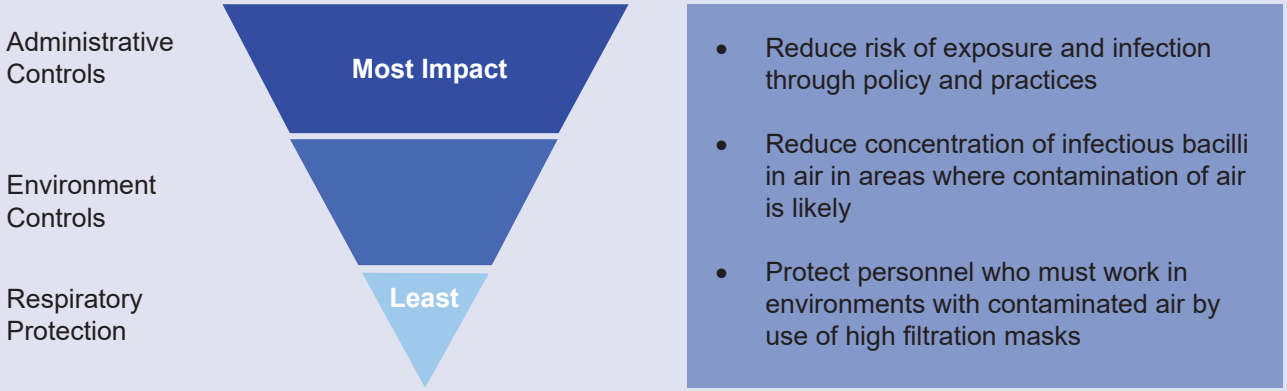
M. tuberculosis (MTB) can be transmitted in any setting, healthcare facilities, congregates (e.g., correctional services, homes for the aged, orphanages) and community settings. The source of transmission is from individuals with undiagnosed TB or not taking appropriate treatment for active TB disease. Individuals having cough, cavitation lesions in the Chest X-ray, bacteriologically confirmed TB and not on TB treatment or ineffective treatment are at higher risk of transmission. People with clinically diagnosed PTB and EP-TB carry minimal risk of transmission. However, performing intrusive aerosolized procedures on such individuals increases the risk of transmission.

The extent of transmission depends on the bacilli load in the environment, the length of exposure and the magnitude of ventilation.

12.2 TB infection prevention and control measures

TB infection prevention and control (TBIPC) is the combination of measures aimed at minimizing the risk of transmission of TB within populations in any setting. There are 3 major strategies of TB Infection Prevention Control (IPC) measures as illustrated in Figure 38 below with the hierarchal impact in order.

Figure 38: The major strategies of TB IPC measures



12.2.1 Administrative Control Measures

The main objectives of administrative measures in healthcare facilities are:

- Prevention from the generation of TB droplet nuclei
- Prevention of staff and patients' exposure to TB
- Implementation of rapid diagnosis and appropriate treatment of TB

The administrative control measures include:

- Formation and regular convention of infection control committees in high-volume facilities (e.g. tertiary and regional referral hospitals, health centers) or at least having a designated IPC focal in a low-volume facility (e.g. clinic)
- Development of IPC implementation plan and regular assessment of the plan at least annually (see Table 67 IPC implementation plan and risk assessment template)
- Regularly conduct in-service training on TBIPC to healthcare workers including support staff
- Provide regular health education on TBIPC to clients including cough etiquette
- Screening to identify presumptive TB clients and referral for TB workout and investigation at all service entry points and offer TPT to those eligible
- Segregation of individual with potential to transmit TB disease to others in both out-patient service departments (e.g. fast tracking of presumptive TB clients or clients with active TB disease) and in patient service department (e.g. having designated TB ward or cubicle for TB patients)
- Patient should be segregated based on infectiousness, type of drugs-resistance TB and conversion status (smear for DS-TB patients and culture for DR-TB patients)
- Promptly diagnose and initiate treatment for individuals diagnosed with active TB disease
- Regular screening of health care workers by questionnaires twice a year and by Chest Xray annually
- Pregnant and HIV-positive staff should be relocated to sections within the department where the risk of TB exposure is the least
- Ensure availability of resources and materials required for IPC plan implementation (e.g. PPE, laboratory reagents, drugs and consumable supply, IEC materials, etc.)

12.2.2 Environmental Control Measures

The second level of hierarchy is the use of environmental control measures. The main objective is to prevent or minimize the concentration of droplet nuclei resulting in minimum nosocomial transmission of M. tuberculosis in an environment and includes the following measures:

- Improving ventilation (natural, mechanical, mixed methods)
- Cleansing of upper room air which includes filtration of air droplets using HEPA filters and disinfection of air particles using Germicidal Ultraviolet (GUV)

12.2.2.1 Improving Ventilation

Improving ventilation dilutes the concentration of air droplets in room air by achieving the required air-exchange rate. There are three methods of ventilation:

- Natural ventilation
- Mechanical ventilation
- Mixed method ventilation

(a) Natural Ventilation

Natural ventilation relies on cross ventilation in a building designed for good air exchange; for example, the use of open doors and windows to bring in air from outside. Augmenting natural ventilation can be applied to any setting by having:

- As much as opened airspace in OPD waiting areas,
- Operable windows in consultation rooms, OPD and in-patient service department (IPD) areas
- Installing fans may be used to facilitate air mixing and movement of air for easy distribution.

Healthcare workers should be seated against the wind direction. If the direction of the airline is unknown, staff should sit near the fresh air source and clients should sit near the exhaust location (see Figure 39).

(b) Mechanical Ventilation

Mechanical ventilation refers to the use of equipment with sufficient power to facilitate air entry into and exhaust from the building. Mechanical ventilation is useful in seeing where there is insufficient natural ventilation. Mechanical ventilation consists of central and local exhaust ventilation.

Central ventilation is the installation of a negative air pressure system in a health facility, especially in IPD (e.g., TB ward, TB hospital) see Figure 40. Local exhaust ventilation is installing an exhaust ventilation system in a specific area (e.g., a sputum booth) see Figure 41 for an example.

Figure 39: Illustration for Proper Sitting Arrangement for HCW and Clients

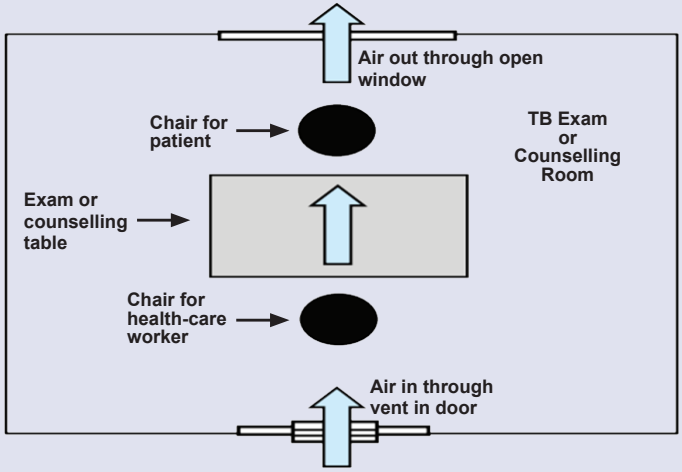


Figure 40: Central Ventilation in a TB Ward

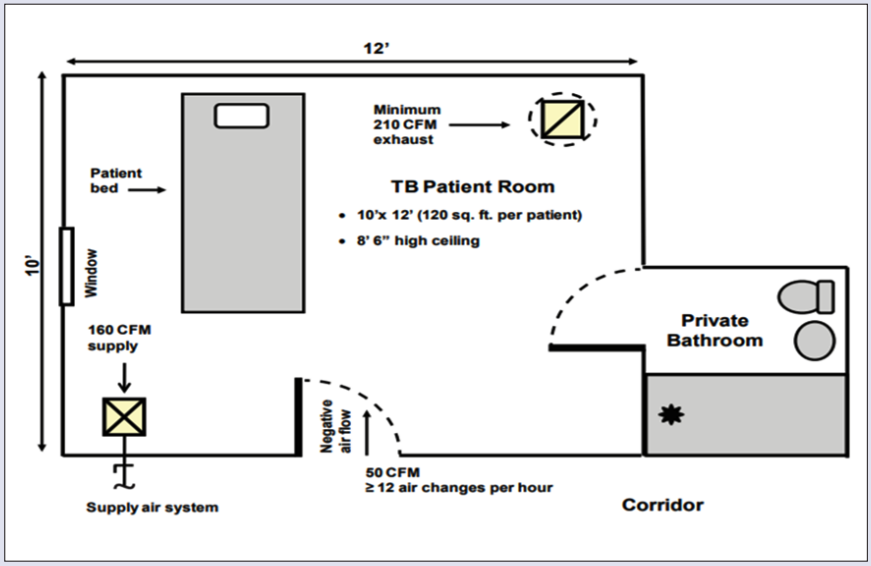
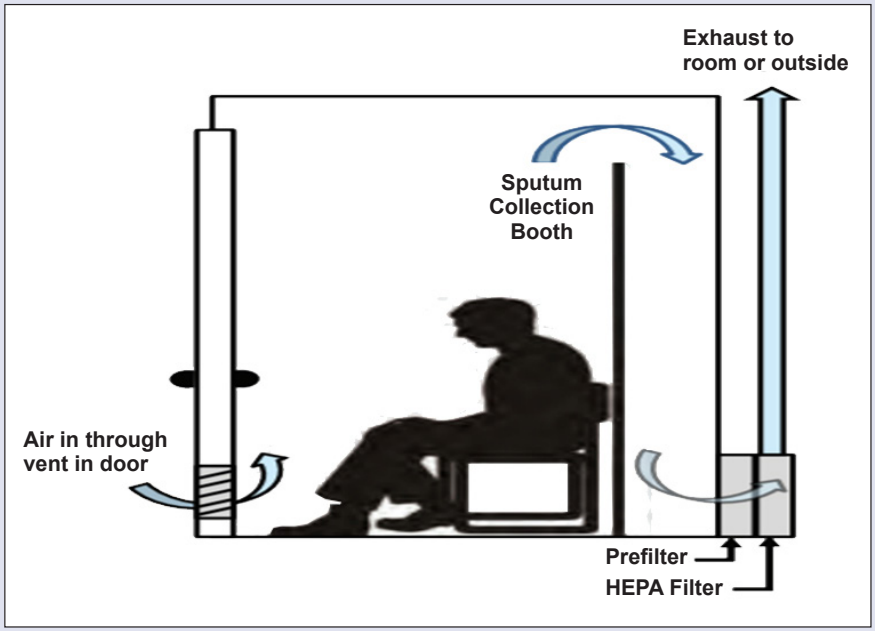


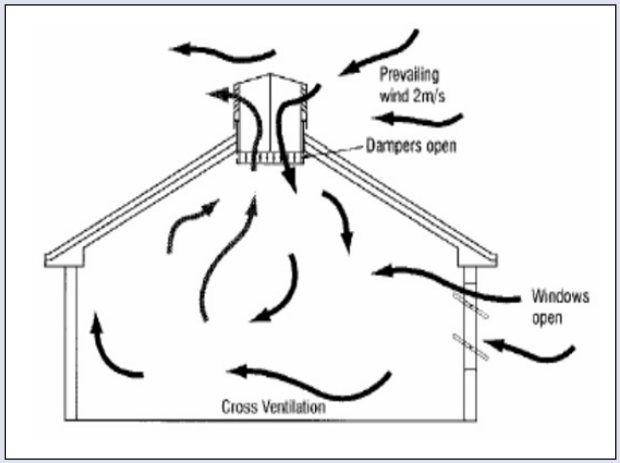
Figure 41: Local Ventilation in Cough Booth



(c) Mixed Method Ventilation

A ventilation system that combines the use of both mechanical and natural ventilation is achieved by installing a wind turbine (Whirly Bird). These devices pull warmer air from the ceiling and push it outside enhancing ventilation without any electricity (see Figure 42). The whirlybird is a suitable option where the electricity supply system is not reliable. This is the most feasible method for Eswatini compared to the above-sophisticated methods.

Figure 42: Whirly bird installed on the rooftop of a health facility

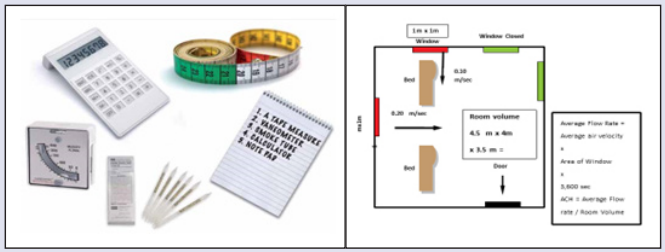


12.2.2.2 Measurement of air-exchange rate

Air Change Per hour (ACH): refers to the total volume of air that flows through a room in 1 hour (cubic meters per hour) divided by the room volume in cubic meters. This is the number of times that the total air volume in a room or space is completely removed and replaced in an hour. The required level of ACH is 12 units per hour.

Figure 43: Illustration of ACH measurement

Measuring ACH



Calculation of ACH

A = Q / V

- Where A is air changes per hour
- Q is the air volume that flows through the room in 1 h
- V is the volume of the room

12.2.2.3 Cleansing of room air and filtration of air-droplets

The air droplets can be filtered by using a HEPA filter. The filters are useful in a setting where a cross-air exchange system cannot be installed (e.g. Intensive care unit, dental clinic, operation theatre, etc.)

Figure 44: HEPA filter installed in a dental clinic

12.2.2.4 Germicidal Ultraviolet Light (GUV)

GUV is an air-cleaning technology that consists of the use of special lamps that give off germicidal ultraviolet irradiation (wavelength=254 nm). The lamps are used to inactivate/kill the tubercle bacilli contained in the droplet nuclei.

Overexposure to UV light can be harmful to the skin and eyes; lamps must be installed in the upper part of rooms or corridors. Regular, appropriate maintenance is essential to ensure GUV lamps are operating correctly.

Figure 45: GUV lights installed in a health facility

In conclusion, many environmental control measures are technologically complex and expensive and require regular maintenance. However, effective application of natural ventilation methods can reduce the risk of spreading M. tuberculosis.

12.3 Personal Respiratory Protection

Respiratory-protection control is the third level of TB infection control measures and consists of the use of personal respiratory equipment in situations that pose a risk of exposure to droplet nuclei. N95 respirators are recommended for HCWs and surgical masks for individuals who are TB presumptive or have TB disease.

Figure 46: Different types of medical respirators and surgical masks

Respirators

- Designed to filter out droplet nuclei from being inhaled by the health-care worker and other individuals.
- Should properly fit different face sizes and features.
- Should **NOT** be worn by the patient

Surgical Masks

- Designed to stop droplet nuclei from being spread (exhaled) by the patient.
- Should **NOT** be worn by the health-care workers

N95 Respirators are made of multiple layers of porous plastic in between and are not resistant to oil.

It filters at least 95% of droplet nuclei of 0.3-micrometer particle size. M. tuberculosis droplet size ranges from 1 to 5 micrometers in diameter.

Other Commonly used N95 Respirators are:

FFP2 **Filtering Face Piece class 2** – a respirator with a bacterial filtration efficiency of 94-95% when challenged with 0.3-micrometer particles.

For proper wearing and storage of respirators refer to figure 46. To ensure the right respirator size and sealing, fit testing is required and should be conducted annually for health workers.

In the absence of a fit test kit perform a basic N95 mask fit test on your own as per below:

- Put the mask on and hold your hands near the edges
- Breathe in and out and try to feel if there is air movement around the edges of the mask
- If you feel air leaking out from the edges of the N95, or if you are wearing glasses and they fog up it is not sealed, adjust the N95 and try again
- If you cannot get a tight seal, try a different size or model

Note: A well-fitting respirator is uncomfortable to use over prolonged periods of time should be used when undertaking risk-prone procedures and should never be used by patients.

N95 Usage – The use of the mask is a week unless it is damaged (e.g. loose, dirty, crushed or wet)

Storage – store/hang in a dry ventilated area

12.4 Special Settings

12.4.1 In health facilities

Special precautions will be observed for presumptive and TB patients in the following areas: laboratory, X-ray department, operation theatre, and ICU in health facilities

- All healthcare workers in these departments should wear N95 masks when offering services to individuals
- Fast track services to clients who are presumptive TB or TB patients to shorten the length of exposure
- Provide surgical masks for PTB patients to wear while accessing the services
- Postpone operation procedure for PTB for 2 weeks after TB treatment initiation if emergency intervention is not required. If emergency intervention (e.g. obstetric emergency) is required time segregation approach (e.g. scheduling infectious patients separately) can be applied for example at the end of the day while the patient is maintained in critical care to stabilize the condition

12.4.2 Admission of TB patients

- Consultations/admissions must be done in rooms with appropriate IPC measures
- Provide isolation wards for known TB patients/ presumptive TB patients if possible
- TB and DR-TB patients with smear or culture positive patients are infectious patients. Those with smear/culture negative or extra-pulmonary TB patients are not generally infectious, especially if they are in treatment.
- Drug susceptible and drug-resistant patient wards should be segregated to avoid cross-transmission
- Infectious patients should remain in the isolation room with the door closed and open windows
- Infectious patients should wear a surgical mask when outside the isolation room and exposed to other patients
- Patients should be educated on TB transmission, reasons for isolation and the importance of practicing cough etiquette
- Staff entering occupied isolation rooms should use respiratory protection devices
- Prioritize cleaning and disinfection of the rooms focusing on frequently touched surfaces and equipment near the patient

12.5 Transferring patients to specialists or emergency services

- HCW should collect the necessary history, investigations, and documents and have them on hand before calling the referring facility
- Call the facility and request the details of the specialist
- Contact the specialist who is supposed to take care of the patient and explain the condition of the patient and the reasons for referral
- Add more information and investigations on the referral as requested by the consultant/specialist.
- Attach another plain sheet on the referral form, if necessary, for more information

12.5.1 Transporting patients

- TB patients should not be denied ambulance services; they have the same rights as any other patient.
- TB patients should not be deprioritized (made lower/last priority) for ambulance services when there is a queue; they have the same rights as any other patient
- Transportation should follow the IPC guidelines, including opening of windows
- If available, an ambulance with the driver's compartment sealed off from the patient and HCW must be used
- Ensure that the TB patient being transported for a medically essential procedure wears a surgical mask
- Drivers, HCWs, and other staff who are transporting people with presumed or confirmed infectious TB disease must wear an N95 respirator
- Prioritize cleaning and disinfecting of the ambulance before and after use by each patient, regardless of TB status
- After use by a TB patient, the ambulance windows must be left open for at least 20 minutes to allow ventilation, before the next patient can be allowed to board

12.5.2 Dialysis, ICU and Theatre Services

- A TB patient should not be denied dialysis, ICU or theatre services irrespective of their infectious state.
- The referring facility and the specialist should agree on what needs to be done before referral.

- The specialist should prepare the necessary IPC measures whilst the patient is on the way as these services are deemed as an emergency.
- The TB patient should wear a surgical mask, while the specialist and other HCWs should wear N95 respirators.
- Designate dialysis, ICU and post-procedure isolation rooms for TB patients or other infectious diseases (lessons learnt from COVID-19). If there is no designated isolation room, a time segregation approach should be considered.
- In the labour room, identify a well-ventilated area to provide delivery service.
- Disinfect the theatre, as per normal theatre procedures, after use by TB patient.
- Wear N95 during intubation.

12.5.3 Discharge plan

- There should be a discharge plan and a system which links TB patients with other local health facilities for continued treatment and monitoring
- For in-patient settings, the health facility should coordinate a discharge plan with the patient started on TB treatment and the health care workers providing out-patient TB services
- Co-management with other diseases should be coordinated with the OPD

12.5.4 Community Settings

Early case detection remains one of the most important interventions for reducing the risk of TB transmission in the community and the household.

Raising awareness and education of TB in the community is important including cough etiquette, keeping the windows open in public transport and crowded buildings.

Perform TB contact investigation, and outbreak investigation as quickly as possible as recommended in the systematic TB Case Finding Chapter.

Include infection control behaviour-change messages as part of treatment literacy to TB patients, family members and treatment supporters. The messages include:

- Promotion of the importance of early identification of cases
- Adherence to treatment
- Educate patients on cough etiquette and respiratory hygiene
- Keep windows and doors open as much as possible

Smear positive, TB patients should:

- Spend as much time as possible outdoors
- Sleep alone in a separate, adequately ventilated room, if possible until the smear is negative
- Spend as little time as possible in congregate settings or on public transport

Family members living with HIV or immuno-compromised conditions, or family members with strong clinical evidence of HIV infection, should not provide care for TB patients with smear / culture-positive results (May use respirators, if available.)

Children should spend as little time in the same living spaces as smear / culture-positive TB patients.

12.5.5 Correctional Services

Tuberculosis occurrence in the correctional services is 5-7 times higher than in the community. Therefore, stringent IPC control measures should be applied. Education to staff and offenders should be carried out regularly. Additional environmental control measures such as installing of UVG lamps with proper maintenance may be necessary.

Special considerations for correctional facilities are:

- All correctional facility staff should be screened for TB annually and provided with TPT / LTBI treatment regardless **of HIV status** if active disease has been ruled out. HIV testing should, however, be encouraged
- All offenders should be screened at initial incarceration and thereafter regularly (see below) including signs and symptoms, history of previous TB, history of TB exposure, and risk factors for TB disease, particularly HIV infection
- In addition, all offenders should be screened at least once a year with signs and symptoms and by CXR annually
    - Those that screen negative should be provided with LTBI treatment if not received before **regardless of HIV status or it can be repeated after TB exposure**
    - ✓ In addition, offenders attending correctional facility clinics should be screened on every clinic visit
    - ✓ Cough surveillance on offenders by trained peers
    - ✓ Early diagnosis and treatment initiation for individuals with presumptive TB
    - ✓ Every dose of medication should be observed to ensure treatment adherence
    - ✓ Segregation of offenders with TB disease until smear is negative, for DR-TB until culture is negative and presumptive TB until they are ruled out active TB disease
    - ✓ Furthermore, all offenders should be screened on release

Link to care for those on TB/DR-TB treatment when released and follow-up to ensure they receive a continuum of care.

12.5.6 Isolation

- Must be done in rooms with appropriate IPC measures
- Infectious patients should remain in the isolation room
- Infectious patients should wear a surgical mask when outside the isolation room and be exposed to other offenders
- Offenders should be educated in TB transmission, reasons for isolation and the importance of practising cough etiquette
- Staff entering occupied isolation rooms should use respiratory protection devices
- Transportation of offenders outside the congregate setting should follow the IPC guidelines

12.6 Recording and reporting of IPC implementation

The TBIPC reporting tool consists of symptomatic TB screening of healthcare workers (HCWs), facility IPC plan, Risk assessment and formation of functional IPC committees. The reports will be collected quarterly and collated annually from the healthcare facilities to the region through the facility manager. The regional Monitoring and evaluation officer and the regional IPC focal will then collect and send the reports to the National TB program for analysis. TB screening report for HCWs will appear in the CMIS and the other quality indicators will appear in the HMIS electronic database.

Table 67: Infection control plan and risk assessment tool

Name of Facility:				
Location:				
Type of Facility:		Hospital/Health Centre/Clinic		
Date of Assessment:		/ /		
Name of Accessor:				
Administrative Control		**Yes**	**No**	**Comment**
Does the facility have an IPC committee or IPC focal?				
Are clients screened for TB at the entry point and segregated (place/time)?				
Are household contacts of TB being followed up and screened for TB?				
Are presumptive TB clients diagnosed early and put on treatment early if diagnosed with TB?				
Are all staff in the health facility screened at least annually?				
Are clients and their family members/caregivers given TB health education including cough etiquette and IPC measures at home?				
Do HCWs and patients practice cough hygiene (cover their cough)?				
Environmental Control				
Are Window and Doors opened most of the time to keep maximum ventilation?				
Do HCWs take downwind positions (against the wind) during consultation/health education/ counselling?				
Are the waiting areas well ventilated?				
Person Respiratory Protection				
Do coughing patients' surgical mask?				
Do HCWs wear FFP2 or N95 masks during consultation with sputum-positive patients or perform high-risk procedures?				
Does the facility have a fit-test program for the HCWs using respirators (FFP2/N95)?				
Findings:				
Recommendations:				

12.7 Proper wearing of respirator

- Hold the respirator in hand with the nose piece at your fingertips, allowing the headbands to hang freely below your hand.
- Press the respirator firmly against your face with the nose piece on the bridge of your nose.
- Stretch and position the top band high on the back of your head. Stretch the bottom band over the head and position it below your ears.
- Using both hands, bold the metal nose piece to the shape of your nose.
- To test fit cup both hands over the respirator and exhale vigorously. If air flows around your nose, tighten the nose piece. If air leaks around the edges, reposition the straps for a better fit.
- Remember, careful observance of these fitting instructions is an important step in safe respirator use.

CHAPTER 13
INTEGRATED MANAGEMENT OF TB AND NON- COMMUNICABLE DISEASE

Certain non-communicable diseases (NCD) can increase the risk of developing TB disease or influence the outcome of TB treatment including diabetes, chronic kidney disease, silicosis, chronic hepatitis, mental health and substance use disorder. Therefore, screening and co-management of TB and NCDs is crucial. In addition, NCDs are growing public health concerns. Diabetes affects 12.8% of adult women and 9.4% of adult men in Eswatini (Global Nutrition Report, 2022[4]) and the prevalence of hypertension among 30-79-year-olds was 43% which is higher than the global average of one out of Hence the country is taking steps to integrate care of TB, HIV and NCDs.

Integrated care of TB and NCDs including diabetes, hypertension and mental health is one of NTCP's strategic plans. NCDs with increased risk of TB are included as targeted risk groups for TB screening in health facilities and communities (refer to TB Case Finding Chapter 3). Co-management of TB chronic liver disease and chronic renal disease are covered in the drug-susceptible TB treatment and monitoring chapter (see Chapter 6). This chapter will focus mainly on integrated management of TB and diabetes, hypertension and mental health.

13.1 Diabetes Mellitus

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. It is a common comorbid condition with TB globally. Diabetes is estimated to account for more than 10% of global TB deaths among HIV-negative individuals. People with diabetes are 3.1 times higher risk of developing TB disease (Jeon CY et al., 2008). They also have an increased risk of having poor TB treatment outcomes with 1.69 times relative risk of combined death and treatment failure and relapse from TB with a relative risk of 3.89 (Bake AM et al., 2011). TB can temporarily cause impaired glucose tolerance which may be a risk factor for developing diabetes.

13.1.1 Screening and diagnosis of diabetes mellitus

The symptoms of type 1 diabetes are frequent urination (polyuria), thirst (polydipsia), constant hunger (polyphagia), weight loss, vision changes and fatigue. The symptoms are the same for type 2 diabetes but can be mild and may take many years to be noticed when complications have arisen. Hence screening/diagnosis by testing blood sugar levels is most reliable. Early diagnosis and regular treatment can prevent serious damage to many body parts, especially blood vessels and nerves causing end-organ damage (e.g. chronic renal failure, retina damage, limb damage due to peripheral neuropathy and poor blood flow, etc).

Blood sugar (random/fasting) levels should be tested at the initiation of TB treatment.

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[4]https://globalnutritionreport.org/resources/nutrition-profiles/africa/southern-africa/eswatini/#:~:text=Eswatini's%20obesity%20prevalence%20is%20higher,and%209.4%25%20of%20adult%20men.

Random blood sugar levels of above 11.1 mmol/l or 200 mg/dl, fasting blood sugar levels of above 7 mmol/l or 100 mg/dl or postprandial (2 hours after meal) blood sugar levels above 11mmol/l or 200 mg/dl are cut-off points to diagnose diabetes. At baseline, use of HbA1c is recommended.

13.1.2 Management of TB and diabetes

TB treatment: The treatment regimen and dosing of anti-TB medication are the same for patients with diabetes.

Non-pharmacological treatment of diabetes

Certain lifestyle changes along with pharmacological treatment can help control blood sugar levels. These include exercise, dietary, another lifestyle, educational, and behavioural change interventions along with **Pharmacological treatment of diabetes**

Metformin is the preferred Firstline drug for type 2 diabetes mellitus management type 2DM.

Insulin may be considered for tight blood glucose control in patients with diabetes and TB.

Indications for insulin use are:

1. New patients with active TB and HbA1c >9% or FBG >11.1mmol/L
2. New patients with active TB and ketonuria and or hyperosmolar symptoms
3. Patients with active TB on two oral agents who are not reaching glucose targets
4. Patients with active TB who are significantly catabolic
5. Patients with active TB with significant liver and or renal dysfunction

Drug-drug interaction

- Rifampicin is a potent hepatic enzyme inducer, increasing the hepatic metabolism of sulphonylurea derivatives such as Glibenclamide, Gliclazide, and Glipizide and therefore lowering their plasma levels.
- The hypoglycaemic effect of Metformin may be increased by rifampicin though it is not metabolized by the P450 enzymes system.
- Thionamides (Ethionamide, Prothionamide) may cause fluctuation of blood sugar level in a person with diabetes comorbidity.
- Insulin has no pharmacokinetic interactions with anti-TB drugs and therefore it may be considered used at the beginning of TB treatment, to achieve faster bacteriological
- The peripheral neuropathy and optic neuritis by Linezolid may potentiate the pre-existing condition among diabetes patients with end-organ disease

In persons with TB/HIV coinfection, drug-drug interaction with ART and hypoglycemic agents are.

1. Co-administration of Metformin (500 mg twice daily) with once-daily DTG increases metformin Cmax and AUC by 66% and 79% and co-administration with twice-daily DTG increases Metformin Cmax and AUC by 111% and 145% respectively.
2. A dose adjustment of Metformin should be considered when co-administering DTG with Metformin to maintain glycemic control.

3. Monitor renal function and blood glucose are recommended when Metformin and DTG are co-administrated. As metformin is eliminated, patients with moderate renal impairment may be at increased risk for lactic acidosis due to increased Metformin concentrations.

Below is a table that illustrates the drug-drug interactions between the most used oral hypoglycemics and the most used antiretroviral drugs in Eswatini.

Table 68: Drug-drug interaction between most used oral hypoglycaemics and ARVs

DRUG INTERACTION TABLE										
Antidiabetic Agent	**TDF/ TAF**	**AZT**	**3TC**	**FTC**	**EFV**	**NVP**	**DTG**	**LPV/r**	**ATV/r**	**DRV/r**
Metformin							↑			
Glibenclamide					↓	↓		↓	↓	↓
Glipizide					↑			↓	↓	↓
Gliquidone					↑			↓	↓	↓
Gliclazide					↑			↓	↓	↓
Glimepiride					↑			↓	↓	↓
***Essential medicines list included atenolol, metoprolol, and carvedilol as alternatives**										
• No interaction										
• Potential interaction with increased or decreased levels of the sulfonylurea which may require dose adjustment of the sulfonylurea. Monitor blood glucose and adjust the sulfonylurea dosage as needed.										
• **CAUTION should be exercised when co-administering metformin with DTG as metformin levels are increased and dose reduction of metformin should be considered.** The US prescribing information recommends limiting the total daily dose of metformin to 1,000 mg when co-administered with DTG. **Renal monitoring is recommended as PLHIV with renal impairment are at increased risk of lactic acidosis due to increased metformin levels in the presence of DTG.**										
↑ Increase in antidiabetic agent level ↓Decrease in antidiabetic agent level										

Source: University of Liverpool, hiv-druginteractions.org

13.1.3 Treatment Monitoring

Blood glucose monitoring should be done at every visit for TB treatment follow-up. If a client is identified as having uncontrolled blood sugar levels, counsel, and support for adherence to a hypoglycaemic agent should be provided. Referral to a specialist physician should be made if blood glucose level is uncontrolled despite good adherence to treatment or complications of diabetes are observed.

Diabetes also increases the risk of cardiovascular disease. Hence proper diagnosis and treatment of hypertension and controlling blood lipid is important in a person with diabetes.

13.1.4 Treatment Literacy Support

Provide information on:

- Dietary and behavioural advice
- Personal Hygiene
- Physical activity (light exercise)
- TB and Diabetes Mellitus management can be successfully treated if adherence to treatment of both diseases is ensured.

13.2 Hypertension

Hypertension, also known as high or raised blood pressure, is a condition in which the blood vessels have persistently raised pressure.

Though there is no established evidence of the link between hypertension and diabetes, screening, diagnosis and co-management of hypertension in persons with TB would benefit clients to have early diagnosis of hypertension and one-stop service for TB and NCD.

13.2.1 Screening and Diagnosis

Many people with hypertension do not notice symptoms and may be unaware until there is a problem due to complications. Hence it is important to screen and diagnose hypertension by taking blood pressure.

Hypertension should be screened and diagnosed at the initiation of TB treatment for all people with TB.

Hypertension is diagnosed if, when it is measured on two different days, the systolic blood pressure readings on both days are ≥140 mmHg and/or the diastolic blood pressure readings on both days is ≥90 mmHg.

Complication of hypertension

Angina, myocardial infarction, heart failure, cardiac dysrhythmia, stroke, end-organ disease (chronic renal failure,

13.2.2 Management

Non-pharmacological management

Lifestyle changes can help lower high blood pressure. These include;

- Eating a healthy, low-salt diet
- Losing weight
- Being physically active
- Quitting tobacco.

Pharmacological management/Linkage to treatment

First-line drug/second-line drug

- ACE inhibitors including enalapril and lisinopril
- Angiotensin-2 receptor blockers (ARBs) including losartan and telmisartan
- Calcium channel blockers including amlodipine and felodipine
- Diuretics including hydrochlorothiazide and chlorthalidone

13.2.3 Monitoring

Blood pressure monitoring should be done at every visit for TB treatment follow-up. If a client is identified as having uncontrolled hypertension, counsel and support for adherence to an antihypertensive agent should be provided.

Referral to a specialist physician should be made if blood pressure level is uncontrolled despite good adherence to treatment or observation of the following signs and symptoms of hypertension complication.

- Severe headaches
- Chest pain
- Dizziness
- Difficulty breathing
- Nausea
- Vomiting
- Blurred vision or other vision changes
- Anxiety
- Confusion
- Buzzing in my ears
- Nosebleeds
- Abnormal heart rhythm

13.2.4 Treatment Literacy Support

Reducing salt intake (to less than 2g daily), eating more fruit and vegetables, being physically active regularly, avoiding the use of tobacco, reducing alcohol consumption, limiting the intake of foods high in saturated fats, eliminating/reducing trans fats in the diet, and reducing stress.

13.3 Mental Health

Definition of terms

Mental disorder: refers to a syndrome characterized by clinically significant disturbance in an individual's cognition, emotional regulation, or behaviour that reflects a dysfunction in the psychological, biological or developmental processes that underlie mental and behavioural functioning. These disturbances are usually associated with stress or impairment in person, family, social, educational, occupational or other important areas of functioning.

Mental health condition: A broad term covering mental disorders and psychosocial conditions. It also covers other mental states associated with significant distress, impairment in functioning or risk of self-harm.

Substance use disorders: refers to a group of disorders that arise from a single or repeated use of substances that have psychoactive properties (e.g. alcohol, cocaine, drugs), including certain medications.

13.3.1 Introduction

Mental health is acknowledged as a public health threat in Eswatini. People continue to experience the effects of mental ill-health conditions. Individuals affected by TB have a higher risk for mental health conditions and TB/HIV coinfected are at higher risk. This comorbidity influences a person's capacity to adhere to taking TB medication and infection control practices which could lead to unfavorable TB treatment outcomes such as treatment failure, death and relapse of TB. Some anti-TB medications are associated with depression, anxiety and/or psychoses (e.g. isoniazid, cycloserine, terizidone, ethionamide), which may require temporary suspension or complete cessation of the suspected agent and/or initiation of adjunct psychopharmacological medication. Hence mental health conditions should be assessed at baseline and regularly throughout TB treatment and managed accordingly. The main mental health conditions that affect individuals with TB are:

- Depressive Disorders
- Anxiety Disorders
- Suicide
- Psychosis
- Substance Use Disorders

13.3.2 Screening and diagnosis of mental health status

Depressive disorder

The common feature of depressive disorder is the presence of sad, empty, or irri mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function.

- Screening for d should be done to all clients accessing services using People Health Questionnaire 9 (PHQ9, see Table 69)
- PHQ 9 can be self-administered or administered by a healthcare provider. It can be used as a screening tool and for follow-up care.
- Clients who score 1-9 in PHQ 9 should be screened every six months and 10 and above should be referred for further assessment by trained clinicians, psychologists or psychiatrists. Those who score 10 and above should be screened with PHQ-9 at every follow-up visit.
- Provisional diagnosis of depression using PHQ-9 score, and recommended action is as below.

Table 69: Provisional diagnosis and recommended action according to PHQ9 score

PHQ-9 Score	Provisional diagnosis	Recommended actions
5-9	Minimal symptoms	Support and educate to call for support if symptoms get worse
10-14	Minor to mild depression or chronic depression (symptoms lasting for 2 years)	Support and watchful waiting. Reassess in 1-2 weeks. Consider starting treatment for psychological support
15-19	Major depression	Needed for specific treatment Refer to psychologist/trained nurse-psychologist
>20	Severe depression	Needed active treatment including pharmacological treatment Refer to a trained medical officer/psychiatrist

For an individual with the thoughts of death or suicidal attempt, immediate referral to a psychologist/ psychiatrist should be made for an effective magment.

Anxiety Disorder

Anxiety is a natural response to a perceived threat. Mild and moderate levels of anxiety are normal and improve an individual's performance. When it becomes excessive fear and related behaviour disturbances, it is defined as anxiety disorder.

PHQ9 can be applied for the screening of anxiety disorder since it is a common co-morbid condition with depressive disorder.

Psychotics Disorder

Psychotic disorder is defined by abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behaviour (including catatonia), and negative symptoms.

If any of these abnormalities are present, refer to the trained mental health clinicians, psychologist and psychiatrist.

13.3.3 Management of mental health disorder

Non-pharmacological management are:

- Psychotherapy with a Clinical Psychologist
- Counselling for minimal and mild Major Depressive Disorder (MDD) may help in a setting where there is no Clinical Psychologist

Pharmacological Management

Major Depressive Disorder

The drugs used in major depressive disorder and dosing are briefly detailed in the table below.

Table 70: Psychotropic drugs used in major depressive disorder

Category	Drugs	Dosage
Firstline anti-depressant	Amitriptyline	25 mg OD at bedtime initially, may gradually increase the dose, maximum dose is 200 mg/24 hours
	Fluoxetine	Initial dose 10-20mg OD at bedtime, may gradually increase the dose, maximum dose is 60-80mg/24 hours
	Sertraline	Initial dose 25-50mg OD at bedtime, may increase gradually, the maximum dose is 200mg/24 hours
Second-line anti-depressant	Duloxetine	Initial dose 30mg at bedtime
	Lorazepam	1-2mg at bedtime
Firstline anti-psychotropics	Haloperidol	Initial dose 1.5-3mg at bedtime, maximum dose 20mg/24 hours
	Sulpride	Initial dose 50mg at bedtime, maximum dose 200mg/24 hours
	Aripiprazole	Initial dose 2-5 mg at bedtime, maximum dose 30mg/24 hours
Secondline anti-psychotrophics	Risperidone	Initial dose 1-2mg at bedtime, maximum dose 8-12mg/24 hours
	Olanzapine	Initial dose 5-10mg at bedtime, maximum dose 25mg/24 hours

Other Prescribing Rules

- Prescribe one anti-depressant or anti-psychotic at a time
- Consider the second line after the maximum dose for at least 8 weeks without significant improvement of symptoms
- Do not prescribe antimuscarinics routinely, manage side effects
- Pregnant women and breastfeeding mothers, defer anti-depressant and refer to a psychiatrist
- Avoid the use of amitriptyline in patients with suicidal tendency
- Risperidone and Olanzapine are contraindicated to patients with Hypertension, Diabetes, obesity and elderly patients
- Avoid Chlorpromazine for patients with Major Depressive Disorder
- Check heart rate, blood pressure, BMI and fasting blood sugar before prescribing olanzapine and risperidone

Drug-drug interaction

Concomitant use of Linezolid and Serotonin re-uptake inhibitors such as fluoxetine, and paroxetine; tricyclic antidepressants: amitriptyline, nortriptyline Serotonin 5-HT1 receptor agonists, MAO inhibitors: phenelzine, isocarboxazid Other serotoninergic agents: meperidine, bupropion, or buspirone, quetiapine may increase serotonin levels which has a potential to develop serotonin syndrome.

13.3.4 Treatment Literacy Support

Provide information to clients that:

- Mental health disorder conditions can happen to anyone
- Treatment response is within 4-6 weeks
- Anti-depressants and psychotropics are not addictive
- Not to engage in alcohol and substance abuse
- Mental health disorders can be successfully treated if adherence is ensured.

13.4 Substance-related addictive disorder

Persons with **alcohol and other substance use** disorders have a significantly higher risk of worse treatment outcomes due to their capacity to adhere to TB medication, higher risk of other comorbidities including HIV, hepatitis B and C and other factors such as delayed access to diagnosis treatment, stigma and discrimination and other related factors to comorbidities such as malnutrition, compromised immune response, potential drug-drug interactions and pills burden. Hence it is essential to screen the substance use disorder and provide adequate psycho-social counselling and support to such persons, recognizing and managing acute and life-threatening substance use-related conditions, and referring for specialized care when needed.

13.4.1 Screening and Diagnosis

Screening using the Alcohol/Substance Use Disorders Identification Test (AUDIT/SUDIT) as below.

A client presents with the problematic pattern of alcohol or substance use that can lead to clinically significant impairment or distress is manifested by at least two of the following, occurring within an a12-month period:

1. Alcohol/substance (e.g. cannabis) is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol/substance use.
3. A great deal of time is spent in activities necessary to obtain alcohol/substance, use it or recover from its effects.
4. Craving, or a strong desire or urge to use alcohol/substance.
5. Recurrent alcohol/substance use failing to fulfil major role obligations at work, school, or home.
6. Continued alcohol/substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7. Important social, occupational, or recreational activities are given up or reduced because of alcohol/substance use.
8. Recurrent alcohol/substance use in situations in which it is physically hazardous.
    - Alcohol/substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
    - Tolerance
    - Withdrawal symptoms

13.4.2 Management

Non-pharmacological management includes Occupational therapy interventions, SUD counselling, Psychotherapy with a Clinical Psychologist, Short to long-term rehabilitation, Family interventions

Pharmacological management includes Managing comorbid conditions and referring if present with intoxication or life-threatening withdrawal symptoms.

13.4.3 Treatment literacy and support

Provide advice on behaviour change whenever in contact with the patient.

- Encourage meaningful occupational engagement, constructive use of free time and leisure pursuits to decrease the probability of relapses.
- Avoid people, places and activities that could potentially lead to relapse.
- Involve the patient's family or caregiver in the management plan by providing information on the impact of drug use, especially the one used by the patient.
- Encourage the patient to attend self-help support groups such as AA, and NA for continuation of care to prevent relapses.
- Identify what will motivate them to change their addictive behaviour. Use these factors to help the person be motivated to change and keep going.

Table 71: Patient Heath Questionnaire-9 (PHQ-9)

Patient Health Questionnaire-9 (PHQ-9)				
Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use (✓) to indicate your answer)	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3

8. Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
For office coding	____0___	+_____	+_____	+_____
			Total Score:	_____

If you checked off <u>any</u> problems, how <u>difficult</u> have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

CHAPTER 14
ZOONOTIC TB, MYCOBACTERIA OTHER THAN TB (MOTT) AND LEPROSY

14.1 Zoonotic TB and MOTT

Zoonotic Tuberculosis (TB) is a form of TB caused by Mycobacterium Bovis, which belongs to the *M. tuberculosis* complex, the closely related group of Mycobacterium species that can cause tuberculosis in humans or other animals. Cattle are the most important animal reservoir for M. Bovis although other animals may also contribute as a reservoir for the pathogen. Since the presentation and diagnostic approach is the same across the MTB complex, it is often not possible to attribute infection directly to M. bovis.

Mycobacteria other than those comprising the *M. tuberculosis* complex are called non-tuberculous mycobacteria (NTM) or mycobacteria other than tuberculosis (MOTT). These mycobacteria may cause pulmonary disease resembling TB and most commonly affect people with an underlying lung disease, such as chronic obstructive pulmonary disease and bronchiectasis. MOTT is found in the environment, in soil, dust, water and bird droppings.

The list of MOTTs that can cause human disease is long. However, species commonly causing disease include *Mycobacterium avium complex (MAC), M. gordonae, M. xenopi, M. abscessus complex (MABC) and M. kansasii.*

14.1.1 Transmission

For zoonotic TB, there are three routes of infection:

- *Oral transmission*, through the consumption of contaminated unpasteurized milk, undercooked or raw meat from animals with M. bovis could also present a risk of transmission of M. bovis to humans.
- *Respiratory transmission* involves inhalation of aerosolized bacilli from the respiratory tract of infected animals.
- *Cutaneous transmission:* involves the traumatic inoculation of M. bovis into the skin during manipulation of carcasses or direct contact with infected animals, resulting in localized skin, tendon, mucosal or lymph node lesions.

Transmission of MOTT is through inhalation of infectious particles from the environmental sources listed above.

14.1.2 Risk Factors

Risk factors for zoonotic TB include:

- Consumption of *unpasteurized* milk
- Consumption of untreated animal products
- Consumption of raw or *undercooked* meat from animals with m. Bovis
- *Direct* contact with infected animals or contaminated animal products.

MOTT / NTM on the other hand, occur mostly as opportunistic infections in immunocompromised patients, although disease may occur in patients with no apparent risk factors.

14.1.3 Clinical Features

It is important to note that in many cases bovine TB is clinically indistinguishable from TB caused by M. tuberculosis with typical symptoms that include a persistent cough, fever, night sweats and weight loss. Although bovine TB can present with pulmonary disease, it often affects sites other than the lungs (extra-pulmonary), such as lymph nodes of the neck and gastrointestinal tract. Bovine TB should therefore be considered in people who present with neck and or abdominal swellings and masses.

The symptoms of pulmonary disease due to MOTT are often nonspecific and include:

1. Chronic cough
2. Increased sputum production
3. Dyspnoea
4. Low-grade fever
5. Malaise
6. Weight loss.

These symptoms overlap significantly with the clinical characteristics of pulmonary TB.

14.1.4 Laboratory Diagnosis

Smear microscopy demonstrates alcohol-acid fast bacilli and the rapid Xpert MTB/Rif or Truenat assay will also be positive for M. bovis which is in the M. tuberculosis complex. These molecular tests, however, will be negative for species of MOTT. Culture remains the gold standard for laboratory confirmation of MOTT. Treatment and outcomes differ depending on the MOTT species, and effective regimen hence MOTT species identification is clinically important. The role of DST in MOTT is to guide the design of optimal treatment.

Diagnosis of MOTT lung disease requires the clinician to integrate clinical, radiographic, and microbiological data. Diagnosis can be confirmed by:

(a) At least *two positive* cultures from sputum, or
(b) *One positive* culture in the case of bronchoscopy wash or lavage, or
(c) A *transbronchial or other lung biopsy* with a positive culture for MOTT or compatible histopathological features such as granulomatous inflammation or stainable AFB and one positive sputum or bronchial wash culture for MOTT regardless of the mycobacterial strain.

Without detailed clinical information, differentiating between contamination of specimens, colonization/infection, and disease is difficult. Laboratory reports of isolates do not always reflect the true incidence of disease. Accurate epidemiologic data is lacking globally because the investigative processes to determine the presence of clinical disease are costly to the healthcare system and the patient.

14.1.5 Treatment

14.1.5.1 Treatment of disease by M. bovis

The recommended treatment for species specifically identified as M. bovis is as shown below. M. bovis is naturally resistant to pyrazinamide hence its inclusion in the intensive phase is not necessary.

Table 72: Treatment of disease by M. bovis

Phase of treatment	Recommended regimen
Intensive phase	2 months RHE*
Continuation phase	7 months RH

** In practice, RHZE may be the available option (as an FDC). If used, the clinician should keep in mind the Z (pyrazinamide) is not effective against M. bovis. If serious side effects occur related to Z, single formulations may be requested*.

14.1.5.2 Treatment of MOTT

The management of MOTT lung disease should be undertaken with the guidance of experienced clinicians backed by reliable laboratory services for mycobacterial cultures and in vitro DST, as it requires prolonged use of costly combinations of multiple drugs with a significant potential for toxicity. Treatment is guided by sensitivity testing of the organism to commonly used antibiotics and should include a combination of at least 3 medicines.

The diagnosis of MOTT lung disease does not always mandate the initiation of therapy against MOTT species. The decision must be made based on the potential risks and benefits of therapy for individual patients. Clinicians may observe asymptomatic patients and those with stable radiographic disease, without invasive workups or treatment, provided the patients do not have decreased host immunity towards MOTT and the patient is educated to avoid aggravating factors such as tobacco smoking. Once the clinician decides to start treatment, the goal of curative therapy in MOTT lung disease is 12 months of culture negativity, and therefore, frequent sputum sampling every 1–2 months is needed.

Patients must be counselled about the disease and its treatment including the regimen, potential benefits, and adverse effects. They must be advised that treatment will be until they have been culture negative for a period of 12 months. Female patients of childbearing age must be advised to prevent pregnancy until cured. Patients must be advised to report any side effects of treatment as soon as possible.

Table 73: Treatment Regimens for MOTT Species

MOTT / NTM	Regimen (Adult Dose)
M. avium complex	• Rifampicin (600mg) • Clarithromycin (500 – 1000mg) (or Azithromycin (250-500mg) • Ethambutol (15mg/kg)
M. kansasii	• Rifampicin (600mg) • Ethambutol (300mg) • Isoniazid (300mg) Pyridoxide 50mg should be added

14.1.6 Treatment Monitoring

Full blood count and the patient's renal and hepatic function must be checked prior to initiating treatment. Renal and liver function should be checked at 12 weekly intervals or as clinically indicated. Management of abnormal results should follow the same principles used in management of MTB. Monthly culture should be performed to monitor the response to treatment throughout the treatment duration.

14.2 Leprosy

Leprosy is a chronic infectious disease caused by the mycobacterial species Mycobacterium leprae (M. leprae). It affects the skin, mucosa of the upper respiratory tract, and the eyes and peripheral nerves (sensory, motor and autonomic nerves). Left untreated, the disease may cause progressive and permanent disabilities. Although Eswatini has eliminated leprosy as a public health threat, health workers should notify the regional TB coordinator of any presumed cases for further assistance with evaluation and linkage to care.

14.2.1 Transmission

Transmission is via droplets from the nose and mouth during close and frequent contact with untreated cases. The skin is the second portal of entry. Prolonged, close contact over months with someone with untreated leprosy is needed to catch the disease. The disease is not spread through casual contact with a person who has leprosy like shaking hands or hugging, sharing meals or sitting next to each other. A patient stops transmitting the disease when they begin treatment.

14.2.2 Risk Factors

Most people are not susceptible to leprosy and only a very small proportion of those exposed develop the disease. There are several factors that increase an individual's risks to developing leprosy. These include older age which may reflect either a weaker immune system or the increased likelihood of lifetime exposure to a multi- bacillary (MB) case.

14.2.3 Clinical Features of Leprosy

Manifestations of Leprosy depend on the infected person's immune response to the bacterium. In many patients, at the time of presentation there will often be signs of nerve damage such as weakness or anaesthesia (loss of sensation) due to a peripheral nerve lesion or a blister, burn or ulcer in an anaesthetic hand or foot.

14.2.4 Diagnosis of Leprosy

A complete history and physical examination in addition to laboratory tests are essential for the diagnosis of leprosy. The main components of the clinical assessment are:

1. History
2. Skin examination
3. Nerve palpation
4. Nerve function impairment (NFI) assessment: voluntary motor sensory test (VM- ST)
5. Eye examination
6. Deformity, disability and psychological assessment

The following are diagnostic of leprosy:

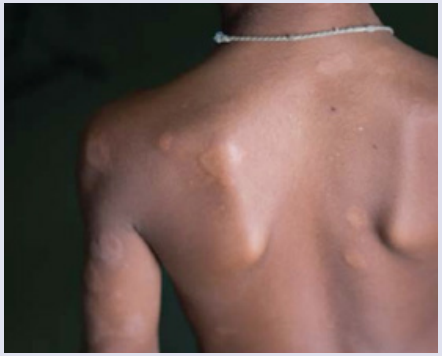
9. *Definite loss* of sensation in a pale (hypo-pigmented) or reddish skin patch.
10. A *thickened* or enlarged *peripheral nerve* with loss of sensation and/or weakness of muscles supplied by the affected nerve.
11. The presence of *acid -fast bacilli* (AFB) in a slit skin smear.

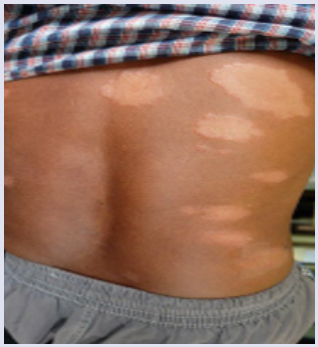
14.2.5 Leprosy Classification

Leprosy is classified into two treatment groups:

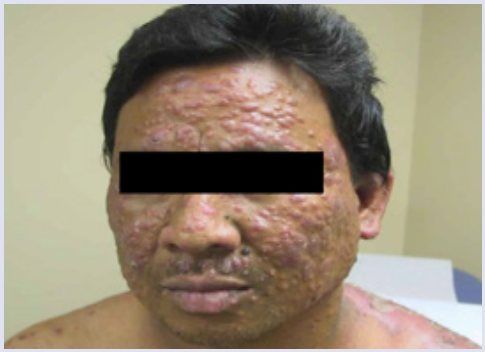
7. **PB (Pauci-bacillary):** usually the PBs have one to five lesions, and the skin smear is usually not required because most smears are always negative. These cases are diagnosed clinically based on the characteristic clinical presentation
8. **MB (multi-bacillary):** MBs have more than six lesions and the skin smear is usually positive. The diagnosis of MBs is more bacteriological than clinical.

Figure 47: Disabilities due to late presentation of leprosy

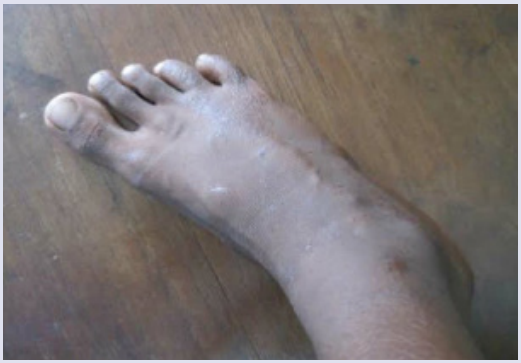




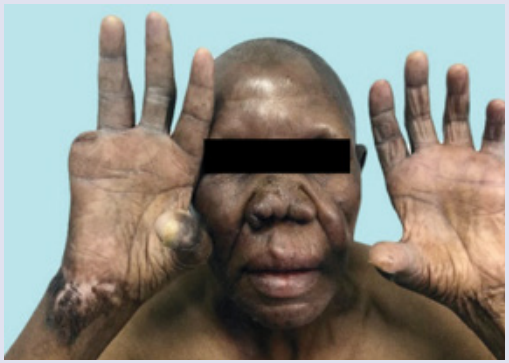
One or more hypopigmented, skin patches with loss of sensation



Leprotic nodules, ear lobes are commonly affected



Thickened nerve with fine nodules on the affected toes



Untreated leprosy can lead to deformity or falling-off of digits (auto-amputation)

14.2.6 Treatment of Leprosy

The recommended regimen consists of a 3-drug regimen of rifampicin, dapsone and clofazimine for all leprosy patients, with a duration of treatment for 6 months for PB leprosy and 12 months for MB leprosy. The recommended regimen, doses and frequencies are shown in table 74 below.

Table 74: Dosing of drugs used in leprosy treatment

Age group	Drug	Dosage & frequency	Duration	
			Multi Bacillary	Pauci Bacillary
Adult	Rifampicin	600 mg once a month	12 months	6 months
	Clofazimine	300 mg once a month and 50 mg daily		
	Dapsone	100 mg daily		
Children (10–14 years)	Rifampicin	450 mg once a month	12 months	6 months
	Clofazimine	150 mg once a month, 50 mg on alternate days		
	Dapsone	50 mg daily		
Children <10 years old or <40kg	Rifampicin	10 mg/kg once month	12 months	6 months
	Clofazimine	100 mg once a month, 50 mg twice weekly		
	Dapsone	2 mg/kg daily		

14.2.7 Preventive Chemotherapy

Case detection and treatment with MDT alone have proven insufficient to interrupt transmission. To boost the prevention of leprosy, with the consent of the index case, WHO recommends tracing household contacts along with neighborhood and social contacts of each patient, accompanied by the administration of a single dose of rifampicin as preventive chemotherapy.

14.2.8 Stigma and Discrimination

People affected by leprosy are often subject to discrimination and stigmatization. This situation has negative effects on access to diagnosis, outcome of treatment and care, in addition to violation of civil, political and social rights. Ending stigma and discrimination is fundamental to ending leprosy. Psychosocial support is needed for leprosy patients to deal with discrimination and stigma.

14.2.9 Classification of leprosy disabilities

Table 75: Disabilities due to late presentation of leprosy

Hands and Feet	
Grade	**Disability**
0	No anaesthesia, no visible deformity or damage
1	Anaesthesia present, no deformity or damage
2	Visible deformity or damage
Eyes	
Grade	**Disability**
0	No eye problems due to leprosy; no evidence of visual loss
1	Eye problems due to leprosy, vision not severely affected (6/6 or better), can count fingers at six meters
2	Severe visual impairment (vision worse than 6/60, inability to count figures at six meters)

14.2.10 Care for Prevention of impairments leading to disability

HCWs should teach patients about the management of limbs and emphasize the following.

9. Ulceration may occur through burns and other injuries due to loss of sensation which impairs the response to injurious stimuli.
10. Joint contractures can occur when muscles are paralyzed, and active and passive exercises should be taught to patients to prevent this complication.
11. Eyes should be inspected in a mirror daily for redness. Redness or visual deterioration should be assessed promptly by health staff. Use of lubricating eye drops, and a clean protective eye mask should be encouraged where there is weakness in the lid closure

12. Inspect footwear for foreign bodies with the potential to damage feet e.g. pebbles in shoes. Carefully trim nails and keep them short. Inspect the feet for reddened inflamed skin (hotspots), blisters or ulceration of anaesthetic areas regularly.
13. Soak feet and hands if there is sensory loss, dryness, fissuring, callosity, or ulcer in water for 10-15 minutes daily.
14. Dry skin should be treated by soaking in water, followed by rubbing with emulsifying ointment or an oil-based lotion preparation.

CHAPTER 15
TUBERCULOSIS MORTALITY REVIEWS

TB death refers to a person with TB disease who died for any reason before starting (for case outcomes), or during treatment (for both case and treatment outcomes). For mortality, it applies to those who died during treatment for any reason. Mortality review (also known as mortality audit) is a means for improving the quality of patient care and outcomes by a systematic review of clinical management of TB deaths to understand circumstances around patient presentation, diagnosis, treatment and death. This allows the identification of gaps in the quality of care and changes to be made to improve outcomes.

According to the Eswatini National TB Program annual report, 2023, mortality among notified DSTB and TB/HIV co-infected patients was 10% and among DR-TB patients was 8%. The observed mortality rate is higher than the target mortality rate of less than 5% for all forms of TB. NTCP therefore recommends systematic mortality reviews to understand the contributing factors and implement targeted interventions to improve treatment success rate. The mortality review should be conducted at the health facility level as well as at the national level.

15.1 The aim and objectives of the mortality review

The mortality review aims to reduce the number of avoidable TB-related deaths in healthcare facilities by improving overall patient care and addressing underlying health systems and patient-related factors that contribute to mortality. Additionally, the review seeks to identify gaps in healthcare worker training needs, enhance communication between facilities and the community regarding the causes of death, and improve documentation of death causes within facilities. Ultimately, the goal is to improve TB treatment outcomes not only at the facility level but also at the national level, thereby reducing the overall burden of TB-related deaths.

15.1.1 Health Facility Mortality Review

The health facility should form a mortality review team (MRT) consisting multi-disciplinary team and conduct mortality reviews whenever there is a TB death.

The mortality reviews are guided by the standard operating procedures (SOPs), the terms of reference (TORs) and standard mortality review tools. The following is procedures for mortality review in health facilities.

The mortality review team in health facilities should comprise of representatives from the key departments of the hospital/clinic including pharmacy, laboratory, physiotherapy, psychosocial, outpatient department (OPD), Ward, maternity, anti-natal care, clinic/hospital management, referral facility representative, quality improvement committee, M&E and regional health management team.

The role of the RHMT is to ensure there is a standardization of the MRM procedure so that all facilities have a standard reference in their supported regions and a fixed schedule in place to discuss cases as soon as possible after death.

The team works with Regional TB Coordinators to address logistical challenges arising e.g. patient initiated in one region and dies in another region.

15.2 Procedures of TB mortality review meeting in a health facility

M. MRM can be done monthly, weekly or whenever a patient dies on a designated day (e.g. every Friday of the week or last Friday of the month).

N. MRMs must be conducted in a non-persecutory manner to ensure full participation from all stakeholders.

O. TB patient referred from an out-patient facility to an in-patient facility results in death, referring facility should send a representative to attend the MRM

P. Clinicians should take turns in presenting patient cases.

Q. The Facility should develop a roster for MRM presentations where all clinicians will be present to ensure full participation.

- In-service committee for bigger facilities or sister in charge for smaller facilities should develop a roster for presentations, departments or clinicians' names
- Clinicians on the roster are responsible for collecting the TB death case file/notes from either the TB clinic or ward for discussion.
  - ✓ The in-service coordinator can remind the presenter if possible.
- The clinician should collect comprehensive information from various sources; chronic care files, TB treatment cards, admission and referral notes, TB registers, Laboratory registers, and community/ family members.
- Data is summarized and forms the basis for the discussions during the MRM.
- Clinicians prepare a PowerPoint presentation of the case, summarizing the case from the day of admission to the day of the death using the Mortality review PowerPoint template.
- In service, the coordinator communicates with key stakeholders; RHMT, hospital management, hospital departments and referring facility the date, time and venue of the MRM.
- The clinician presents the case during the MRM.
- SMO or the appointed chair in his absence coordinates the discussion.
- Key issues and action points identified should be reported in the next MRM indicating whether they have been addressed or not.
- Facility data clerk/any designated person captures discussion points in the MRM register and attendance is also captured.
- Carbon copies of mortality review registers and reports should be sent to SID and NTCP.

R. TB clinic focal person ensures that the MRM form is completed by the presenting clinician and M.E/data clerk, filed and sent to NTCP via regional SID.

S. The hospital management team should participate in MR meetings to identify health system or administrative challenges that may be contributing to poor patient outcomes.

T. SMT ensures HCWs in all departments take part in MRM so that it is institutionalized and sustainable.

U. Hospital management may incorporate mortality reviews for other departments if this approach is seen to bring a multidisciplinary team to the discussions.

v. RHMT is encouraged to take part in all proceedings and also perform Quarterly supervision to review the progress of the activity

15.3 National Mortality Review

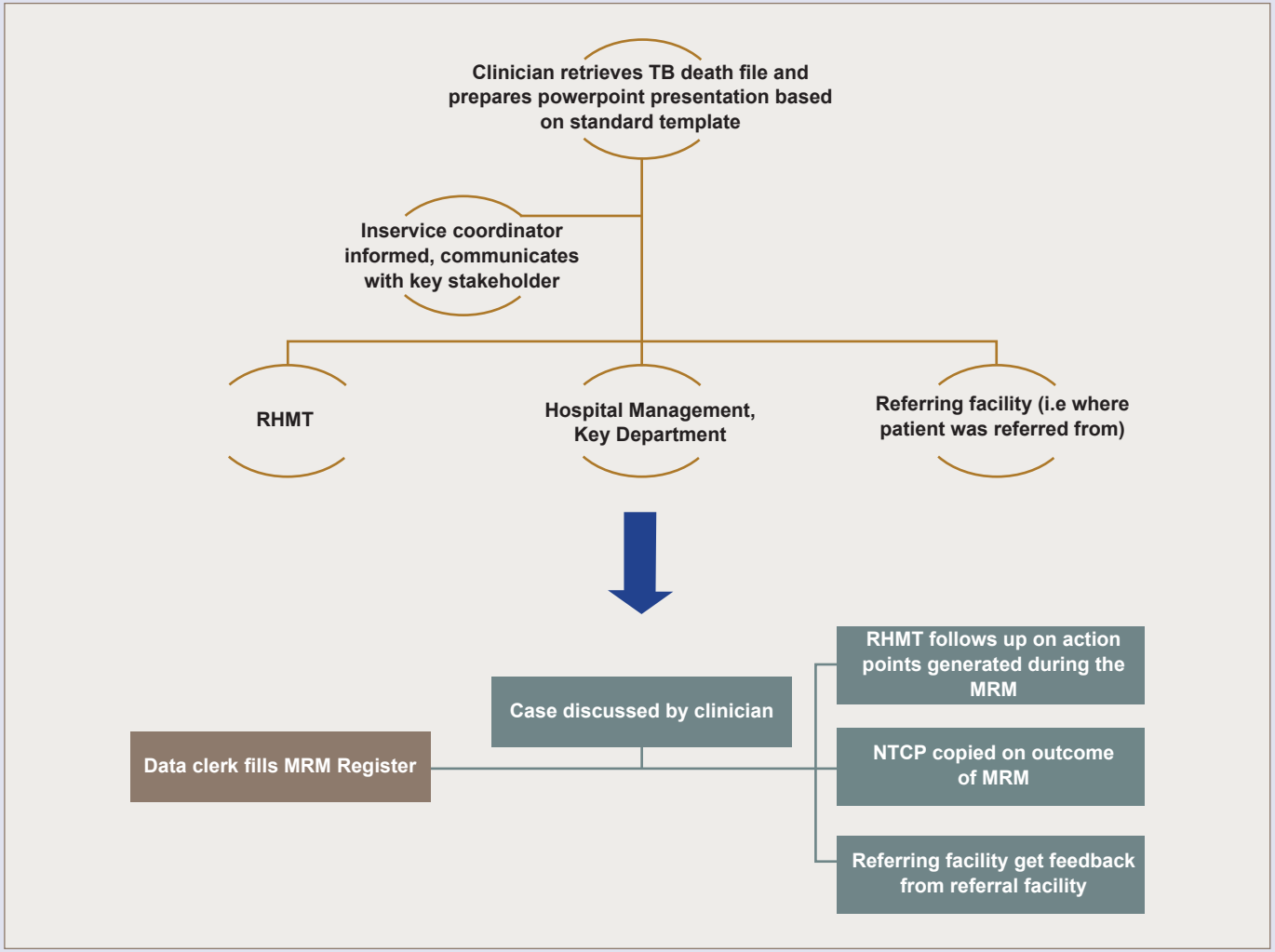
The National Mortality Review Task team is responsible for reviewing the national mortality report quarterly, as compiled by the M & E officer. The findings from the review will inform programming aimed at improving outcomes for TB patients.

The national mortality review task team is also responsible for conducting quarterly integrated TB/HIV mortality reviews. The national mortality reports will be disseminated to stakeholders through the existing technical working groups (TWGs) and RHMTs. The task team comprises NTCP, SNAP, IPs, and PEPFAR/CDC.

15.4 Responsibilities of Mortality Review Team Members

- **National mortality review task team**: review and analyze the mortality review data and information conducted by health facilities quarterly. Develop a change package to address the gaps/factors contributing to TB deaths. Provide support for the implementation of the change package.
- **RHMT** : provide supervision and ensure all facilities in the region conduct monthly mortality review meetings.
- **Hospital management:** ensure that all departments involved in patient care are represented during the mortality review meetings.
- **The head of management chairs** and facilitates the discussion during the mortality review meetings. He/She is responsible for choosing another chair during his/her absence.
- **Regional Technical/Clinical advisor/Mentors**: assist the head of management with some decisions related to TB services.
- **Clinicians:** Present case notes and provide constructive peer review of the clinical management of Tuberculosis.
- **Clinical Services Support Staff:** Identifying system problems that impact patient care.
- **TB Focal person:** The nurse or doctor in charge of the TB clinic assists with information to the clinician presenting, ensuring the MR form is complete and filed in the TB clinic.
- **Quality Improvement Committee:** Identify key areas for QIPs to improve patient care.
- **Referring facility representative:** Clinical input and system challenges (if any, e.g. no ambulance to refer the patient on time).
- **Monitoring and Evaluation:** Recording data on the number of participants for MRM, the number of MRMs conducted per quarter and capturing MRM findings in the Mortality Review register.
- Providing statistics and data-based guidance as required.

Figure 48: Process of Mortality Review



15.5 Recording and Reporting

The TB Mortality review is a process to capture/document all patients who have died after diagnosis of TB. Individual case reviews should be recorded using the case review report form (see Table 77). The component of the case review report form includes demographics, health facility name, treatment started date, death of death and a case summary (brief details of medical history, physical examination, investigation and treatment including for comorbidities), and major gaps identified (if any) for clinical management and health system, and comment on if the death is preventable or not. Any death should also be recorded in the TB Mortality Register and Logbook (see Table 78).

Who should record in the logbook

- The referring facility or the facility taking care of the patient.
- When updating the logbook-should also use information from the facility where a patient died.
- Collect case report forms from the facility where a patient died and file in the TB clinic.

Where did the patient die?	Mortality Review Team/responsible facility	Who Reports?
Home/ Community	Facility team where the patient is registered + Zonal/Cluster mentoring team	Facility where patient is registered
Outpatient	Facility team where a patient died + Zonal/Cluster mentoring team+ Referring facility	Facility where patient is registered
During referral	Facility team where patient finally arrives + Zonal/ Cluster mentoring team+ Referring facility	Facility where patient is registered
In the ward/inpatient	Facility team where a patient died + Zonal/Cluster mentoring team+ Referring facility	Facility where patient is registered

This information recorded in the logbook will be aggregated every quarter into a Mortality review summary sheet and sent to Regional strategic information offices through relevant channels. The register is in duplicate to allow one page to go to the regional office/ NTCP whilst the other with the name remains in the facility (see Table 78 for TB Mortality register and logbook). The consolidated regional mortality summary report and the case report forms are then submitted to the NTCP M&E officer for compilation into a national report.

15.6 Monitoring and Evaluation

The mortality review activities will be monitored and reviewed semi-annually. Table 59 below describes the framework of M&E for mortality review activities. The regional SID will collate data and present it to the region during RHMT meetings and also during the regional TB and HIV semi-annual review meetings.

NTCP M&E will also collate data and present to national stakeholders during National TB and HIV semi-annual review meetings.

Table 76: M&E framework of mortality review

Objective	Indicator	Target	Output	Responsible Person
Provide stewardship to ensure regular MRM in facilities	Number of MRMs being conducted in the facilities monthly	1 MRM per month per facility	All facilities conducting monthly MRMs	RHMT
Increase participation in MRM to ensure ownership by the facility staff	Number of hospital personnel representing key departments at each MRM	1 personnel from each key department in monthly MRM	Active participation by all HCWs in MRMs	Hospital management
Identify clinical/patient factors that contribute to TB-related mortality	Number of clinical/patient challenges identified during each MRM	At least 2 clinical gaps and 2 patient-related gaps per MRM	All TB-related death cases thoroughly discussed, clinical/ patient gaps identified, and remedial actions taken.	Clinician, all MRM participants
Identify health systems challenges that contribute to TB-related mortality	Number of health system challenges identified as contributing to deaths during MRM	At least 1 challenge identified per MRM	System challenges identified and remedial actions taken to resolve them	Clinical Services support, referring facility staff, all participants
Ensure standardized approach to MRM	Availability of printed SOPs, MRM IEC materials, and registers	SOPs, IEC materials, and registers available in all wards and TB units in the region	All HCWs conversant with MRM SOPs and process flow	TB regional coordinator Regional partner TB thematic lead
Ensure regional Feedback/dissemination	Number of dissemination meetings	At least 1feedback session per quarter	RHMT and facilities aware of regional contributory factors to TB deaths	Regional SID RHMT Regional partner thematic lead

Table 77: Case review report forms (CRFs) for documenting TB mortality review outcomes

TB Mortality Case Review Report Form	Section C: Case Assessment
Section A: General Information Date:	**Major Clinical Management - RELATED gaps identified**
Name:_____ Surname:_____	1. _____
Age: _____ Sex: _____	2. _____
Date of Referral / Date of Admission / Date of Death	3. _____
_____ _____ _____	4. _____
Diagnosis: _____	5. _____
Treatment given: _____	**Major Health Systems i RELATED gap identified**
_____	1. _____
Facility Name: _____	2. _____
	3. _____
Section B: Case Summary	4. _____
	5. _____
	Major Patient Related gaps identified
	1. _____
	2. _____
	3. _____
	4 . _____
	5. _____
	Was the death preventable? (tick one box)
	Definitely ☐ Probably ☐ Probably Not ☐
	Definitely Not ☐ Don't Know ☐

Table 78: TB Mortality Register and Logbook

Reporting Month:								TB Mortality Review Report:														
Facility Name:																						
Patient Demographics												TB / HIV										
Name & Surname	TB Number	Date of Birth (dd/mm/yyyy)	Sex (F/M)	Weight (kg)	Height (meters)	BMI at diagnosis	Date of TB diagnosis (dd/mm/yyyy)	Type of TB (DS / DR)	Disease Site (P/EP) Circle appropriate	Confirmation Bateriological / Clinical (Circle appropriate)	Date of TB Treatment Initiation (dd/mm/yyyy)	(HIV Status R/N R / U K)	On ART (Yes / No)	Date of ART Initiation (dd/mm/yyyy)	Date of ART initiation (dd/ mm/yyy)	Latest CD4 and Date	Comor-bidities	Cause of death	Date Died (dd/mm/yyyy)	Outpatient / inpatient	Recomme-ndations	Addressed (Y/N)
									P / EP	Baterio-logical / Clinical						CD4 Count Date						
									P / EP	Baterio-logical / Clinical						CD4 Count Date						
									P / EP	Baterio-logical / Clinical						CD4 Count Date						
									P / EP	Baterio-logical / Clinical						CD4 Count Date						
									P / EP	Baterio-logical / Clinical						CD4 Count Date						
									P / EP	Baterio-logical / Clinical						CD4 Count Date						
									P / EP	Baterio-logical / Clinical						CD4 Count Date						
									P / EP	Baterio-logical / Clinical						CD4 Count Date						

CHAPTER 16
REFERRALS AND LINKAGES IN TB SERVICES

16.1 Community Referrals and Linkages

Community cadres who are involved in community-based TB care and preventive activities are active case finders (ACF) and rural health motivators (RHM).

Their responsibilities are:

- Conduct TB screening for all community members during household home visits
- Collect sputum samples (stool samples in case of children <15 years old who cannot produce sputum)
- Refer clients to health facilities
- Provide treatment adherence support to people on TB treatment or TPT
- Offer HIV self-testing to presumptive TB clients

Who to refer to the health facility:

- Children living/history of living with a person on TB
- People who have screened positive for TB, but CAN NOT produce sputum
- People who have screened positive for TB but REFUSE to produce sputum
- People who are diagnosed with TB, but delay in starting treatment
- People who are eligible for TPT, but delay in starting TPT
- TB patients who are experiencing drug side effects
- TB Patients who have stopped taking their medication

How to refer clients:
A “Community to Facility” referral tool is used to refer clients.

The community-to-facility referral process:

1. Complete the National Community to Health Facility referral form and follow the community-facility referral process:
2. Duplicate forms are filled and distributed: 1st to Client, 2nd remains in referral book.
3. Physically submit the names of the referred clients to the TB Screening Officer to ensure that ‘expected’ community referrals are appointed in the Appointment Register.

Responsibility of the receiving health facility:
If the client arrives at the preferred site, provide health care appropriately and provide feedback to the referring community cadres

If the client does not arrive:

4. Contact the client and document the reappointment date on the appointment register.
5. Engage the referring RHM/ACF for a home visit to be conducted.

16.2 Inter-facility referrals

For referring to a patient for TB treatment initiation, follow the following referral procedures.

(a) Write down a facility-to-facility referral form for the client
(b) Call the BMU where the client will be referred to and schedule an appointment for the client
(c) Appoint the client for follow up in the facility appointment register
(d) After the day of the agreed date to visit the TB basic management unit (BMU), call the BMU to ask if client has honored the appointment.

Responsibilities of the receiving BMU site are:

(e) The receiving facility should document the expected appointment date in the Appointment Register, to ensure that the patient can be followed up in the event they do not honour this visit.
(f) When the client arrives at the preferred site, provide health care appropriately
(g) If the client does not arrive, conduct patient follow-up and engage the referring facility for a home visit to be conducted

Special Considerations for the diagnosis of TB in children:

- Write down a facility-to-facility referral form for the child
- Call the facility where the child will be referred to and schedule an appointment
- Appoint the child for follow-up in the referring facility appointment register
- After the day of the agreed date to visit the facility, call the facility to follow up if client has honoured the appointment
- Follow up with the caregiver if the child did not reach the health facility and reappoint in the facility appointment register

16.2.1 Treatment site to another treatment site for DSTB (BMU-BMU)

TB clients are free to access healthcare services wherever convenient for them. It is very important that a system is put in place for the continuum of health care for TB clients, hence guidance is provided to ensure that clients complete their TB treatment.

- For clients who are already on treatment in your facility and need to be (e.g. DR clients) or request to be referred to another facility:
  - ✓ Complete the facility-to-facility referral form of Call the receiving facility to arrange for an appointment for the referred client o After the day of the agreed date to visit the BMU, call the facility to follow up if client has honoured appointment

The receiving facility should:

- Document this expected appointment date in the Appointment Register, to ensure that the patient can be followed up in the event they do not honor this visit.
- Provide health care appropriately If the client arrives at the preferred site
- If client does not arrive, undertake the following actions:
    1. At the end of the appointment date, Nurse/TB adherence officer should call the patient to remind them about appointment and then reappoint the client on the agreed date
    2. If call is unsuccessful, engage the referring facility for home visit to be conducted by the ACF/RHM/ on the following day
    3. If home visit attempt is unsuccessful, conduct home visit through the Adherence officer/Defaulter Tracers with the aim to schedule an appointment for the client to come back
    4. If the home visit attempt is unsuccessful, engage the facility nurse to conduct home visit.
    5. Document follow up attempt on the patient file patient file (DS) or lost to follow up tracking logbook.
    6. Document the reappointment date for the client in the appointment register

16.2.2. Down-Referral from hospital or health Centre to clinic

- The TB Outpatient Unit must be informed of all in-patient cases diagnosed to ensure *immediate registration and prevent under-reporting*, ensure that any discharged client that skips going via the TB Unit can be tracked for continuity of care and to ensure *adequate patient education on TB*. The hospital or health centre must ensure that any TB deaths before discharge are adequately captured in its TB register and scheduled for discussion in mortality review meetings.
- Patients coming from the wards must always be discharged via the TB Outpatient Unit for the *necessary documentation and to ensure that linkages for referrals can be tracked*.
- DS TB clients may be downreferred to start or continue treatment at a clinic.
- Patients may only be downreferred from a hospital or health centre to a clinic if all the following criteria are met:
    - ✓ Vital signs are normal.
    - ✓ Patient is ambulant and clinically stable.
    - ✓ Haemoglobin is ≥8g/dl.
    - ✓ Creatinine and potassium are normal.
    - ✓ Patients do not take dose-adjusted medication.
    - ✓ Liver function tests are normal and no history of drug-induced hepatitis during the current TB treatment course.
    - ✓ Patient will not require regular close monitoring by a doctor.
    - ✓ Patient not diagnosed with TB meningitis.
- Pleural effusion if:
    - ✓ Fluid has been drained (large effusions)
    - ✓ Fluid not purulent or blood-stained.
    - ✓ Kaposi's sarcoma has been ruled out.
    - ✓ Resistance to first-line drugs has been ruled out using GeneXpert and LPA on pleural fluid and sputum.

16.2.3 DS-TB site to DR-TB site

For clients who are initially initiated on DS TB treatment and then the lab results confirm DR TB, the client needs to be referred to a DR TB clinic. The facility should:

- Complete the facility-to-facility referral tool.
- Call the receiving facility to arrange for an appointment for the referred client.
- After the day of the agreed date to visit the BMU, call the facility to check if the client has an honored appointment.

The receiving facility should:

- Document this expected appointment date in the Appointment Register, to ensure that the patient can be followed up in the event they do not honour this visit.
- Provide health care appropriately If the client arrives at the preferred site
- If the client does not arrive:
  - ✓ At the end of the appointment date, the nurse/TB adherence officer should call the patient to remind them about the appointment and then reappoint the client on the agreed date
  - ✓ If the call is unsuccessful, engage the referring facility for a home visit to be conducted by the ACF/RHM on the following day
  - ✓ If an attempt at a home visit is unsuccessful, conduct a home visit through the Adherence Officer/Defaulter Tracers to schedule an appointment for the client to come back
  - ✓ If the home visit attempt is unsuccessful, engage the facility nurse to conduct a home visit.
  - ✓ Document follow-ups attempt on the Defaulter/Treatment interrupter tracing card (pink card)
  - ✓ Document the reappointment date for the client in the appointment register

16.2.4 DR-TB Site to Local Clinic

Clients with drug-resistant TB are managed at the DR TB facilities in the country. For those clients who need to be referred down to the local health facilities for further management to a local health facility e.g. Daily injectable, they need to be down referred to their local health facility.

1. Complete facility-to-facility referral tool.
2. Complete appropriately the full history of the patient, current medication, dosage and duration on the referral tool for the next health care worker to be informed of patient history and medication needs.
3. Call the receiving facility to arrange for an appointment for the referred client on the following day after the referral.
4. On the day of the agreed date to visit the health facility, call the facility to check if the client has honoured the appointment.

Receiving facility:

5. If the client has not arrived at the preferred site, the Nurse/Adherence officer should call the client to remind them about going to the facility and request the next re-appointment date.
6. It is important that the client does not miss an appointment since it will interrupt adherence
7. If the client does not come on the re-appointed day, arrange to be followed up by community cadres including RHM, ACF, Expert Clients and Adherence Officer.

CHAPTER 17
MONITORING, EVALUATION AND SUPPORTIVE SUPERVISION

Monitoring is the systematic and routine collection of information from projects and programs for four main purposes:

- To learn from experiences to improve practices and activities in the future.
- To have internal and external accountability of the resources used and the results obtained.
- To make informed decisions on the future of the initiative.
- To promote the empowerment of beneficiaries of the initiative.

Monitoring is a periodically recurring task beginning during the planning stage of a project or program. Monitoring allows results, processes, and experiences to be documented and used as a basis for decision-making and learning. Monitoring is checking progress against plans. The data acquired through monitoring is used for evaluation.

Evaluation is assessing, as systematically and objectively as possible, a completed project or program (or a phase of an ongoing project or program that has been completed). Evaluations appraise data and information that inform strategic decisions, thus improving the project or program in the future.

Evaluations should help to conclude five main aspects of the intervention:

- Relevance
- Effectiveness
- Efficiency
- Impact
- Sustainability

Information gathered on these aspects during the monitoring process provides the basis for the evaluative analysis.

Surveillance is the systematic collection, analysis, and reporting of data related to TB infection and disease. The goal of TB surveillance is to help public health agencies prevent the spread of disease, control and treat it, and identify priority needs. The World Health Organization (WHO) has guided TB surveillance since the mid-1990s, including standardized definitions, forms, registers, and reports.

17.1 Description of TB Surveillance System and forms and registers used in the TB program

Before transitioning to CMIS, the NTCP used a (manual) paper-based data management system. It was challenging for the NTCP to track TB patients across different health facilities and monitor their response to treatment. With CMIS, all TB patient's medical history will be available to the healthcare workers at all facilities using the system.

The following forms and registers form the basis for the development of the TB Modules in the Client Management Information System (CMIS).

Presumptive TB Register (PTB 01)

Once a patient is presumed to have TB during screening in the OPD or other entry points, they are registered in the Presumptive TB Register by HCW who performed the TB screening. The Presumptive TB Register contains sociodemographic information about TB patients, history of TB, where the patient is referred for diagnosis, diagnosis result details, TB management suggestions, and details where the patient is referred for management. A new serial number will be assigned at the beginning of each month while using this register. The register is the same for both DS and DR TB.

Laboratory Request Form (TB 02)

This form is filled in by HCWs when requesting tests for diagnosis of TB and for follow-up purposes. There is only one Laboratory Request Form that will be used for both DS and DR TB diagnosis as well as follow-up. Once the tests are done, the lab reports back the test results of Smear Microscopy and Xpert MTB Ultra/ Rif, TB LAM testing using the same Form. Results of LPA and Culture DST are given in separate forms using Laboratory Report Form (LPA and Culture DST).

Laboratory Register (TB 03)

This register is present in the Laboratories where the bacteriological tests for TB are carried out. The Program keeps the same register for all the different types of laboratory processes even within the same laboratory. All types of testing are recorded in the same register (a. Sputum Smear Microscopy, GeneXpert, LPA, Culture DST, TB LAM. Once the results are obtained, they are sent back to the treatment centre.

DS-TB Register (TB 04)

Once a patient is referred from the diagnosing department to the TB treatment unit (TB BMU) for management of TB, they are first registered in the TB register. This register contains details of patients' particulars, diagnosis details, registration category details and treatment details, sputum conversion and treatment outcome details with other additional details on contact investigation, and smoking habits. This register will be the basis for filling out the TB case finding report and cohort reports. The register is updated for each patient on months 0, 2/3, 5, and end of treatment for DS TB.

DR-TB Register (TB 05)

Once a patient is referred from the diagnosing department to the TB treatment unit (TB BMU) for management of TB, they are first registered in the TB register. This register contains details of patients' particulars, diagnosis details, registration category details and treatment details, sputum conversion and outcome details with other additional details on contact investigation, and smoking habits. The register is updated for each patient on months 0, 2/3, 5, 9, 12, 18, and end of treatment for DR TB.

DST TB treatment Card (TB 06)

Once on the TB register, a TB patient card is also issued by the TB focal person which has further details of the patient with daily Treatment Adherence monitoring aspects. These are kept at the health facility level and updated every day when a patient comes for a check-up or refill. It is updated every month when the patients come to health facilities to collect their medicine.

Patient Identity Card (TB 07)

Once the treatment card is issued, the Patient's identity card is also issued to be kept by the patient, which has all the information from the treatment card and is updated every day.

DR-TB Patient File (TB 08)

Information relevant to the start and continuation of second-line treatment in a TB patient is entered into the patient's file. The Patient File is kept at the treatment center or with the health care worker providing DRTB services. A record of the administration of drugs is kept on the file. The file, or a copy of it, must always follow the patient (e.g. from a specialized hospital to an ambulatory facility). The DRTB Patient file is usually opened after a decision is taken to start the patient on treatment and s/he is registered in the (Second line) DRTB treatment register. It is the primary source of information to update this register. Information on the DR-TB Patient file is organized in several blocks: The section on patient information includes demographic and clinical details: Patient name, Address/telephone, Sex, Date of birth (or Age), Initial weight, and Site of disease. The site of disease is denoted as "pulmonary" and "extrapulmonary" in the same way as for basic TB management. This section also includes the Second-line TB treatment registration number (the unique register number assigned at the start of treatment) and the Date of registration.

Contact Tracing Logbook (TB 08)

After a case is registered in the TB register, TB focal persons are responsible for ensuring that Index cases and their contacts are listed and contact investigation of close household contacts of all the PBC index cases is carried out to assess their TB status. TB Champions are given the list of index cases that they use while carrying out contact tracing in the community. If there is presumptive TB among contacts identified during screening, the TB champion is expected to collect a spot sputum specimen, if it is not possible to collect sputum, a separate Referral Form (TB 11) is filled out and issued by the TB Champion and referred for further diagnosis. All the information is then recorded for all contacts screened in this form and is submitted back to the TB BMU. The same form will be used to access contacts of drug-sensitive and/or drug-resistant TB.

Contact and TPT Register (TB 09)

Once Household contacts are referred from the community, they are then registered in the Contact Tracing and/or TB Preventive Therapy (TBPT) Register at the TB BMU. This register contains details of the contact, their TB status, the information regarding TPT if provided for all ages, and PLHIV enrolled among those contacts, etc. This register contains the details of the client's particulars, and their TPT regimen details including weight, doses, and outcome.

Referral / Transfer form (TB 10)

These forms are filled when a patient needs to be referred to or transferred from one centre to the next. This contains information on the patient's particular, diagnostic details, treatment category, and regimen details along with details from where and the reason for referral/transfer out. It also has the acknowledgement slip which needs to be filled out and sent back by the receiving center.

Community Referral Form (TB 11)

These forms are provided to TB Champions and are used while referring presumptive TB clients from the community (during contact tracing) to the health facilities for further diagnosis or can also be used for referring a TB patient if they have side effects or require other tests and follow-up, which they identify in the community.

17.2 Monitoring of TB Case Detection and Treatment Activities

Monitoring TB control activities is important to assess progress and identify areas that need improvement. The National TB Control Program monitors the following indicators:

TB case detection indicators

- **Monitoring done at the National level**
  - (i) The proportion of presumptive TB cases detected at different levels (national, and regional levels). The monitoring is done for all forms of TB.
  - (ii) The proportion of TB cases detected (all forms) among presumptive TB cases and enrolled under treatment at different levels (national, regional). The monitoring is done for all forms of TB.
  - (iii) The Cohort analysis (sputum conversion and treatment outcome) of the registered TB cases.
  - (iv) The proportion of household contacts identified, screened and put on TPT at different levels (national, and regional)

- **Monitoring done at the health facility level**
  - (i) The proportion of presumptive TB among total visits.
  - (ii) The proportion of presumptive TB tested for TB.
  - (iii) The proportion of presumptive TB tested who are bacteriologically confirmed and treated for TB.
  - (iii) The proportion of household contacts screened for TB was found negative and put on TPT.
  - (v) Daily adherence of patients under DOT
  - (vi) Contact tracing of index TB cases and the proportion of contacts tested for TB, diagnosed with TB, and treated for TB.

- **TB Treatment Monitoring**
  - (i) *Sputum conversion:* This indicator refers to the conversion of sputum-positive TB to sputum-negative TB and is measured as the proportion of new sputum smear-positive cases converted to negative at the end of 2 months.
  - (ii) *Culture conversion (Interim outcome):* Culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative at 6 months post-initiation. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

- **TB Treatment Outcome Indicators**

  TB Treatment Outcome: This refers to treatment outcomes for new bacteriologically confirmed and clinically diagnosed cases, bacteriologically confirmed, and clinically diagnosed retreatment cases registered in a specified

period. Treatment Outcome indicators are measured as a proportion of new and retreatment bacteriological and clinically diagnosed cases with the following treatment outcomes.

(a) Cured
(b) Treatment Completed
(c) Treatment Failed
(d) Died
(e) Lost to follow-up.
(f) Not evaluated

*Treatment Success rate (proportion of cured plus treatment completed) The most important treatment outcome is the cure rate for bacteriologically confirmed patients. The desired treatment success rate for Eswatini is more than 90%.

17.3 Supervisory support to TB Basic Management Units

Supervision, monitoring, and evaluation are distinct managerial steps. In practice, these three activities are closely linked, with considerable overlap and a common approach. Supervision involves mostly programming activities, conducted from upper to lower levels of the health system by clinicians and/or managerial TB staff.

Supervision is the observation of health workers in their workplace, performed regularly (every 1 to 6 months), to develop their knowledge, perfect their skills, solve problems, correct errors, improve attitudes towards their work, and increase staff motivation. It is also termed “on-the-spot training”. Supervision should be educative and supportive, not punitive. The supervisory relationship should be positive and encouraging for the supervised staff.

Supervision and monitoring can be of great benefit to the improvement of program performance. The objectives of supervision are similar whether performed through an external monitoring mission or during routine supervisory activities by NTCP i.e. to ensure the quality of work according to the program’s planning and implementation targets and the recommended practices. Good TB control depends on proper and regular monitoring and supervision.

Supervisory visits aim to:

- Reinforce and promote the use of good diagnostic, treatment, and drug-use practices, as detailed in the national guidelines.
- Help healthcare workers to transfer learning skills to clinical work in facilities.
- Identify problems faced by healthcare workers in managing TB cases so that they can be solved without delay on the spot or with other partners during meetings.
- Stimulate health worker team spirit and motivation.
- Provide technical advice and guidance to health workers to enhance their knowledge and encourage a positive attitude and good practices.
- Become informed of the opinions of TB patients concerning service delivery and expectations.

Supervisory visits should involve five main units: the laboratory, the pharmacy, the in-patient ward, general and TB-specific outpatient facilities, and the office where records and reports are kept.

During field visits, supervisors (TB Program staff and partners) will make observations and carry out interviews, sometimes with the aid of a supervisory checklist. However, much of what supervisors do is problem-solving and training. Problem-solving and on-the-spot training should always refer to the national TB guidelines and national training manual. If problems cannot be corrected on the spot, the supervisor should make a written record, identify potential causes, and propose solutions.

The key components and subcomponents of the **National TB Strategy** should also be considered during supervision and monitoring activities. Priority should be given to serious weak points to focus on problem-solving. The main function of the field visit is not only to gather quantitative data, which should be available before the visit starts but also to observe the organization and delivery of TB services, to discuss problems, and to assess the validity of the data.

Supervision will mostly be provided by one qualified and knowledgeable member of the TB program staff and/or Implementing partner staff. Additional members of the supervision team may include the medical supervisor, the laboratory supervisor, pharmacists, nurses, and trainees.

Supervision will be carried out at all levels of the health infrastructure, with regular visits to all implementing units. Visits should be arranged to selected institutions, organizations, and individuals, and TB patients eventually at home at the peripheral level informed by gaps identified from data. The supervisory team should prepare a draft report during the visit and provide it to the TB staff responsible for immediate action. The main recommendations should be discussed and, if possible, agreed upon during the visit. The report should be short and must include:

- Actions taken since the last visit.
- Main achievements and constraints observed during the visit.
- Recommendations and proposed next steps before the next visit to overcome problems or improve program performance.

A five-year plan and an annual operational plan of work facilitate the management process by providing references and standards for comparison during each management period, including supervisory and monitoring activities. The NTCP will implement a regular monitoring and supervision mechanism to ensure that activities are conducted as planned in the five-year and annual operational plans, respecting good practices recommended in the technical guidelines. Preparing new mid-term and long-term plans is based on a periodic and regular evaluation of the program.

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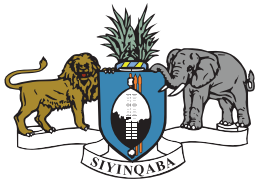
NOTES



The Global Fund
To Fight AIDS, Tuberculosis and Malaria

MOH
HIV/AIDS
SNAP
SWAZILAND NATIONAL AIDS PROGRAMME

Stop TB Partnership

icap Global Health

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GEORGETOWN UNIVERSITY

Elizabeth Glaser
Pediatric AIDS Foundation
Fighting for an AIDS-free generation

URC

BAYLOR COLLEGE OF MEDICINE
Children's Foundation
ESWATINI

Health Promotion
ESWATINI
Healthy Lifestyle

NERCHA

Eswatini Health Laboratory Service

World Health Organization

NTCP
National Tuberculosis Control Programme

PEPFAR
U.S. President's Emergency Plan for AIDS Relief